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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AXSOME MALTA LTD. and AXSOME THERAPEUTICS, INC., **Plaintiffs,** **v.** **ALKEM LABORATORIES LTD., AUROBINDO PHARMA USA, INC., AUROBINDO PHARMA LIMITED, HETERO USA INC., HETERO LABS LIMITED UNIT-V, HETERO LABS LTD., and HIKMA PHARMACEUTICALS USA INC.,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiffs Axsome Malta Ltd. and Axsome Therapeutics, Inc. (together, "Axsome"), by their undersigned attorneys, for their Complaint against defendants Alkem Laboratories Ltd. ("Alkem"), Aurobindo Pharma USA, Inc., and Aurobindo Pharma Limited (together, "Aurobindo"), Hetero USA Inc., Hetero Labs Limited Unit-V, and Hetero Labs Ltd. (collectively, "Hetero"), and Hikma Pharmaceuticals USA Inc. ("Hikma") (Alkem, Aurobindo, Hetero, and Hikma, collectively, "Defendants"), allege as follows:

Nature of the Action

1. This complaint is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Defendants' submission of their respective Abbreviated New Drug Application ("ANDA") Nos. 218722 ("Alkem's ANDA"), 218725 ("Aurobindo's ANDA"), 218654 ("Hetero's ANDA"), and 218016 ("Hikma's ANDA"), with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of Axsome's solriamfetol oral tablets drug products prior to the expiration of one or more of United States Patent Nos. 11,969,404 ("the '404 patent"), 11,986,454 ("the '454 patent"), 11,986,455 ("the '455 patent"), 11,998,639 ("the '639 patent"), 12,005,036 ("the '036 patent"), 12,036,194 ("the '194 patent"), and 12,064,411 ("the '411 patent") (collectively, "the patents-in-suit"). Axsome is the owner of the patents-in-suit.

The Parties

2. Plaintiff Axsome is a biopharmaceutical company focused on developing novel therapies for central nervous system ("CNS") conditions that have limited treatment options. One such therapy, Sunosi® (solriamfetol) oral tablets, is a dopamine and norepinephrine reuptake inhibitor ("DNRI") indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea.

3. Axsome Malta Ltd. is a corporation organized and existing under the laws of the Republic of Malta, having its principal place of business at Pinto Business Centre, Level 4, Office 4, Mill Street, Qormi, Triq il-Mithna Hal, Malta, QRM 3104.

4. Axsome Therapeutics, Inc. is a corporation organized and existing under the laws of Delaware, having its principal place of business at One World Trade Center, 22nd Floor, New York, New York 10007.

5. On information and belief, Defendant Alkem is a corporation organized and existing under the laws of India, having a principal place of business at Devashish Building, Alkem House, Senapati Bapat Road, Lower Parel, Mumbai, 400 013, Maharashtra, India.

6. On information and belief, Defendant Aurobindo Pharma USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 279 Princeton Hightstown Road, East Windsor, New Jersey 08520.

7. On information and belief, Defendant Aurobindo Pharma Limited is a corporation organized and existing under the laws of India, having a principal place of business at Galaxy Floors: 22-24, Plot No. 1, Survey No. 83/1, Hyderabad Knowledge City, Raidurg Pamkaktha, Ranga Reddy District, Hyderabad, Telangana, India, 500032.

8. On information and belief, Defendant Hetero USA Inc. is a corporation organized and existing under the laws of Delaware, having a principal place of business at 1035 Centennial Avenue, Piscataway, NJ 08854.

9. On information and belief, Defendant Hetero Labs Limited Unit-V is a corporation organized and existing under the laws of India, having a principal place of business at Polepally, Jadcherla, Mahabubnagar – 509301, Andhra Pradesh, India.

10. On information and belief, Defendant Hetero Labs Ltd. is a corporation organized and existing under the laws of India, having a principal place of business at 7-2-A2, Hetero Corporate Industrial Estates, Sanath Nagar, Hyderabad 500 018, Andhra Pradesh, India.

11. On information and belief, Defendant Hikma is a corporation organized and existing under the laws of Delaware, having a principal place of business at 200 Connell Drive, 4th Floor, Berkeley Heights, New Jersey 07922.

12. On information and belief, Defendants are all pharmaceutical companies that formulate, manufacture, package, and market generic drug products for distribution in the District of New Jersey and throughout the United States.

The Patents-in-Suit

13. On April 30, 2024, the USPTO duly and lawfully issued the '404 patent, entitled, "Methods of Providing Solriamfetol Therapy to Subjects with Impaired Renal Function." The face of the '404 patent identifies Katayoun Zomorodi as the inventor. A copy of the '404 patent is attached hereto as Exhibit A.

14. On May 21, 2024, the USPTO duly and lawfully issued the '454 patent, entitled, "Methods of Providing Solriamfetol Therapy to Subjects with Impaired Renal Function." The face of the '454 patent identifies Katayoun Zomorodi as the inventor. A copy of the '454 patent is attached hereto as Exhibit B.

15. On May 21, 2024, the USPTO duly and lawfully issued the '455 patent, entitled, "Methods of Providing Solriamfetol Therapy to Subjects with Impaired Renal Function." The face of the '455 patent identifies Katayoun Zomorodi as the inventor. A copy of the '455 patent is attached hereto as Exhibit C.

16. On June 4, 2024, the USPTO duly and lawfully issued the '639 patent, entitled, "Formulations of (R)-2-Amino-Phenylpropyl Carbamate." The face of the '639 patent identifies Clark Patrick Allphin and Edwin Gerard Walsh as the inventors. A copy of the '639 patent is attached hereto as Exhibit D.

17. On June 11, 2024, the USPTO duly and lawfully issued the '036 patent, entitled, "Methods of Administering Solriamfetol to Lactating Women." The face of the '036 patent identifies Herriot Tabuteau as the inventor. A copy of the '036 patent is attached hereto as Exhibit E.

18. On July 16, 2024, the USPTO duly and lawfully issued the '194 patent, entitled, "Methods of Administering Solriamfetol to Lactating Women." The face of the '194 patent identifies Herriot Tabuteau as the inventor. A copy of the '194 patent is attached hereto as Exhibit F.

19. On August 20, 2024, the USPTO duly and lawfully issued the '411 patent, entitled, "Methods of Administering Solriamfetol to Lactating Women." The face of the '411 patent identifies Herriot Tabuteau as the inventor. A copy of the '411 patent is attached hereto as Exhibit G.

The Sunosi® Drug Product

20. Axsome holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for solriamfetol oral tablets, Eq. 75 mg base and Eq. 150 mg base ("NDA No. 211230"), which is sold under the trademark Sunosi®. Sunosi® is a DNRI indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea. The claims of the patents-in-suit cover, *inter alia*, formulations of solriamfetol and methods of using solriamfetol to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea.

21. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Sunosi®.

Jurisdiction and Venue: Alkem

22. This Court has jurisdiction over the subject matter of Counts I and II against Alkem pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

23. As set forth below, the Court has personal jurisdiction over Alkem by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

24. On information and belief, Alkem purposefully has conducted and continues to conduct business in this Judicial District.

25. On information and belief, Alkem is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

26. On information and belief, this Judicial District will be a destination for the generic version of Axsome's solriamfetol oral tablets drug products for which Alkem seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 218722 ("Alkem's Proposed Product").

27. This Court has personal jurisdiction over Alkem because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey.

28. On information and belief, Alkem is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0400132325.

29. Alkem has consented to personal jurisdiction in this Court in numerous recent actions arising out of its ANDA submissions and has filed counterclaims in such cases. *See, e.g.*, *Azurity Pharm., Inc. v. Alkem Labs. Ltd.*, Civil Action No. 22-cv-0143 (D.N.J.); *Celgene Corp. v. Alkem Labs. Ltd.*, Civil Action No. 18-cv-11265 (D.N.J.); *Valeant Pharm. N. Am. LLC*

v. Alkem Labs. Ltd., Civil Action No. 18-cv-13905 (D.N.J.); *Sumitomo Dainippon Pharma Co. v. Alkem Labs. Ltd*., Civil Action No. 18- cv-14787 (D.N.J.). Alkem has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

30. Alkem did not contest personal jurisdiction in this Court in related action *Axsome Malta Ltd., et al v. Alkem Laboratories Ltd., et al.*, Civil Action No. 23-20354 (MCA)(LDW) (D.N.J.) (consolidated).

31. In the alternative, this Court has personal jurisdiction over Alkem because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Axsome's claims arise under federal law; (b) Alkem is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Alkem has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Alkem satisfies due process.

32. At least because, on information and belief, Alkem is a foreign company, venue is proper in this Judicial District with respect to Alkem pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b). Also, for at least the reasons set forth above in Paragraphs 24-30, venue is proper in this Judicial District with respect to Alkem pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Jurisdiction and Venue: Aurobindo

33. This Court has jurisdiction over the subject matter of Counts III and IV against Aurobindo pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

34. As set forth below, the Court has personal jurisdiction over both Aurobindo Pharma USA, Inc. and Aurobindo Pharma Limited by virtue of, *inter alia*, their systematic and continuous contacts with the State of New Jersey.

35. On information and belief, Aurobindo purposefully has conducted and continues to conduct business in this Judicial District.

36. On information and belief, Aurobindo is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

37. On information and belief, this Judicial District will be a destination for the generic version of Axsome's solriamfetol oral tablets drug products for which Aurobindo seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 218725 ("Aurobindo's Proposed Product").

38. This Court has personal jurisdiction over Aurobindo Pharma Limited because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Aurobindo Pharma USA, Inc., a company with a regular and established physical place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Aurobindo Pharma USA, Inc.

39. This Court has personal jurisdiction over Aurobindo Pharma USA, Inc. because, *inter alia*, on information and belief, Aurobindo maintains a regular and established, physical place of business at 279 Princeton Hightstown Road, East Windsor, New Jersey 08520.

40. On information and belief, Aurobindo Pharma USA, Inc. is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0100921223.

41. On information and belief, Aurobindo Pharma USA, Inc. will work in concert with Aurobindo Pharma Limited toward the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including Aurobindo's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

42. Aurobindo has consented to personal jurisdiction in this Court in numerous recent actions arising out of its ANDA submissions and has filed counterclaims in such cases. *See, e.g.*, *Theravance Biopharma R&D IP, LLC, et al. v. Eugia Pharma Specialities Limited, et al.*, Civil Action No. 1:23-cv-00926 (Aurobindo Pharma USA, Inc., Aurobindo Pharma Limited); *Forest Lab'ys, LLC, et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 2:17-cv-11679 (Aurobindo Pharma USA, Inc., Aurobindo Pharma Limited); *Boehringer Ingelheim Pharms., Inc., et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 3:17-cv-07887 (Aurobindo Pharma USA, Inc.); *Mitsubishi Tanabe Pharma Corp., et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 1:17-cv-05005 (Aurobindo Pharma USA, Inc.). Aurobindo has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

43. Aurobindo consented to personal jurisdiction in this Court in related action *Axsome Malta Ltd., et al v. Alkem Laboratories Ltd., et al.*, Civil Action No. 23-20354 (MCA)(LDW)(D.N.J.) (consolidated).

44. In the alternative, this Court has personal jurisdiction over Aurobindo Pharma Limited because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Axsome's claims arise under federal law; (b) Aurobindo Pharma Limited is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Aurobindo Pharma Limited has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Aurobindo Pharma Limited satisfies due process.

45. At least because, on information and belief, Aurobindo Pharma Limited is a foreign company, venue is proper in this Judicial District with respect to Aurobindo Pharma Limited pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b). Also, for at least the reasons set forth above in Paragraphs 35-43, venue is proper in this Judicial District with respect to Aurobindo Pharma USA, Inc. pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Jurisdiction and Venue: Hetero

46. This Court has jurisdiction over the subject matter of Counts V through XI against Hetero pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

47. As set forth below, the Court has personal jurisdiction over each of Hetero USA Inc., Hetero Labs Limited Unit-V, and Hetero Labs Ltd. by virtue of, *inter alia*, their systematic and continuous contacts with the State of New Jersey.

48. On information and belief, Hetero purposefully has conducted and continues to conduct business in this Judicial District.

49. On information and belief, Hetero is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

50. On information and belief, this Judicial District will be a destination for the generic version of Axsome's solriamfetol oral tablets drug products for which Hetero seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 218654 ("Hetero's Proposed Product").

51. This Court has personal jurisdiction over Hetero Labs Ltd. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Hetero USA Inc., a company with a regular and established physical place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey, including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero USA Inc.

52. This Court has personal jurisdiction over Hetero Labs Limited Unit-V because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in the State of New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Hetero USA Inc., a company with a regular and established physical place of business in New Jersey; and (2) maintains extensive and systematic contacts with the State of New Jersey,

including through the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Hetero USA Inc.

53. This Court has personal jurisdiction over Hetero USA Inc. because, *inter alia*, on information and belief, Hetero USA Inc. maintains a regular and established, physical place of business at 1035 Centennial Avenue, Piscataway, NJ 08854.

54. On information and belief, Hetero USA Inc. is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0400362826.

55. On information and belief, Hetero USA Inc. will work in concert with Hetero Labs Limited Unit-V and/or Hetero Labs Ltd. toward the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including Hetero's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

56. Hetero has consented to personal jurisdiction in this Court in recent actions arising out of its ANDA submissions and has filed counterclaims in such cases. *See, e.g., Celgene Corporation v. Annora Pharma Private Limited, et al.,* C.A. No. 3-18-cv-11220 (D.N.J.) (Hetero USA Inc.); *Celgene Corporation v. Hetero Labs Limited, et al.,* Civil Action No. 2-19-cv-15449 (SDW)(LDW) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd., Hetero Labs Ltd. Unit-V); *Celgene Corporation v. Hetero Labs Limited, et al.,* Civil Action No. 2-19-cv-05797 (ES)(MAH) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd., Hetero Labs Ltd. Unit-V); *Celgene Corporation v. Hetero Labs Limited, et al.,* Civil Action No. 2-18-cv-17463 (SDW)(LDW) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd., Hetero Labs Ltd. Unit-V); *Celgene Corporation v. Hetero Labs Limited, et al.,* Civil Action No. 2-18-cv-14111

(ES)(MAH) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd., Hetero Labs Ltd. Unit-V); *Celgene Corporation v. Hetero Labs Limited, et al.,* Civil Action No. 2-17-cv-03387 (ES)(MAH) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd., Hetero Labs Ltd. Unit-V); *Otsuka Pharm. Co., Ltd. v. Hetero Drugs Ltd., et al.,* Civil Action No. 1-15-cv-00161 (JBS)(KMW) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd.); *AstraZeneca AB, et al. v. Hetero USA Inc., et al.,* Civil Action No. 1-16-cv-02442 (RMB)(JS) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd.); and *BTG Int'l Ltd., et al. v. Actavis Labs. FL, Inc., et al.,* Civil Action No. 2-15-cv-05909 (KM)(JBC) (D.N.J.) (Hetero USA Inc., Hetero Labs Ltd., Hetero Labs Ltd. Unit-V). Hetero has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

57. Hetero did not contest personal jurisdiction in this Court in related action *Axsome Malta Ltd., et al v. Alkem Laboratories Ltd., et al.*, Civil Action No. 23-20354 (MCA)(LDW)(D.N.J.) (consolidated).

58. In the alternative, this Court has personal jurisdiction over Hetero Labs Ltd. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Axsome's claims arise under federal law; (b) Hetero Labs Ltd. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Hetero Labs Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Hetero Labs Ltd. satisfies due process.

59. In the alternative, this Court has personal jurisdiction over Hetero Labs Limited Unit-V because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as

(a) Axsome's claims arise under federal law; (b) Hetero Labs Limited Unit-V is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Hetero Labs Limited Unit-V has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Hetero Labs Limited Unit-V satisfies due process.

60. At least because, on information and belief, Hetero Labs Ltd. and Hetero Labs Limited Unit-V are foreign companies, venue is proper in this Judicial District with respect to Hetero Labs Ltd. and Hetero Labs Limited Unit-V pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b). Also, for at least the reasons set forth above in Paragraphs 48-57, venue is proper in this Judicial District as to Hetero USA Inc. pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Jurisdiction and Venue: Hikma

61. This Court has jurisdiction over the subject matter of Counts XII through XVIII against Hikma pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

62. As set forth below, the Court has personal jurisdiction over Hikma by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

63. On information and belief, Hikma purposefully has conducted and continues to conduct business in this Judicial District.

64. On information and belief, Hikma is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

65. On information and belief, this Judicial District will be a destination for the generic version of Axsome's solriamfetol oral tablets drug products for which Hikma seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 218016 ("Hikma's Proposed Product").

66. On information and belief, Hikma is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0100487525 and is registered as manufacturer and wholesaler with the New Jersey Department of Health under Registration No. 5002130.

67. This Court has personal jurisdiction over Hikma because, *inter alia*, on information and belief, Hikma maintains a regular and established, physical place of business at 200 Connell Drive, 4th Floor, Berkeley Heights, New Jersey 07922.

68. Hikma has consented to personal jurisdiction in this Court in numerous recent actions arising out of its ANDA submissions and has filed counterclaims in such cases. *See, e.g.*, *Celgene Corp. v. West-Ward Pharma Int'l Ltd., et al.*, Civil Action No. 2:18-cv-13477 (D.N.J.); *Celgene Corporation v. Hikma Pharmaceuticals USA Inc.*, Civil Action No. 21-20459 (SDW)(LDW) (D.N.J.); *Celgene Corporation v. Hikma Pharmaceuticals USA, Inc.*, Civil Action No. 21-10398 (SDW)(LDW) (D.N.J.). Hikma has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

69. Hikma did not contest personal jurisdiction in this Court in related action *Axsome Malta Ltd., et al v. Alkem Laboratories Ltd., et al.*, Civil Action No. 23-20354 (MCA)(LDW) (D.N.J.) (consolidated).

70. For at least the reasons set forth above in Paragraphs 63-69, venue is proper in this Judicial District with respect to Hikma pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Acts Giving Rise To Counts I-II Against Alkem

71. Pursuant to Section 505 of the FFDCA, Alkem submitted ANDA No. 218722 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Alkem's Proposed Product, before the patents-in-suit expire.

72. No earlier than August 11, 2023, Alkem sent written notice of a Paragraph IV Certification ("Alkem's First Notice Letter") to Axsome. According to Alkem's First Notice Letter, Alkem submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Alkem's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

73. No earlier than March 29, 2024, Alkem sent written notice of a Paragraph IV Certification ("Alkem's Second Notice Letter") to Axsome. According to Alkem's Second Notice Letter, Alkem submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Alkem's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

74. No earlier than June 26, 2024, Alkem sent written notice of a Paragraph IV Certification ("Alkem's Third Notice Letter") to Axsome. According to Alkem's Third Notice Letter, Alkem submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United

States of Alkem's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

75. On information and belief, Alkem provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), indicating that it seeks to obtain approval of its ANDA to engage in the commercial manufacture, use, or sale of Alkem's Proposed Product before the expiration of the Orange Book patents with respect to Sunosi®.

76. On information and belief, following FDA approval of Alkem's ANDA, Alkem will make, use, offer to sell, or sell Alkem's Proposed Product throughout the United States, or import such a generic product into the United States.

Acts Giving Rise To Counts III-IV Against Aurobindo

77. Pursuant to Section 505 of the FFDCA, Aurobindo submitted ANDA No. 218725 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Aurobindo's Proposed Product, before the patents-in-suit expire.

78. No earlier than August 10, 2023, Aurobindo Pharma USA, Inc. sent written notice of a Paragraph IV Certification ("Aurobindo's First Notice Letter") to Axsome. According to Aurobindo's First Notice Letter, Aurobindo submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

79. No earlier than December 8, 2023, Aurobindo Pharma Limited sent written notice of a Paragraph IV Certification ("Aurobindo's Second Notice Letter") to Axsome. According to Aurobindo's Second Notice Letter, Aurobindo submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use,

offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

80. No earlier than February 13, 2024, Aurobindo Pharma Limited sent written notice of a Paragraph IV Certification ("Aurobindo's Third Notice Letter") to Axsome. According to Aurobindo's Third Notice Letter, Aurobindo submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

81. No earlier than February 27, 2024, Aurobindo Pharma Limited sent written notice of a Paragraph IV Certification ("Aurobindo's Fourth Notice Letter") to Axsome. According to Aurobindo's Fourth Notice Letter, Aurobindo submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

82. No earlier than May 21, 2024, Aurobindo Pharma Limited sent written notice of a Paragraph IV Certification ("Aurobindo's Fifth Notice Letter") to Axsome. According to Aurobindo's Fifth Notice Letter, Aurobindo submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

83. No earlier than July 9, 2024, Aurobindo Pharma Limited sent written notice of a Paragraph IV Certification ("Aurobindo's Sixth Notice Letter") to Axsome. According to Aurobindo's Sixth Notice Letter, Aurobindo submitted an ANDA pursuant to Section 505 of

the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

84. On information and belief, Aurobindo provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), indicating that it seeks to obtain approval of its ANDA to engage in the commercial manufacture, use, or sale of Aurobindo's Proposed Product before the expiration of the Orange Book patents with respect to Sunosi®.

85. On information and belief, following FDA approval of Aurobindo's ANDA, Aurobindo will make, use, offer to sell, or sell Aurobindo's Proposed Product throughout the United States, or import such a generic product into the United States.

Acts Giving Rise To Counts V-XI Against Hetero

86. Pursuant to Section 505 of the FFDCA, Hetero submitted ANDA No. 218654 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Hetero's Proposed Product, before certain patents-in-suit expire.

87. No earlier than August 15, 2023, Hetero sent written notice of a Paragraph IV Certification ("Hetero's First Notice Letter") to Axsome. According to Hetero's First Notice Letter, Hetero submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

88. No earlier than December 1, 2023, Hetero sent written notice of a Paragraph IV Certification ("Hetero's Second Notice Letter") to Axsome. According to Hetero's Second Notice Letter, Hetero submitted an ANDA pursuant to Section 505 of the FFDCA seeking

approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

89. No earlier than March 11, 2024, Hetero sent written notice of a Paragraph IV Certification ("Hetero's Third Notice Letter") to Axsome. According to Hetero's Third Notice Letter, Hetero submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

90. On information and belief, Hetero provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), indicating that it seeks to obtain approval of its ANDA to engage in the commercial manufacture, use, or sale of Hetero's Proposed Product before the expiration of the Orange Book patents with respect to Sunosi®.

91. On information and belief, following FDA approval of Hetero's ANDA, Hetero will make, use, offer to sell, or sell Hetero's Proposed Product throughout the United States, or import such a generic product into the United States.

Acts Giving Rise To Counts XII-XVIII Against Hikma

92. Pursuant to Section 505 of the FFDCA, Hikma submitted ANDA No. 218016 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Hikma's Proposed Product, before the patents-in-suit expire.

93. No earlier than August 1, 2023, Hikma sent written notice of a Paragraph IV Certification ("Hikma's First Notice Letter") to Axsome. According to Hikma's First Notice Letter, Hikma submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to

engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

94. No earlier than March 18, 2024, Hikma sent written notice of a Paragraph IV Certification ("Hikma's Second Notice Letter") to Axsome. According to Hikma's Second Notice Letter, Hikma submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

95. No earlier than August 22, 2024, Hikma sent written notice of a Paragraph IV Certification ("Hikma's Third Notice Letter") to Axsome. According to Hikma's Third Notice Letter, Hikma submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

96. No earlier than September 3, 2024, Hikma sent written notice of a Paragraph IV Certification ("Hikma's Fourth Notice Letter") to Axsome. According to Hikma's Fourth Notice Letter, Hikma submitted an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product before expiration of certain patents listed in the Orange Book with respect to Sunosi®.

97. On information and belief, Hikma provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), indicating that it

seeks to obtain approval of its ANDA to engage in the commercial manufacture, use, or sale of Hikma's Proposed Product before the expiration of the Orange Book patents with respect to Sunosi®.

98. On information and belief, following FDA approval of Hikma's ANDA, Hikma will make, use, offer to sell, or sell Hikma's Proposed Product throughout the United States, or import such a generic product into the United States.

Count I: Infringement of the '194 Patent by Alkem

99. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

100. Alkem's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Alkem's Proposed Product, prior to the expiration of the '194 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

101. A justiciable controversy exists between Axsome and Alkem as to the infringement of the '194 patent.

102. Unless enjoined by this Court, upon FDA approval of Alkem's ANDA, Alkem will infringe one or more claims of the '194 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Alkem's Proposed Product in the United States.

103. Unless enjoined by this Court, upon FDA approval of Alkem's ANDA, Alkem will induce infringement of one or more claims of the '194 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Alkem's Proposed Product in the United States. On information and belief, upon FDA approval of

Alkem's ANDA, Alkem will intentionally encourage acts of direct infringement with knowledge of the '194 patent and knowledge that its acts are encouraging infringement.

104. Unless enjoined by this Court, upon FDA approval of Alkem's ANDA, Alkem will contributorily infringe one or more claims of the '194 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Alkem's Proposed Product in the United States. On information and belief, Alkem knew and knows that Alkem's Proposed Product is designed for a use that infringes one or more claims of the '194 patent, and Alkem's Proposed Product lacks a substantial non-infringing use.

105. Failure to enjoin Alkem's infringement of the '194 patent will substantially and irreparably damage and harm Axsome.

106. Axsome does not have an adequate remedy at law.

107. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '411 Patent by Alkem

108. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

109. Alkem's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Alkem's Proposed Product, prior to the expiration of the '411 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

110. A justiciable controversy exists between Axsome and Alkem as to the infringement of the '411 patent.

111. Unless enjoined by this Court, upon FDA approval of Alkem's ANDA, Alkem will infringe one or more claims of the '411 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Alkem's Proposed Product in the United States.

112. Unless enjoined by this Court, upon FDA approval of Alkem's ANDA, Alkem will induce infringement of one or more claims of the '411 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Alkem's Proposed Product in the United States. On information and belief, upon FDA approval of Alkem's ANDA, Alkem will intentionally encourage acts of direct infringement with knowledge of the '411 patent and knowledge that its acts are encouraging infringement.

113. Unless enjoined by this Court, upon FDA approval of Alkem's ANDA, Alkem will contributorily infringe one or more claims of the '411 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Alkem's Proposed Product in the United States. On information and belief, Alkem knew and knows that Alkem's Proposed Product is designed for a use that infringes one or more claims of the '411 patent, and Alkem's Proposed Product lacks a substantial non-infringing use.

114. Failure to enjoin Alkem's infringement of the '411 patent will substantially and irreparably damage and harm Axsome.

115. Axsome does not have an adequate remedy at law.

116. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '194 Patent by Aurobindo

117. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

118. Aurobindo's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product, prior to the expiration of the '194 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

119. A justiciable controversy exists between Axsome and Aurobindo as to the infringement of the '194 patent.

120. Unless enjoined by this Court, upon FDA approval of Aurobindo's ANDA, Aurobindo will infringe one or more claims of the '194 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Aurobindo's Proposed Product in the United States.

121. Unless enjoined by this Court, upon FDA approval of Aurobindo's ANDA, Aurobindo will induce infringement of one or more claims of the '194 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Aurobindo's Proposed Product in the United States. On information and belief, upon FDA approval of Aurobindo's ANDA, Aurobindo will intentionally encourage acts of direct infringement with knowledge of the '194 patent and knowledge that its acts are encouraging infringement.

122. Unless enjoined by this Court, upon FDA approval of Aurobindo's ANDA, Aurobindo will contributorily infringe one or more claims of the '194 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing

Aurobindo's Proposed Product in the United States. On information and belief, Aurobindo knew and knows that Aurobindo's Proposed Product is designed for a use that infringes one or more claims of the '194 patent, and Aurobindo's Proposed Product lacks a substantial non-infringing use.

123. Failure to enjoin Aurobindo's infringement of the '194 patent will substantially and irreparably damage and harm Axsome.

124. Axsome does not have an adequate remedy at law.

125. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '411 Patent by Aurobindo

126. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

127. Aurobindo's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Aurobindo's Proposed Product, prior to the expiration of the '411 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

128. A justiciable controversy exists between Axsome and Aurobindo as to the infringement of the '411 patent.

129. Unless enjoined by this Court, upon FDA approval of Aurobindo's ANDA, Aurobindo will infringe one or more claims of the '411 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Aurobindo's Proposed Product in the United States.

130. Unless enjoined by this Court, upon FDA approval of Aurobindo's ANDA, Aurobindo will induce infringement of one or more claims of the '411 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Aurobindo's Proposed Product in the United States. On information and belief, upon FDA approval of Aurobindo's ANDA, Aurobindo will intentionally encourage acts of direct infringement with knowledge of the '411 patent and knowledge that its acts are encouraging infringement.

131. Unless enjoined by this Court, upon FDA approval of Aurobindo's ANDA, Aurobindo will contributorily infringe one or more claims of the '411 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Aurobindo's Proposed Product in the United States. On information and belief, Aurobindo knew and knows that Aurobindo's Proposed Product is designed for a use that infringes one or more claims of the '411 patent, and Aurobindo's Proposed Product lacks a substantial non-infringing use.

132. Failure to enjoin Aurobindo's infringement of the '411 patent will substantially and irreparably damage and harm Axsome.

133. Axsome does not have an adequate remedy at law.

134. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '404 Patent by Hetero

135. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

136. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '404 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

137. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '404 patent.

138. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '404 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

139. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '404 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '404 patent and knowledge that its acts are encouraging infringement.

140. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '404 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '404 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

141. Failure to enjoin Hetero's infringement of the '404 patent will substantially and irreparably damage and harm Axsome.

142. Axsome does not have an adequate remedy at law.

143. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI: Infringement of the '454 Patent by Hetero

144. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

145. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '454 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

146. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '454 patent.

147. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '454 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

148. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '454 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of

Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '454 patent and knowledge that its acts are encouraging infringement.

149. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '454 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '454 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

150. Failure to enjoin Hetero's infringement of the '454 patent will substantially and irreparably damage and harm Axsome.

151. Axsome does not have an adequate remedy at law.

152. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII: Infringement of the '455 Patent by Hetero

153. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

154. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '455 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

155. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '455 patent.

156. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '455 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

157. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '455 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '455 patent and knowledge that its acts are encouraging infringement.

158. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '455 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '455 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

159. Failure to enjoin Hetero's infringement of the '455 patent will substantially and irreparably damage and harm Axsome.

160. Axsome does not have an adequate remedy at law.

161. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VIII: Infringement of the '639 Patent by Hetero

162. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

163. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '639 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

164. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '639 patent.

165. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '639 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

166. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '639 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '639 patent and knowledge that its acts are encouraging infringement.

167. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '639 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows

that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '639 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

168. Failure to enjoin Hetero's infringement of the '639 patent will substantially and irreparably damage and harm Axsome.

169. Axsome does not have an adequate remedy at law.

170. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IX: Infringement of the '036 Patent by Hetero

171. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

172. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '036 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

173. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '036 patent.

174. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '036 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

175. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '036 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's

Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '036 patent and knowledge that its acts are encouraging infringement.

176. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '036 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '036 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

177. Failure to enjoin Hetero's infringement of the '036 patent will substantially and irreparably damage and harm Axsome.

178. Axsome does not have an adequate remedy at law.

179. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count X: Infringement of the '194 Patent by Hetero

180. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

181. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '194 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

182. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '194 patent.

183. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '194 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

184. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '194 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '194 patent and knowledge that its acts are encouraging infringement.

185. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '194 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '194 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

186. Failure to enjoin Hetero's infringement of the '194 patent will substantially and irreparably damage and harm Axsome.

187. Axsome does not have an adequate remedy at law.

188. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XI: Infringement of the '411 Patent by Hetero

189. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

190. Hetero's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hetero's Proposed Product, prior to the expiration of the '411 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

191. A justiciable controversy exists between Axsome and Hetero as to the infringement of the '411 patent.

192. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will infringe one or more claims of the '411 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States.

193. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will induce infringement of one or more claims of the '411 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, upon FDA approval of Hetero's ANDA, Hetero will intentionally encourage acts of direct infringement with knowledge of the '411 patent and knowledge that its acts are encouraging infringement.

194. Unless enjoined by this Court, upon FDA approval of Hetero's ANDA, Hetero will contributorily infringe one or more claims of the '411 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hetero's Proposed Product in the United States. On information and belief, Hetero knew and knows

that Hetero's Proposed Product is designed for a use that infringes one or more claims of the '411 patent, and Hetero's Proposed Product lacks a substantial non-infringing use.

195. Failure to enjoin Hetero's infringement of the '411 patent will substantially and irreparably damage and harm Axsome.

196. Axsome does not have an adequate remedy at law.

197. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XII: Infringement of the '404 Patent by Hikma

198. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

199. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '404 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

200. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '404 patent.

201. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '404 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

202. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '404 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's

Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '404 patent and knowledge that its acts are encouraging infringement.

203. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '404 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '404 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

204. Failure to enjoin Hikma's infringement of the '404 patent will substantially and irreparably damage and harm Axsome.

205. Axsome does not have an adequate remedy at law.

206. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XIII: Infringement of the '454 Patent by Hikma

207. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

208. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '454 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

209. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '454 patent.

210. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '454 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

211. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '454 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '454 patent and knowledge that its acts are encouraging infringement.

212. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '454 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '454 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

213. Failure to enjoin Hikma's infringement of the '454 patent will substantially and irreparably damage and harm Axsome.

214. Axsome does not have an adequate remedy at law.

215. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XIV: Infringement of the '455 Patent by Hikma

216. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

217. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '455 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

218. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '455 patent.

219. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '455 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

220. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '455 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '455 patent and knowledge that its acts are encouraging infringement.

221. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '455 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows

that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '455 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

222. Failure to enjoin Hikma's infringement of the '455 patent will substantially and irreparably damage and harm Axsome.

223. Axsome does not have an adequate remedy at law.

224. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XV: Infringement of the '639 Patent by Hikma

225. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

226. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '639 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

227. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '639 patent.

228. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '639 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

229. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '639 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's

Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '639 patent and knowledge that its acts are encouraging infringement.

230. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '639 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '639 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

231. Failure to enjoin Hikma's infringement of the '639 patent will substantially and irreparably damage and harm Axsome.

232. Axsome does not have an adequate remedy at law.

233. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XVI: Infringement of the '036 Patent by Hikma

234. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

235. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '036 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

236. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '036 patent.

237. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '036 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

238. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '036 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '036 patent and knowledge that its acts are encouraging infringement.

239. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '036 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '036 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

240. Failure to enjoin Hikma's infringement of the '036 patent will substantially and irreparably damage and harm Axsome.

241. Axsome does not have an adequate remedy at law.

242. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XVII: Infringement of the '194 Patent by Hikma

243. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

244. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '194 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

245. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '194 patent.

246. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '194 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

247. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '194 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '194 patent and knowledge that its acts are encouraging infringement.

248. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '194 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows

that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '194 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

249. Failure to enjoin Hikma's infringement of the '194 patent will substantially and irreparably damage and harm Axsome.

250. Axsome does not have an adequate remedy at law.

251. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count XVIII: Infringement of the '411 Patent by Hikma

252. Axsome repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

253. Hikma's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Hikma's Proposed Product, prior to the expiration of the '411 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

254. A justiciable controversy exists between Axsome and Hikma as to the infringement of the '411 patent.

255. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will infringe one or more claims of the '411 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States.

256. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will induce infringement of one or more claims of the '411 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's

Proposed Product in the United States. On information and belief, upon FDA approval of Hikma's ANDA, Hikma will intentionally encourage acts of direct infringement with knowledge of the '411 patent and knowledge that its acts are encouraging infringement.

257. Unless enjoined by this Court, upon FDA approval of Hikma's ANDA, Hikma will contributorily infringe one or more claims of the '411 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Hikma's Proposed Product in the United States. On information and belief, Hikma knew and knows that Hikma's Proposed Product is designed for a use that infringes one or more claims of the '411 patent, and Hikma's Proposed Product lacks a substantial non-infringing use.

258. Failure to enjoin Hikma's infringement of the '411 patent will substantially and irreparably damage and harm Axsome.

259. Axsome does not have an adequate remedy at law.

260. This case is an exceptional one, and Axsome is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF AGAINST ALKEM

WHEREFORE, Plaintiff Axsome respectfully requests the following relief:

(A) A Judgment that Alkem infringed one or more claims of each of the patents-in-suit asserted against Alkem by submitting ANDA No. 218722;

(B) A Judgment that Alkem has infringed, and that Alkem's making, using, offering to sell, selling, or importing Alkem's Proposed Product will infringe one or more claims of each of the patents-in-suit asserted against Alkem;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 218722 be a date no earlier than the later of the expiration of each

patent-in-suit asserted against Alkem, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Alkem and its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from making, using, offering to sell, selling, or importing Alkem's Proposed Product until after the expiration of each of the patents-in-suit asserted against Alkem, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Alkem, its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from practicing any formulation or method claimed in the patents-in-suit asserted against Alkem, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit asserted against Alkem, until after the expiration of each such patent-in-suit, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Alkem's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of each of the patents-in-suit asserted against Alkem;

(G) To the extent that Alkem has committed any acts with respect to the formulations or methods claimed in the patents-in-suit asserted against Alkem, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Axsome damages for such acts;

(H) If Alkem engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Alkem's Proposed Product prior to the expiration of

the patents-in-suit asserted against Alkem, a Judgment awarding damages to Axsome resulting from such infringement, together with interest;

(I) A Judgment declaring that each patent-in-suit asserted against Alkem remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Axsome its attorneys' fees, costs, and expenses incurred in this action; and

(K) Such further and other relief as this Court may deem just and proper.

PRAYER FOR RELIEF AGAINST AUROBINDO

WHEREFORE, Plaintiff Axsome respectfully requests the following relief:

(A) A Judgment that Aurobindo infringed one or more claims of each of the patents-in-suit asserted against Aurobindo by submitting ANDA No. 218725;

(B) A Judgment that Aurobindo has infringed, and that Aurobindo's making, using, offering to sell, selling, or importing Aurobindo's Proposed Product will infringe one or more claims of each of the patents-in-suit asserted against Aurobindo;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 218725 be a date no earlier than the later of the expiration of each patent-in-suit asserted against Aurobindo, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Aurobindo and its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from making, using, offering to sell, selling, or importing Aurobindo's Proposed Product until after the expiration of each of the patents-in-suit asserted against Aurobindo, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Aurobindo, its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from practicing any formulation or method claimed in the patents-in-suit asserted against Aurobindo, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit asserted against Aurobindo, until after the expiration of each such patent-in-suit, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Aurobindo's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of each of the patents-in-suit asserted against Aurobindo;

(G) To the extent that Aurobindo has committed any acts with respect to the formulations or methods claimed in the patents-in-suit asserted against Aurobindo, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Axsome damages for such acts;

(H) If Aurobindo engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Aurobindo's Proposed Product prior to the expiration of the patents-in-suit asserted against Aurobindo, a Judgment awarding damages to Axsome resulting from such infringement, together with interest;

(I) A Judgment declaring that each patent-in-suit asserted against Aurobindo remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Axsome its attorneys' fees, costs, and expenses incurred in this action; and

(K) Such further and other relief as this Court may deem just and proper.

PRAYER FOR RELIEF AGAINST HETERO

WHEREFORE, Plaintiff Axsome respectfully requests the following relief:

(A) A Judgment that Hetero infringed one or more claims of each of the patents-in-suit asserted against Hetero by submitting ANDA No. 218654;

(B) A Judgment that Hetero has infringed, and that Hetero's making, using, offering to sell, selling, or importing Hetero's Proposed Product will infringe one or more claims of each of the patents-in-suit asserted against Hetero;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 218654 be a date no earlier than the later of the expiration of each patent-in-suit asserted against Hetero, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Hetero and its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from making, using, offering to sell, selling, or importing Hetero's Proposed Product until after the expiration of each of the patents-in-suit asserted against Hetero, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Hetero, its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from practicing any formulation or method claimed in the patents-in-suit asserted against Hetero, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit asserted against Hetero, until after the expiration of each such patent-in-suit, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Hetero's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of each of the patents-in-suit asserted against Hetero;

(G) To the extent that Hetero has committed any acts with respect to the formulations or methods claimed in the patents-in-suit asserted against Hetero, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Axsome damages for such acts;

(H) If Hetero engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Hetero's Proposed Product prior to the expiration of the patents-in-suit asserted against Hetero, a Judgment awarding damages to Axsome resulting from such infringement, together with interest;

(I) A Judgment declaring that each patent-in-suit asserted against Hetero remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Axsome its attorneys' fees, costs, and expenses incurred in this action; and

(K) Such further and other relief as this Court may deem just and proper.

PRAYER FOR RELIEF AGAINST HIKMA

WHEREFORE, Plaintiff Axsome respectfully requests the following relief:

(A) A Judgment that Hikma infringed one or more claims of each of the patents-in-suit asserted against Hikma by submitting ANDA No. 218016;

(B) A Judgment that Hikma has infringed, and that Hikma's making, using, offering to sell, selling, or importing Hikma's Proposed Product will infringe one or more claims of each of the patents-in-suit asserted against Hikma;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 218016 be a date no earlier than the later of the expiration of each patent-in-suit asserted against Hikma, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Hikma and its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from making, using, offering to sell, selling, or importing Hikma's Proposed Product until after the expiration of each of the patents-in-suit asserted against Hikma, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Hikma, its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from practicing any formulation or method claimed in the patents-in-suit asserted against Hikma, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit asserted against Hikma, until after the expiration of each such patent-in-suit, or any later expiration of exclusivity to which Axsome is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Hikma's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of each of the patents-in-suit asserted against Hikma;

(G) To the extent that Hikma has committed any acts with respect to the formulations or methods claimed in the patents-in-suit asserted against Hikma, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Axsome damages for such acts;

(H) If Hikma engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Hikma's Proposed Product prior to the expiration of the patents-in-suit asserted against Hikma, a Judgment awarding damages to Axsome resulting from such infringement, together with interest;

(I) A Judgment declaring that each patent-in-suit asserted against Hikma remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Axsome its attorneys' fees, costs, and expenses incurred in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: September 16, 2024

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matters captioned *Axsome Malta Ltd., et al. v. Alkem Lab'ys Ltd., et al.*, Civil Action No. 23-20354 (MCA)(LDW) (D.N.J.) (consolidated), *Axsome Malta Ltd., et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 24-7511 (MCA)(LDW) (D.N.J.), *Axsome Malta Ltd., et al. v. Alkem Laboratories Ltd.*, Civil Action No. 24-8365 (MCA)(LDW) (D.N.J.), and *Axsome Malta Ltd., et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 24-8624 (MCA)(LDW) (D.N.J.) are related to the matter in controversy because the matter in controversy involves the same plaintiffs, some of the same patents, and some of the same defendants, and because Defendants are seeking FDA approval to market a generic version of the same pharmaceutical product.

Dated: September 16, 2024

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EXHIBIT A

US011969404B2

(12) **United States Patent**
Zomorodi

(10) **Patent No.: US 11,969,404 B2**
(45) **Date of Patent: *Apr. 30, 2024**

(54) **METHODS OF PROVIDING SOLRIAMFETOL THERAPY TO SUBJECTS WITH IMPAIRED RENAL FUNCTION**

(71) Applicant: **Axsome Malta Ltd.**, Qormi (MT)

(72) Inventor: **Katayoun Zomorodi**, San Jose, CA (US)

(73) Assignee: **AXSOME MALTA LTD.**, Qormi (MT)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/295,138**

(22) Filed: **Apr. 3, 2023**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 17/479,121, filed on Sep. 20, 2021, which is a continuation of application No. 17/149,406, filed on Jan. 14, 2021, now Pat. No. 11,160,779, which is a continuation of application No. 16/824,560, filed on Mar. 19, 2020, now Pat. No. 10,940,133.

(51) **Int. Cl.**

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A61K 9/00	(2006.01)
A61K 31/27	(2006.01)
A61P 25/26	(2006.01)

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CPC ***A61K 31/325*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 31/27*** (2013.01); ***A61P 25/26*** (2018.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to methods for decreasing adverse effects associated with solriamfetol ([R]-2-amino-3-phenyl-propylcarbamate) therapy in subjects with impaired renal function. In particular, the invention provides an optimized dose escalation scheme for subjects with moderate renal impairment which results in the subjects having increased tolerance to adverse effects associated with the administration of solriamfetol. The invention also provides adjusted dosing for safe therapeutic use of solriamfetol in subjects having severe renal impairment.

18 Claims, 9 Drawing Sheets

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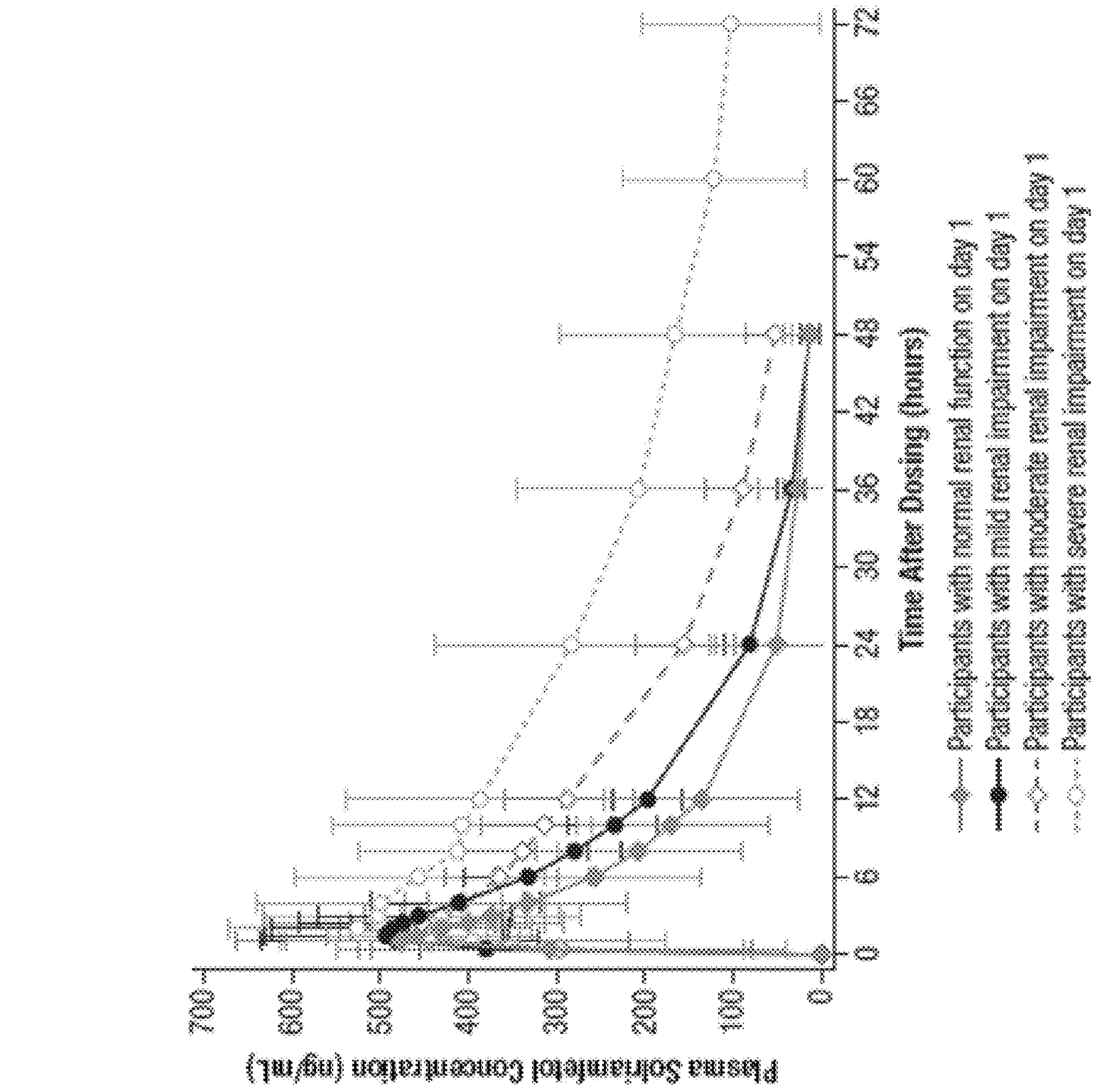

Plasma Sotalambetol Concentration (ng/mL)
700
600
500
400
300
200
100
0
Time After Dosing (hours)
0
6
12
18
24
30
36
42
48
54
60
66
72
Participants with normal renal function on day 1
Participants with mild renal impairment on day 1
Participants with moderate renal impairment on day 1
Participants with severe renal impairment on day 1

FIG. 1A

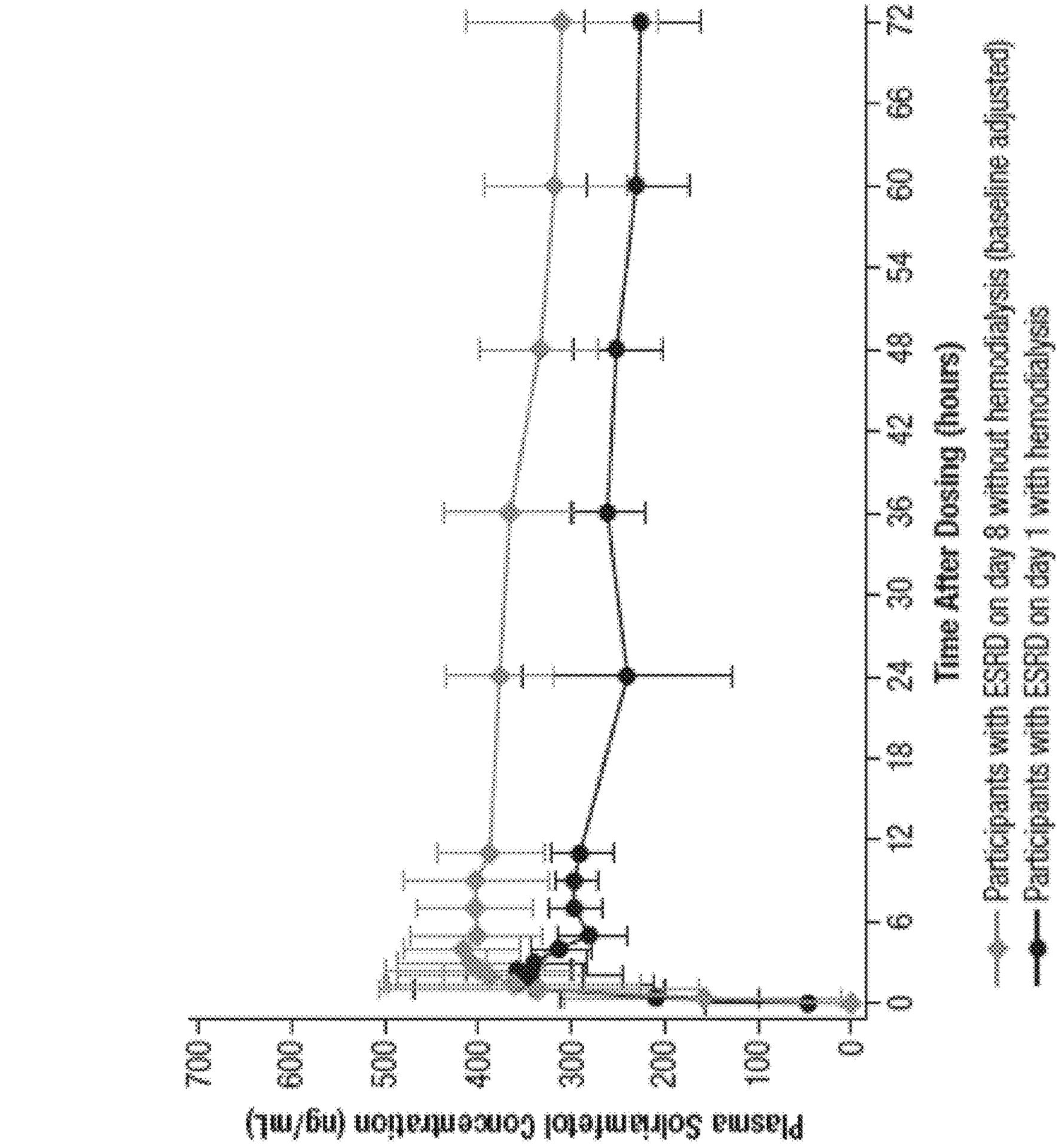

Plasma Sotrovimab concentration (ng/mL)
700
600
500
400
300
200
100
0
Time After Dosing (hours)
0
6
12
18
24
30
36
42
48
54
60
66
72
Participants with ESRD on day 8 without hemodialysis (baseline adjusted)
Participants with ESRD on day 1 with hemodialysis

FIG. 1B

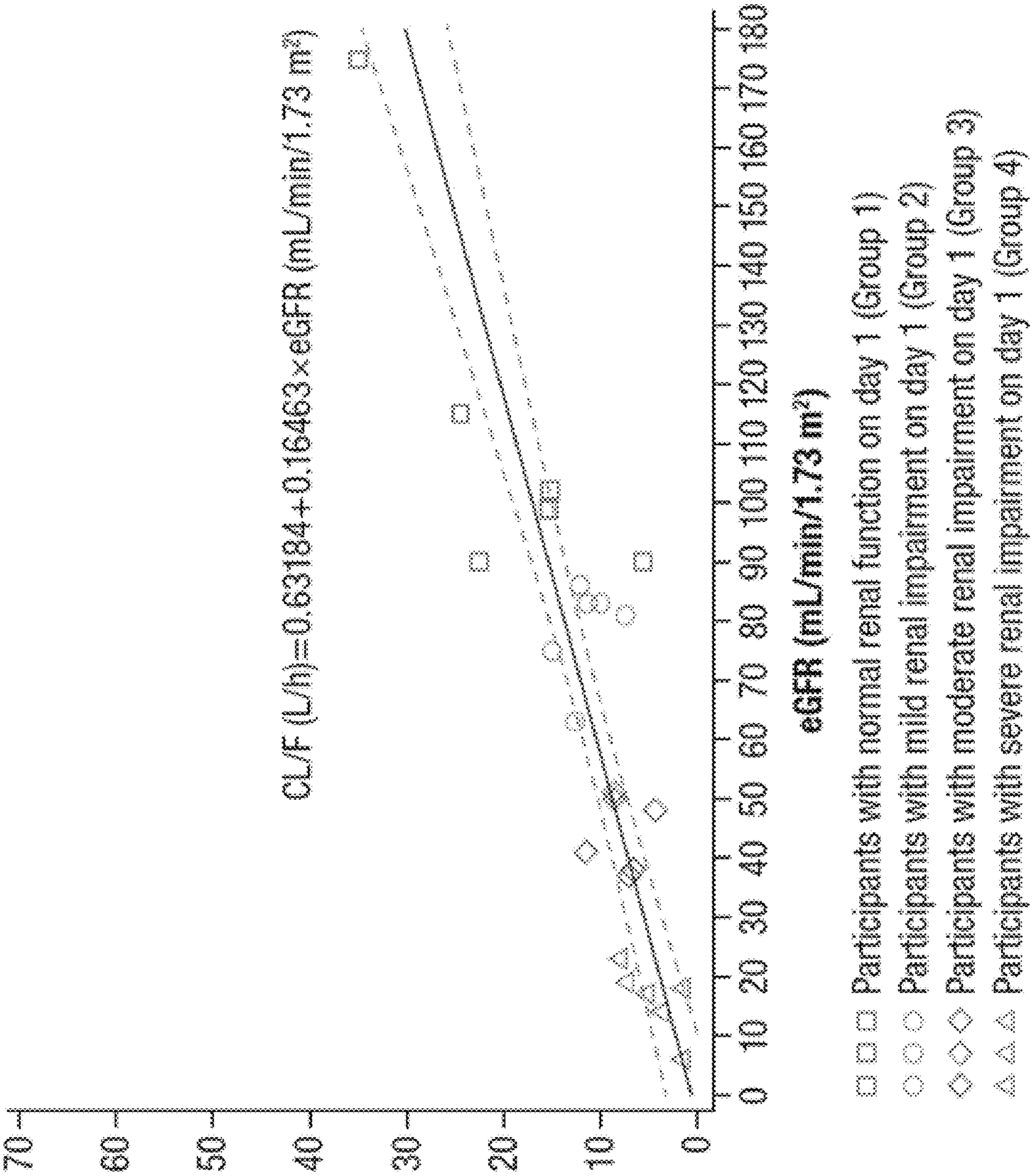

CL/F (L/h)=0.63184+0.16463×eGFR (mL/min/1.73 m²)
CL/F (L/h)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
eGFR (mL/min/1.73 m²)
Participants with normal renal function on day 1 (Group 1)
Participants with mild renal impairment on day 1 (Group 2)
Participants with moderate renal impairment on day 1 (Group 3)
Participants with severe renal impairment on day 1 (Group 4)

FIG. 2

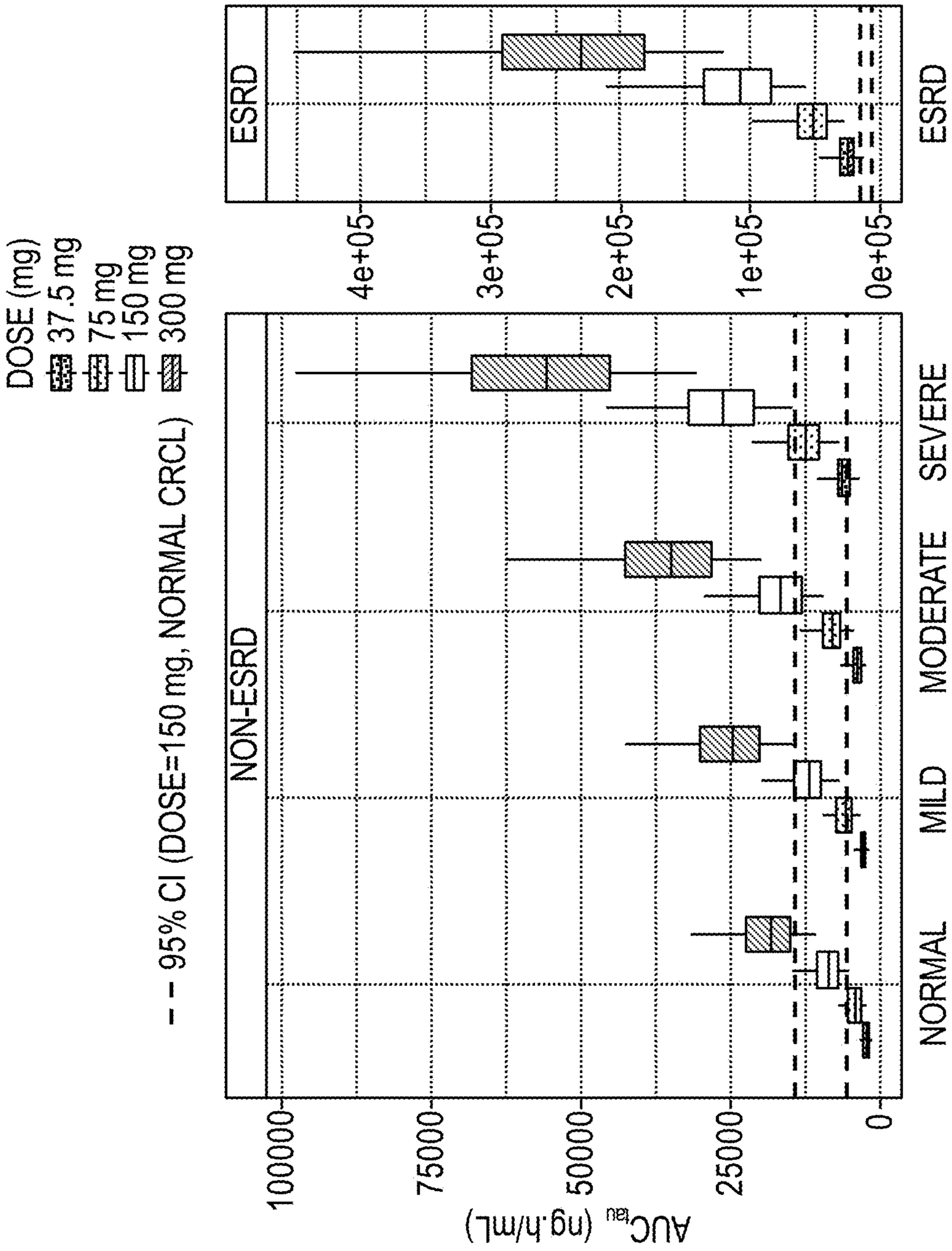

DOSE (mg)
37.5 mg
75 mg
150 mg
300 mg
- - 95% CI (DOSE=150 mg, NORMAL CRCL)
ESRD
NON-ESRD
4e+05
3e+05
2e+05
1e+05
0e+05
100000
75000
50000
25000
0
AUC$_{tau}$ (ng.h/mL)
NORMAL
MILD
MODERATE
SEVERE
CREATININE CLEARANCE CATEGORIES

FIG. 3

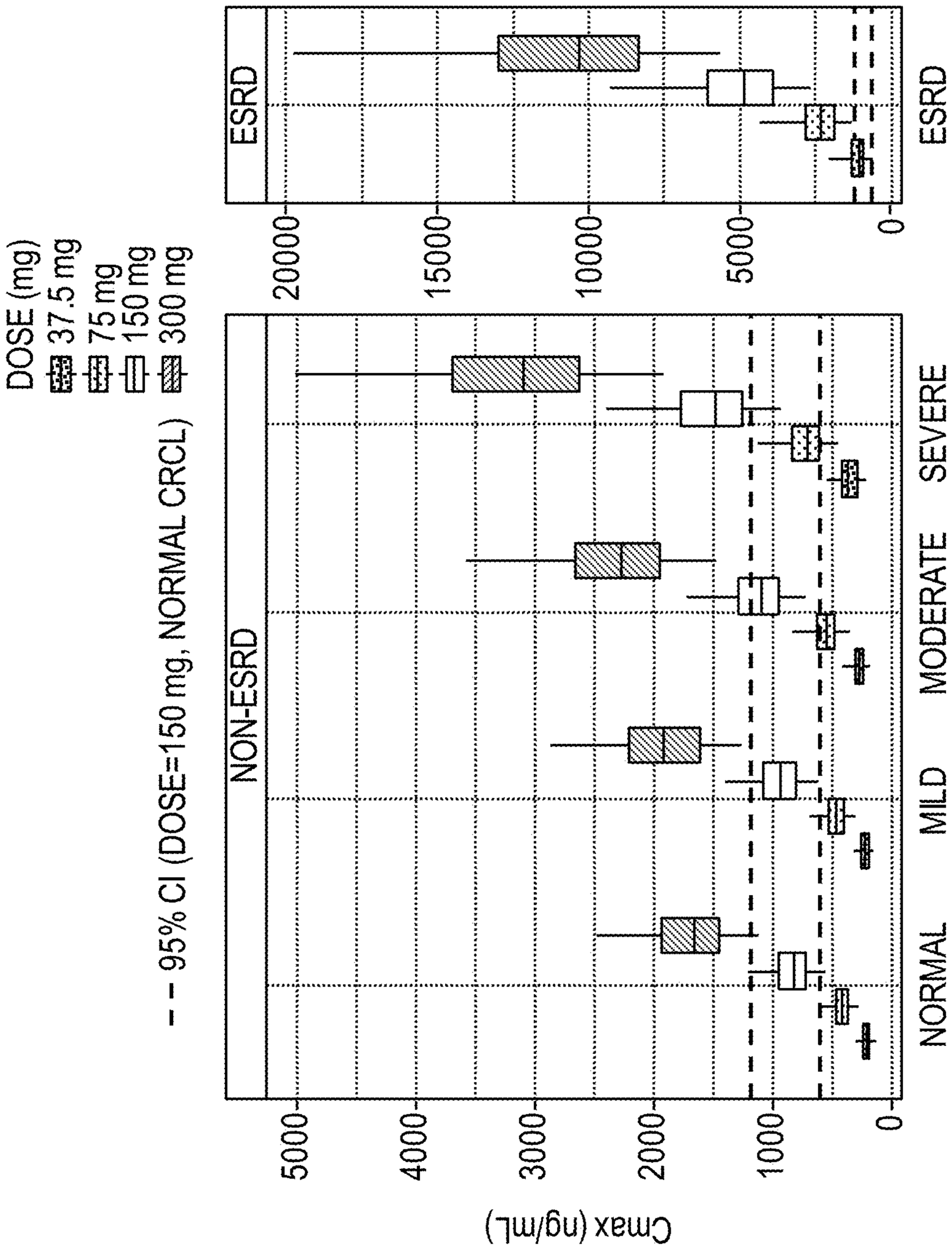

ESRD
NON-ESRD
20000
15000
10000
5000
0
5000
4000
3000
2000
1000
0
Cmax (ng/mL)
NORMAL
MILD
MODERATE
SEVERE
CREATININE CLEARANCE CATEGORIES
DOSE (mg)
37.5 mg
75 mg
150 mg
300 mg
- - 95% CI (DOSE=150 mg, NORMAL CRCL)

FIG. 4

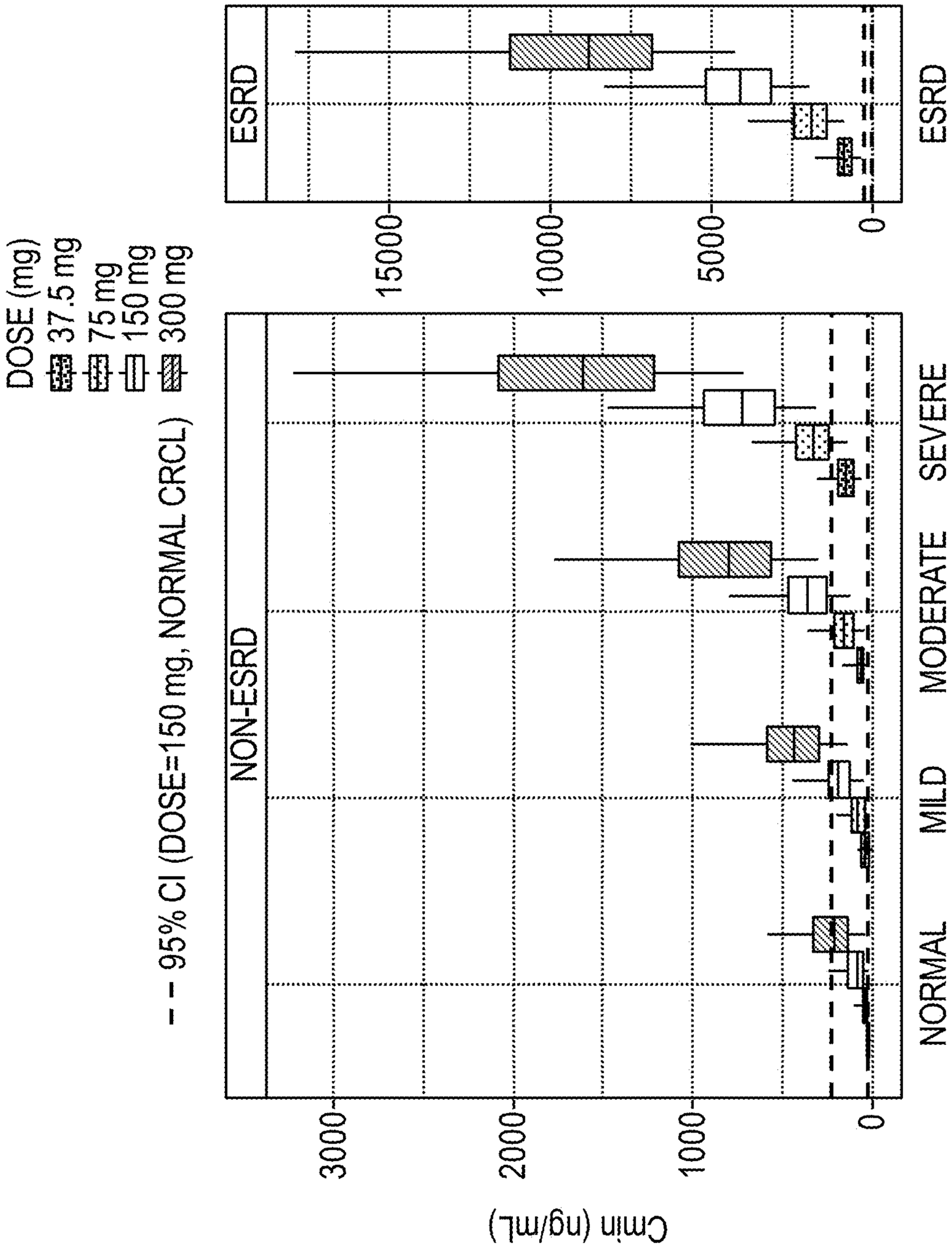

ESRD
NON-ESRD
15000
10000
5000
0
3000
2000
1000
0
Cmin (ng/mL)
NORMAL
MILD
MODERATE
SEVERE
CREATININE CLEARANCE CATEGORIES
DOSE (mg)
37.5 mg
75 mg
150 mg
300 mg
– – 95% CI (DOSE=150 mg, NORMAL CRCL)

FIG. 5

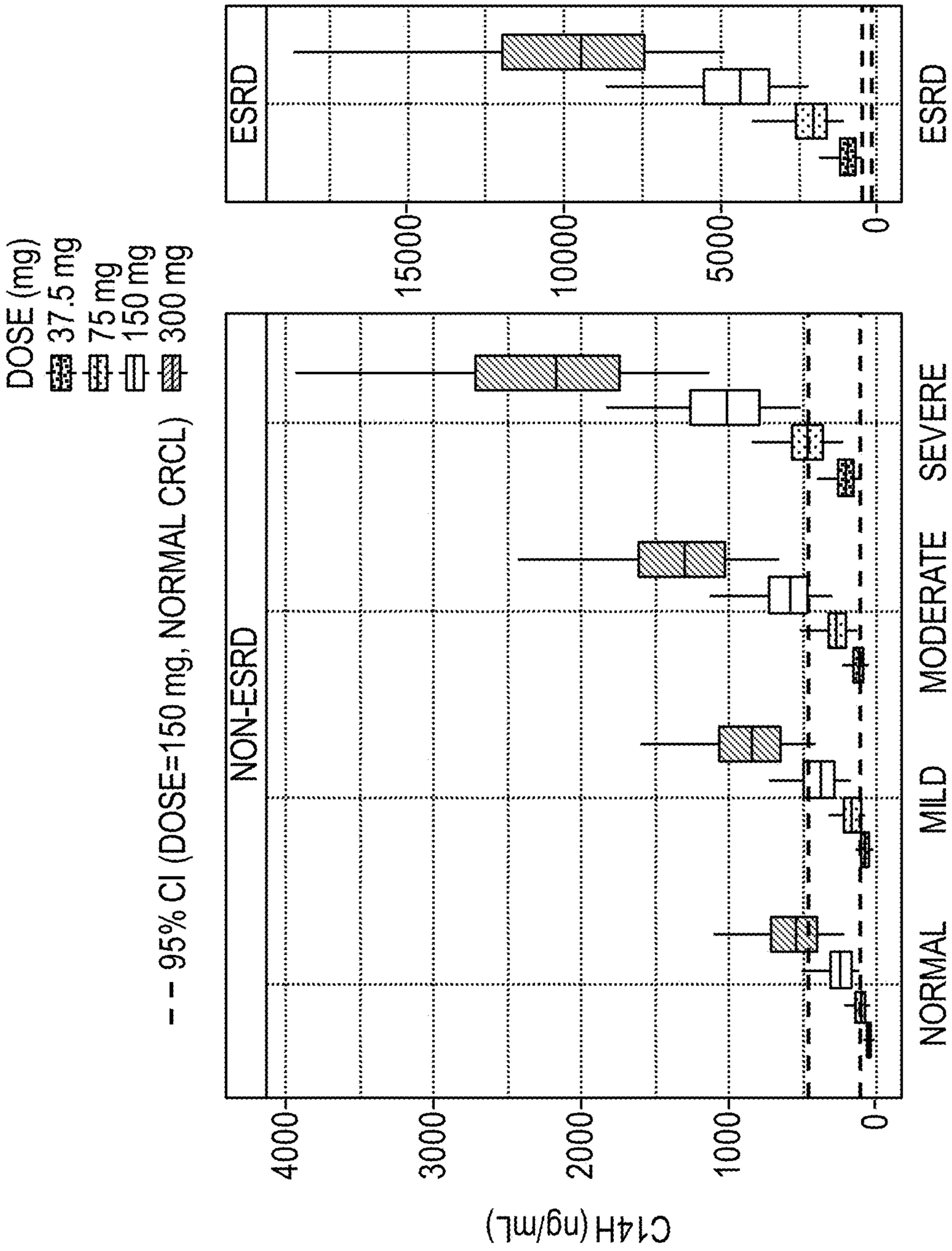

ESRD
15000
10000
5000
0
ESRD
DOSE (mg)
37.5 mg
75 mg
150 mg
300 mg
- - 95% CI (DOSE=150 mg, NORMAL CRCL)
NON-ESRD
4000
3000
2000
1000
0
C14H (ng/mL)
NORMAL
MILD
MODERATE
SEVERE
CREATININE CLEARANCE CATEGORIES

FIG. 6

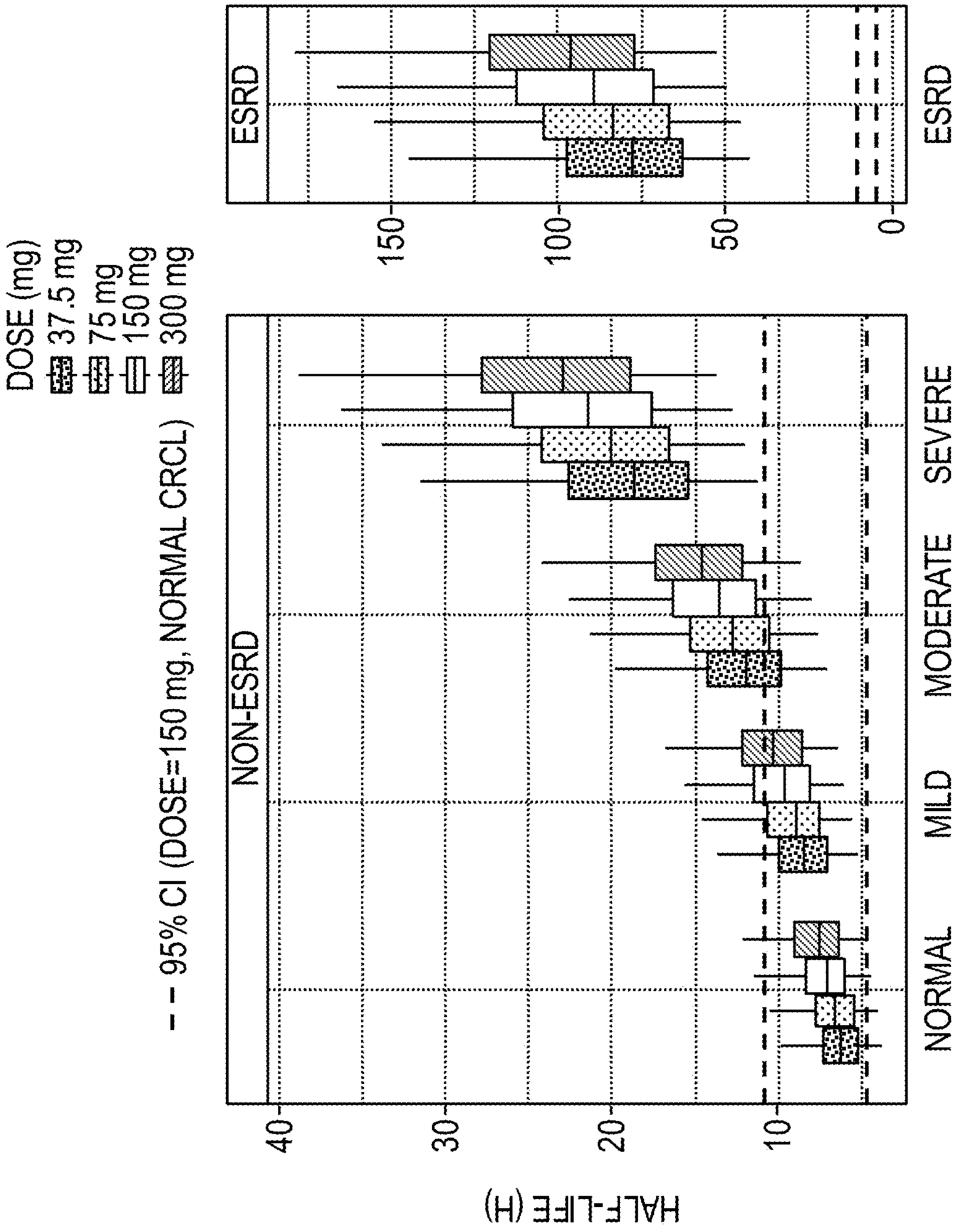

DOSE (mg)
37.5 mg
75 mg
150 mg
300 mg
- - 95% CI (DOSE=150 mg, NORMAL CRCL)
ESRD
NON-ESRD
150
100
50
0
40
30
20
10
HALF-LIFE (H)
NORMAL
MILD
MODERATE
SEVERE
CREATININE CLEARANCE CATEGORIES

FIG. 7

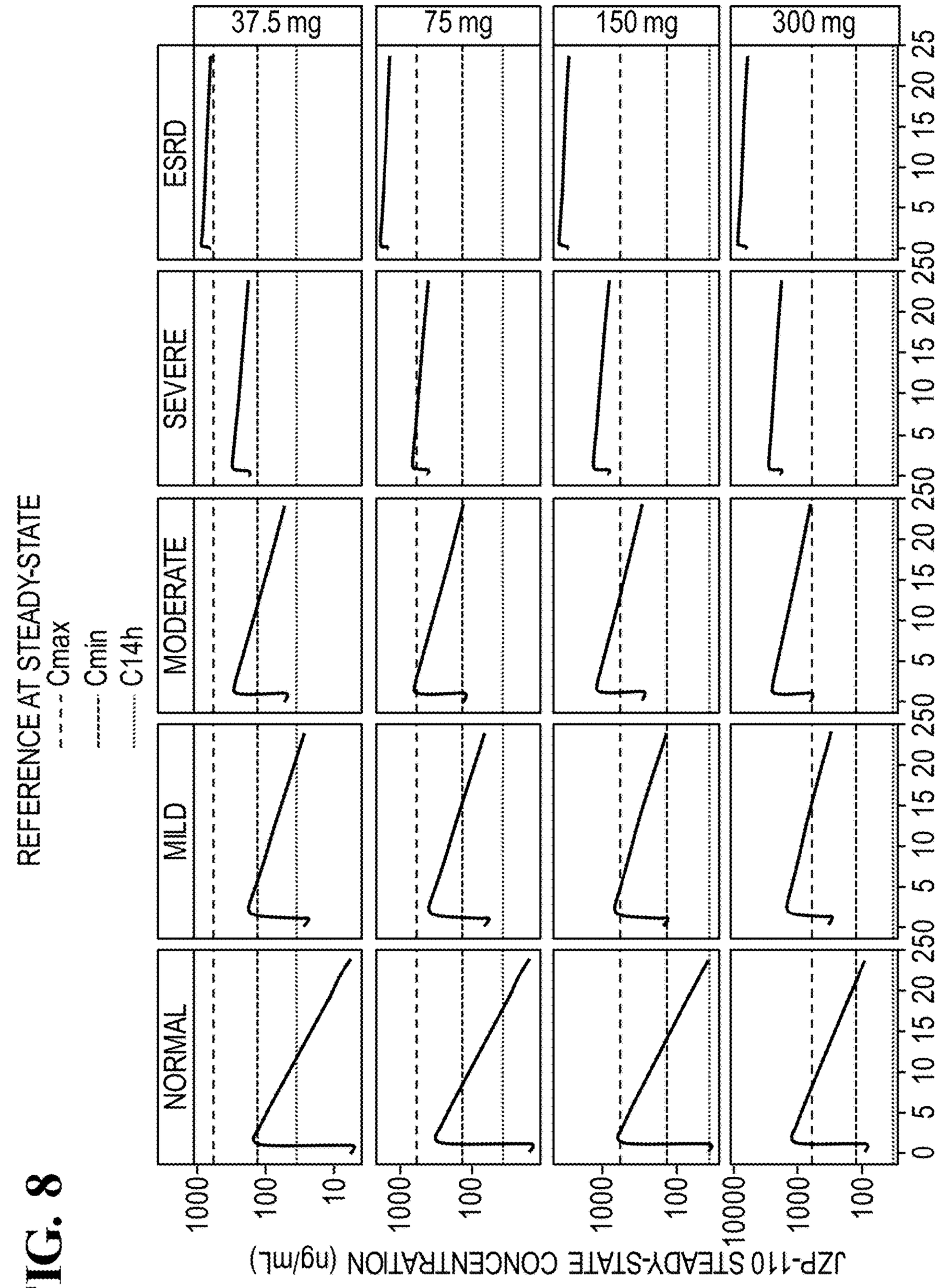

37.5 mg
75 mg
150 mg
300 mg
ESRD
SEVERE
MODERATE
MILD
NORMAL
REFERENCE AT STEADY-STATE
Cmax
Cmin
C14h
0 5 10 15 20 25 50 100 250
TIME AFTER DOSE (h)
1000
100
10
10000
JZP-110 STEADY-STATE CONCENTRATION (ng/mL)

FIG. 8

METHODS OF PROVIDING SOLRIAMFETOL THERAPY TO SUBJECTS WITH IMPAIRED RENAL FUNCTION

STATEMENT OF PRIORITY

This application is a continuation of and claims priority to U.S. patent application Ser. No. 17/479,121, filed Sep. 20, 2021, which is a continuation of and claims priority to U.S. patent application Ser. No. 17/149,406, filed Jan. 14, 2021, now U.S. Pat. No. 11,160,779, which is a continuation of and claims priority to U.S. patent application Ser. No. 16/824,560, filed Mar. 19, 2020, now U.S. Pat. No. 10,940,133, the entire contents of each of which is incorporated by reference herein in its entirety.

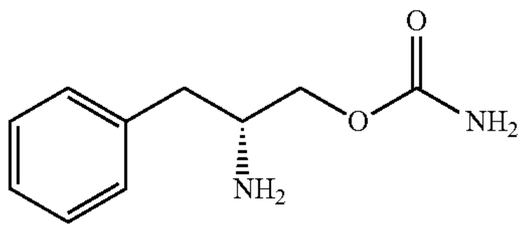
FIELD OF THE INVENTION

The invention relates to methods for decreasing adverse effects associated with solriamfetol ([R]-2-amino-3-phenylpropylcarbamate) therapy in subjects with impaired renal function. In particular, the invention provides an optimized dose escalation scheme for subjects with moderate renal impairment which results in the subjects having increased tolerance to adverse effects associated with the administration of solriamfetol. The invention also provides adjusted dosing for safe therapeutic use of solriamfetol in subjects having severe renal impairment.

BACKGROUND OF THE INVENTION

APC and its phenylalanine analogs have demonstrated application in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, attention deficit/hyperactivity disorder and others. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; 9,359,290; and 9,610,274 and U.S. Publication No. 2015/0018414. The structure of the free base of APC is given below as Formula I.

(I)



Those of skill in the art will appreciate that methods for producing APC (which also has other names) and related compounds can be found in U.S. Pat. Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817.

[R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) is a selective dopamine and norepinephrine reuptake inhibitor. At micromolar concentrations, APC-HCl can selectively bind and inhibit reuptake at dopamine and norepinephrine transporters without promoting monoamine release (See, Carter L, Baladi M, Black J, JZP-110: a dopamine-norepinephrine reuptake inhibitor (DNRI) with robust wake-promoting effects and low abuse potential. Poster presented at: Winter Conference on Brain Research; Jan. 23-28, 2016; Breckenridge, Colorado. Poster #Su23, 2016; and Baladi M G, Forster M J, Gatch M B, et al., Characterization of the neurochemical and behavioral

effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther.* 2018; 366:367-376).

As those of skill may recognize, APC-HCl (also referred to as solriamfetol HCl) has been approved by the FDA and EMA as a wake-promoting agent for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea (OSA). Phase 3 trials conducted with APC-HCl on patients having narcolepsy and OSA demonstrated statistically significant reductions in excessive daytime sleepiness measured on the patient-reported Epworth Sleepiness Scale and improvement in objective assessment of wakefulness using the Maintenance of Wakefulness Test. Significantly higher percentages of participants treated with APC-HCl in these trials also reported improvement on the Patient Global Improvement of Change scale relative to placebo at all evaluated time points. See, Johns M W, A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep.* 1991; 14(6):540-545); Thorpy M J, Dauvilliers Y, Shapiro C, et al., A randomized, placebo-controlled, phase 3 study of the safety and efficacy of JZP-110 for the treatment of excessive sleepiness in patients with narcolepsy, *Sleep,* 2017; 40 (suppl): A250; Schweitzer P K, Rosenberg R, Zammit G K, et al., Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial, *Am J Respir Crit Care Med.* 2018; Dec. 6; and Strollo P J, Jr., Hedner J, Collop N, et al., Solriamfetol for the treatment of excessive sleepiness in obstructive sleep apnea: A placebo-controlled randomized-withdrawal study. *Chest.* 2018; Nov. 21.

The most common adverse reactions or effects associated with APC-HCl therapy include headache, nausea, decreased appetite, anxiety, nervousness, panic attack, dry mouth, and diarrhea. Many of these effects can interfere with everyday activities and quality of life. Data from 12-week placebo-controlled clinical trials comparing various doses of solriamfetol support the conclusion that these adverse effects are dose-dependent and that they are exacerbated when APC-HCl is administered at higher doses. Additionally, solriamfetol has been shown to rely on renal excretion of unchanged drug as its primary route of elimination. The fact that the mean renal clearance of APC-HCl is 3 times the glomerular filtration rate suggest that its renal clearance is most likely attributed to a combination of passive diffusion and active renal tubular secretion by multiple cation transporters working in concert, with minimal tubular reabsorption. Therefore, administration of APC-HCl to patients with impaired renal function (which entails reduced passive diffusion and active renal tubular secretion) would be expected to result in higher APC-HCl exposure in this patient population. Prior to the present inventor's discovery however, it was not known what dose, if any, or escalation of APC-HCl would be safe for the renally impaired given the drug's unique pharmacological profile.

SUMMARY OF THE INVENTION

The present invention addresses an unmet medical need by providing methods of administering APC-HCl to renally impaired subjects in a manner that minimizes adverse effects. Of the methods provided is a dose escalation scheme for administering APC-HCl to patients with mild renal impairment, which involves an initial daily dose equivalent to 75 mg APC and waiting until after at least 3 days to reach the maximum daily dose equivalent to 150 mg APC. In another aspect of the invention, the dose escalation scheme of the present invention provides APC-HCl to patients with

moderate renal impairment at an initial daily dose equivalent to 37.5 mg APC and in a manner such that maximum dosage is not reached until after at least five days (in some embodiments of the invention, at least seven days); the method allows for a maximum dosage equivalent to 75 mg APC per day to be administered to a patient so as to reduce the incidence of adverse effects associated with the administration of APC-HCl by tailoring dose escalation to account for tolerance development in the patient. For patients with severe renal impairment (who have further reduced passive diffusion and active renal tubular secretion as compared with moderately impaired patients), the invention provides an alternative dosing regimen involving a daily maximum dose equivalent to 37.5 mg APC. The present inventor, based on analyses of the pharmacokinetics and safety profile of APC-HCl in conjunction with population PK simulations, has additionally discovered that use of APC-HCl should be avoided for patients with end-stage renal disease (with or without hemodialysis).

As such, provided according to embodiments of the present invention are methods of providing APC-HCl to a renally impaired subject in need thereof according to a dose escalation regimen, the method comprising providing to the subject a first oral daily dose equivalent to 37.5 mg APC from day one to day n_1 of the dose escalation regimen; and providing to the subject a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen, wherein n is an integer equal to or greater than 5 and n_2 is equal to the sum of n+1, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC, and wherein the renally impaired subject has an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2.

Further provided according to embodiments of the invention are methods of providing APC-HCl to a renally impaired subject with narcolepsy in need thereof, the method comprising providing to the subject an oral daily dose equivalent to 37.5 mg APC, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent 37.5 mg APC; and wherein the renally impaired subject has an eGFR of about 15 ml/min/1.73 m^2 to about 29 ml/min/1.73 m^2.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of guiding APC therapy in a renally impaired subject with narcolepsy in need thereof, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Further provided according to embodiments of the invention are methods of guiding APC therapy in a renally impaired subject with obstructive sleep apnea in need thereof, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising: administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; increasing the daily dose to a maximum dose equivalent to 75 mg APC after at least 7 days; wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl therapy in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising administering to the

subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of <15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily after at least 3 days; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease. In some embodiments of the invention, the subject is being treated with the above dosing regimen for excessive daytime sleepiness associated with narcolepsy.

In other embodiments of the invention, methods of reducing toxicity of APC-HCl therapy in a renally impaired subject with obstructive sleep apnea comprise: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of <15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 37.5 mg APC once daily and doubling the dose at intervals of at least 3 days to a maximum dose equivalent to 150 mg APC; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

The present invention is explained in greater detail in the drawings herein and the specification set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows the mean (SD) plasma of APC-HCl concentration-time profiles following a single dose equivalent to 75-mg APC for participants with normal renal function and mild-to-severe renal impairment.

FIG. **1**B shows the mean (SD) plasma APC-HCl concentration-time profiles following a single dose equivalent to 75-mg APC for participants with end-stage renal disease with and without hemodialysis.

FIG. **2** shows the apparent oral clearance (CL/F) versus day-1 estimated glomerular filtration rate (eGFR) for Groups 1-4. The broken lines represent the 90% confidence intervals.

FIG. **3** shows results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (narcolepsy/OSA, tablet, fasting conditions) by renal function—AUCtau.

FIG. **4** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—Cmax.

FIG. **5** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—Cmin.

FIG. **6** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—C14 h.

FIG. **7** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—half-life.

FIG. **8** shows the results of simulations to support dosing in sub-populations—adult patients (Narcolepsy/OSA, tablet, fasting conditions)—individual PK profile (Semi-Log Scale).

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. For example, features illustrated with respect to one embodiment can be incorporated into other embodiments, and features illustrated with respect to a particular embodiment can be deleted from that embodiment. In addition, numerous variations and additions to the embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety for all purposes.

As used herein, "a," "an," or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even 0.1% of the specified amount.

The term "consists essentially of" (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition. The term "materially altered," as applied to a composition, refers to an increase or decrease in the therapeutic effectiveness of the composition of at least about 20% or more as compared to the effectiveness of a composition consisting of the recited components.

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, prevention or delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Treat" or "treating" or "treatment" refers to any type of action that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art.

"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., *Remington's Pharmaceutical Science;* 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds

"concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

The compound [R]-2-amino-3-phenylpropylcarbamate (APC) or solriamfetol is also named (R)-(beta-amino-benzenepropyl) carbamate or O-carbamoyl-(D)-phenylalaninol and has alternatively been called ADX-N05, SKL-N05, SK-N05, YKP10A, and R228060. The hydrochloride salt of the compound is named [R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) or solriamfetol HCl.

A "disorder or condition amenable to treatment" refers to any disorder or condition in which administration of APC to a subject results in the treatment of one or more symptoms of the disorder in the subject. Disorders amenable to treatment with APC include, without limitation, excessive daytime sleepiness, fatigue, drug addiction, sexual dysfunction, depression, fibromyalgia syndrome, attention deficit/hyperactivity disorder, restless legs syndrome, bipolar disorder, cataplexy, obesity, and smoking cessation.

In some embodiments, APC may be used to treat and/or prevent excessive daytime sleepiness (EDS). See U.S. Pat. Nos. 8,440,715; 8,877,806; 9,604,917; and 10,351,517; incorporated by reference herein in their entirety. EDS may be due to, without limitation, a central nervous system (CNS) pathologic abnormality, stroke, narcolepsy, idiopathic CNS hypersomnia, sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder, Alzheimer's disorder, bipolar disorder, cardiac ischemia, misalignments of the body's circadian pacemaker with the environment, or jet lag; or a subject doing shift work or taking sedating drugs.

In some embodiments, APC may be used to treat and/or prevent fatigue. See U.S. Pat. Nos. 8,741,950; 9,464,041; 9,999,609; and 10,507,192; incorporated by reference herein in their entirety. Fatigue may be due to, without limitation, a disease, disorder or condition such as depression, cancer, multiple sclerosis, Parkinson's disease, Alzheimer's disease, chronic fatigue syndrome, fibromyalgia, chronic pain, traumatic brain injury, AIDS, and osteoarthritis. Fatigue may be due to, without limitation, a treatment or medication such as chemotherapy, radiation therapy, bone marrow transplant, and anti-depressant treatment.

In some embodiments, APC may be used to treat drug addiction. See U.S. Pat. No. 8,232,315, incorporated by reference in its entirety. In some embodiments, the addicted drug may be nicotine, opioid, cocaine, amphetamine, methamphetamine, ethanol, heroin, morphine, phencyclidine (PCP), and methylenedioxymethamphetamine (MDMA).

In some embodiments, APC may be used to treat sexual dysfunction. See U.S. Pat. No. 8,552,060, incorporated by reference herein in its entirety. In some embodiments, the treatment may increase interest in sex and/or the ability to have an orgasm. In some embodiments, the sexual dysfunction may be due to treatment with a therapeutic agent, including without limitation, selective serotonin reuptake inhibitors (SSRIs); selective serotonin and norepinephrine reuptake inhibitors (SNRIs); older tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAO-inhibitors), reversible inhibitors of monoamine oxidase (RIMAs), ter-

tiary amine tricyclics and secondary amine tricyclic antidepressants, e.g., therapeutic agents such as fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, 5-MCA-NAT, lithium carbonate, isocarboxazid, phenelzine, tranylcypromine, selegiline, moclobemide, kappa opioid receptor antagonists; selective neurokinin antagonists, corticotropin releasing factor (CRF) antagonists, antagonists of tachykinins, α-adrenoreceptor antagonists, amitriptyline, clomipramine, doxepin, imipramine, venlafaxine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

In some embodiments, APC may be used as an adjunctive therapy to treat depression. See U.S. Pat. No. 8,729,120, incorporated by reference herein in its entirety. In some embodiments, APC is administered to a subject in conjunction with an antidepressant such as, without limitation, fluoxetine, amitriptyline, clomipramine, doxepin, imipramine, trimipramine or a pharmaceutically acceptable salt thereof.

In some embodiments, APC may be used to treat fibromyalgia syndrome. See U.S. Pat. Nos. 8,927,602 and 9,688,620; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to treat attention deficit/hyperactivity disorder (ADHD) or diminish symptoms associated with ADHD. See U.S. Pat. Nos. 8,895,609; 9,663,455; and 10,202,335; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to treat restless legs syndrome. See U.S. Pat. No. 8,623,913, incorporated by reference herein in its entirety.

In some embodiments, APC may be used to treat bipolar disorder. See U.S. Pat. Nos. 9,610,274 and 9,907,777; incorporated by reference herein in their entirety. In some embodiments, APC may be used to diminish manic symptoms in a subject suffering from bipolar disorder.

In some embodiments, APC may be used to treat cataplexy. See U.S. Pat. Nos. 9,359,290; 9,585,863; and 10,259,780; incorporated by reference herein in their entirety. In some embodiments, the cataplexy is secondary to a condition that lowers hypocretin levels in a subject, such as a brain tumor, astrocytoma, glioblastoma, glioma, subependynoma, craniopharyngioma, arterio-venous malformations, ischemic events, multiple sclerosis, head injury, brain surgery, paraneoplastic syndromes, Neimann-Pick type C disease, or encephalitis.

In some embodiments, APC may be used to treat obesity, reduce body weight, reduce or prevent body weight gain, reduce food intake, or treat pathological eating. See U.S. Pat. Nos. 9,226,910; 9,649,291; and 10,105,341; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to promote cessation or reduction in the smoking and/or chewing of tobacco or nicotine-containing products and/or to prevent relapse of the same. See US Publication No. 2015/0018414, incorporated by reference herein in its entirety.

Methods of Treating Excessive Daytime Sleepiness

Provided according to embodiments of the present invention are methods of treating excessive daytime sleepiness in a renally impaired subject in need thereof, comprising administering to the subject an APC salt, such as APC-HCl. In some embodiments, such methods comprise administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject. In particular embodiments, such methods further include increasing the dose to a maximum equivalent of 75 mg APC once daily after at least 7 days. In some embodiments of the invention, the subject has narcolepsy, OSA, or both.

Further provided according to some embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject in need thereof that comprise administering to the subject an APC salt, such as APC-HCl, at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of guiding the treatment of excessive daytime sleepiness in a renally impaired subject in need thereof, comprising:

(a) determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

(b) administering to the subject the dose of an APC salt (e.g., APC-HCl) recommended for subjects without renal impairment if the subject has mild renal impairment; or administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject an APC salt if the subject has end stage renal disease.

In some embodiments, the methods further comprise measuring the eGFR in the subject prior to step (a).

Also provided according to other embodiments of the present invention are methods of reducing toxicity of an APC salt (e.g., APC-HCl) in a renally impaired subject, comprising administering to the subject the APC salt at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of the APC salt. In particular embodiments, such methods further include increasing the dose to a maximum equivalent of 75 mg APC once daily after at least 7 days. "Reducing toxicity," as used herein, refers to reducing the number and/or severity of adverse reactions or effects associated with APC-HCl therapy relative to the number and/or severity of adverse reactions or effects in the absence of the methods of the invention.

Provided according to some embodiments of the present invention are methods of reducing toxicity of an APC salt (e.g., APC-HCl) in a renally impaired subject, such methods comprising administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby reducing the toxicity of the APC salt in the subject.

Further, provided according to embodiments of the present invention are methods of reducing toxicity of an APC salt in a renally impaired subject, comprising:

(a) determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

(b) administering to the subject the dose of an APC salt recommended for subjects without renal impairment if

the subject has mild renal impairment; or administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject an APC salt if the subject has end stage renal disease. In some embodiments, the methods further comprise measuring the estimated glomerular filtration rate in the subject prior to step (a).

The methods of the invention may be used to treat any disorder or condition amenable to treatment with APC. Disorders amenable to treatment with APC include, without limitation, excessive daytime sleepiness, fatigue, sleep apnea, drug addiction, sexual dysfunction, depression, fibromyalgia syndrome, attention deficit/hyperactivity disorder, restless legs syndrome, bipolar disorder, cataplexy, obesity, as well as induction of smoking cessation.

Excessive Daytime Sleepiness

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift.

In some embodiments of the invention, treating excessive daytime sleepiness in a subject in need thereof may result in the decrease the subject's score on the Epworth Sleepiness Scale (ESS) by 5 or more points, e.g., by 10 or more points, e.g., by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more points or any range therein. In some embodiments, the amount of APC salt administered is sufficient to decrease the subject's score on the ESS to a level that is considered normal, e.g., 10 or less. In certain embodiments, at least about 5% of the treated subjects achieve the specified score, e.g., at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

The ESS is a subjective sleepiness test that is well known in the art and routinely used to measure the sleepiness level of a subject. The scale is intended to measure daytime sleepiness through the use of a short questionnaire that asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives. The scores for the eight questions are added together to obtain a single number that estimates the subject's average sleep propensity (ASP). A number in the 0-10 range is considered to be normal while 11-12 indicates mild excessive sleepiness, 13-15 indicates moderate excessive sleepiness, and 16 or higher indicates severe excessive sleepiness. Narcolepsy patients have an average score of about 17. Obstructive sleep apnea (OSA) patients with excessive sleepiness have an average score of about 15.

In some cases, treating excessive daytime sleepiness in a subject in need thereof results in an increase the subject's score on the maintenance of wakefulness test (MWT) by at least 5 minutes, e.g., at least 10 minutes or 15 minutes, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 minutes or more or any range therein. In certain embodiments, at least about 5% of the treated subjects achieve the specified score, e.g., at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

The MWT is an objective test used to measure how alert a subject is during the day. The test consists of four sleep trials with two hours in between the trials. The first trial is performed 1.5-3 hours after the subject's normal wake-up time. Sensors are placed on the head, face, and chin to detect when the subject is asleep and awake during the test. The subject sits quietly in bed with his or her back and head supported by a pillow and is asked to sit still and look straight ahead while trying to stay awake as long as possible. Each trial lasts 40 minutes or until the subject is asleep for 90 seconds. Between trials, the subject stays out of bed and occupies himself or herself to remain awake. Falling asleep in an average of less than eight minutes is considered abnormal. About 40-60% of subjects with normal sleep stay awake for the entire 40 minutes of all four trials.

The baseline measurement for determining a change in test results, such as ESS and MWT, may be performed before the subject has been administered APC or at a timepoint during a course of treatment of APC at which a baseline determination is desired. One or more subsequent determinations of test results may be made at any time after administration of one or more doses of APC. For example, determination of a change in test results may be made 1, 2, 3, 4, 5, or 6 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks after the administration of APC has begun or after the baseline determination was made.

The methods of the invention may be effective no matter the cause of the EDS, but in some embodiments of the invention, the EDS is associated with narcolepsy or obstructive sleep apnea (OSA). In other embodiments, the cause of the EDS may be, without limitation, central nervous system (CNS) pathologic abnormalities, stroke, idiopathic CNS hypersomnia; sleep deficiency, other sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder (ADHD), Alzheimer's disorder, major depression, bipolar disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work, or sedating drugs.

The methods of the invention may also be used to increase wakefulness and/or alertness in a subject in need thereof.

Renal Impairment

In embodiments of the present invention, the renal status of the subject may be determined by measuring the "estimated glomerular filtration rate" or "eGFR" of the individual. The eGFR in mL/min/1.73 m^2 is calculated by the Modification of Diet in Renal Disease [MDRD] equation:

$$\text{(eGFR in mL/min)/1.73 m}^2 = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if black)}.$$

Further details regarding the calculation of the eGFR may be found in, e.g., Levey A S, Coresh J, Greene T, Marsh J, Stevens L A, Kusek J W, Van Lente F: Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Ann Intern Med. 2009; 150(9):604-12.

Renal impairment status based on Food and Drug Administration (FDA) guidance is as follows.

Normal: eGFR 90 mL/min/1.73 m^2

Mild: eGFR 60-89 mL/min/1.73 m^2 (i.e., 60 to <90)

Moderate: eGFR 30-59 mL/min/1.73 m^2 (i.e., 30 to <60)

Severe: eGFR 15-29 mL/min/1.73 m^2 (i.e., 15 to <30) and not on hemodialysis

End-stage renal disease (ESRD): eGFR<15 mL/min/1.73 m^2 and not on hemodialysis or on hemodialysis

See, Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis and Impact on Dosing and Labeling. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) February 2010. As used herein, a "renally impaired subject" may have mild, moderate, or severe renal impairment, or may have ESRD.

APC Salts

The methods of the present invention may be carried out using compounds, formulations and unit dosage forms provided herein. In some embodiments, the formulations and dosage forms may include pharmaceutically acceptable salts of APC ("APC salt"), which also includes hydrates, solvates, clathrates, inclusion compounds, and complexes thereof.

In some embodiments of the invention, the APC salt is a hydrochloride salt (APC-HCl). However, suitable salts of APC also include, without limitation, acetate, adipate, alginate, aspartate, benzoate, butyrate, citrate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, hydroxynapthoate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, can be employed in the preparation of salts useful as intermediates in obtaining the compound of the invention and their pharmaceutically acceptable acid addition salts. APC salts include those having quaternization of any basic nitrogen-containing group therein.

The discussion herein is, for simplicity, provided without reference to the addition of deuterium atoms, but the APC salts may further include non-ordinary isotopes. Those skilled in the art will appreciate that the APC salt can contain one or more asymmetric centers and thus occur as racemates and racemic mixtures and single optical isomers. In embodiments of the present invention, the APC salt stereoisomer is preferred, but formulations according to embodiments of the invention may include both (R) and (S) isomers in a racemic mixture, or in any ratio of the isomers. In particular embodiments, the (R)-2-amino-3-phenylpropyl carbamate salt stereoisomer is present at a greater concentration than the (S)-2-amino-3-phenylpropyl carbamate salt stereoisomer, and in some embodiments, the formulation includes the 2-amino-3-phenylpropyl carbamate salt as a substantially enantiomerically pure (R)-2-amino-3-phenylpropyl carbamate salt stereoisomer such as having an enantiomeric excess of greater than 80%, 90%, 95%, or 99%. In some embodiments, the (R)-2-amino-3-phenylpropyl carbamate salt is enantiomerically pure, and in some cases is enantiomerically pure (R)-2-amino-3-phenylpropyl carbamate hydrochloride. When the (R)-2-amino-3-phenylpropyl carbamate salt is referenced specifically, it is understood that the dosage (e.g., 37.5 mg or 75 mg) refers to the equivalent weight of the (R) enantiomer only.

The APC salt(s) may be obtained or synthesized by methods known in the art and as described herein. Details of reaction schemes for synthesizing APC have been described in U.S. Pat. Nos. 5,705,640; 5,756,817; 5,955,499; and 6,140,532, all incorporated herein by reference in their entirety.

APC Salt Formulations

Any suitable dosage form comprising the APC salts may be used in the methods of the invention. In some embodiments, the dosage formulation comprises the APC salt (which is pharmaceutically acceptable) and a pharmaceutically acceptable carrier. In some embodiments, the dosage form is an oral dosage form, e.g., a tablet or a capsule, e.g., an immediate release dosage form.

In some embodiments, the dosage form is an immediate release tablet that releases at least 85%, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99%, of the APC salt contained therein within a period of less than 15 minutes after administration of the tablet to a subject. See, for example, U.S. Pat. No. 10,195,151, incorporated herein by reference in its entirety.

Formulations of the APC salt, including immediate release formulations, may be processed into unit dosage forms suitable for oral administration, such as for example, filled capsules, compressed tablets or caplets, or other dosage form suitable for oral administration using conventional techniques. Immediate release dosage forms prepared as described may be adapted for oral administration, so as to attain and maintain a therapeutic level of the compound over a preselected interval. In certain embodiments, an immediate release dosage form as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or polygonal. In one such embodiment, the surfaces of the immediate release dosage form may be flat, round, concave, or convex. In some embodiments, the shape may be selected to maximize surface area, e.g., to increase the rate of dissolution of the dosage form.

In particular, when the immediate release formulations are prepared as a tablet, the immediate release tablets may contain a relatively large percentage and absolute amount of the compound and so may be expected to improve patient compliance and convenience by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets as described herein can be administered, by oral ingestion, e.g., closely spaced, in order to provide a therapeutically effective dose of the compound to the subject in a relatively short period of time.

Where desired or necessary, the outer surface of an immediate release dosage form may be coated, e.g., with a color coat or with a moisture barrier layer using materials and methods known in the art.

In some embodiments, the dosage formulation is an immediate release compressed tablet, the tablet comprising: the APC salt thereof in an amount of about 90-98% by weight of the tablet; at least one binder in an amount of about 1-5% by weight of the tablet; and at least one lubricant in an amount of about 0.1-2% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises: the APC salt thereof in an amount of about 91-95% by weight of the tablet; at least one binder in an amount of about 2-3% by weight of the tablet; at least one lubricant in an amount of about 0.1-1% by weight of the tablet; and optionally, a cosmetic film coat in an amount of about 3-4% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained

therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises: the APC salt thereof in an amount of about 93.22% by weight of the tablet; at least one binder (e.g., hydroxypropylcellulose) in an amount of about 2.87% by weight of the tablet; at least one lubricant (e.g., magnesium stearate) in an amount of about 0.52% by weight of the tablet; and optionally, a cosmetic film coat (e.g., Opadry® II yellow) in an amount of about 3-4% by weight of the tablet; wherein the tablet releases at least 85% of the APC salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In some embodiments, the composition is an immediate release oral dosage form of an APC salt, the oral dosage form comprising: the APC salt thereof in an amount of about 90-98% by weight of the oral dosage form; at least one binder in an amount of about 1-5% by weight of the oral dosage form; and at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form; wherein the oral dosage form releases at least 85% of the APC salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject.

In certain embodiments, the tablet does not comprise a disintegrant. The term "disintegrant," as used herein, refers to an agent added to a tablet to promote the breakup of the tablet in an aqueous environment. The tablets of the present invention are advantageous in that they dissolve rather than disintegrate. In the present invention the presence of disintegrant in the formulation may actually slow down release of APC.

In certain embodiments, the APC salt is present in an amount of about 90%, 90.5%, 91%, 91.5%, 92%, 92.5%, 93%, 93.5%, 94%, 94.5%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, or 98% by weight of the tablet or any value or range therein. In certain embodiments, the APC salt thereof is present in an amount of about 90% to about 98%, about 92% to about 98%, about 94% to about 98%, about 96% to about 98%, about 90% to about 92%, about 90% to about 94%, about 90% to about 96%, about 92% to about 94%, about 92% to about 96%, or about 94% to about 96%.

In certain embodiments, the at least one binder is present in an amount of about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the tablet or any value or range therein. In certain embodiments, the at least one binder is present in an amount of about 1% to about 5%, about 2% to about 5%, about 3% to about 5%, about 4% to about 5%, about 1% to about 2%, about 1% to about 3%, about 1% to about 4%, about 2% to about 3%, about 2% to about 4%, or about 3% to about 4%. The tablet may comprise at least one binder, e.g., 1, 2, 3, 4, 5, or more binders.

In certain embodiments, the at least one binder is selected from at least one of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, sodium carboxymethylcellulose, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate or any combination thereof. In some embodiments, the at least one binder is hydroxypropyl cellulose.

In certain embodiments, the at least one lubricant is present in an amount of about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, or 2.0% by weight of the tablet or any value or range therein. In certain embodiments, the at least one lubricant is present in an amount of about 0.1% to about 2.0%, about 0.5% to about 2.0%, about 1.0% to about 2.0%, about 1.5% to about 2.0%, about 0.1% to about 0.5%, about 0.1% to about 1.0%, about 0.1% to about 1.5%, about 0.5% to about 1.0%, about 0.5% to about 1.5%, or about 1.0% to about 1.5%. The tablet may comprise at least one lubricant, e.g., 1, 2, 3, 4, 5, or more lubricants. Where the immediate release formulation is provided as a tableted dosage form, still lower lubricant levels may be achieved with use of a "puffer" system during tableting. Such systems are known in the art, commercially available and apply lubricant directly to the punch and die surfaces rather than throughout the formulation.

In certain embodiments, the at least one lubricant is selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate or any combination thereof. In some embodiments, the at least one lubricant is magnesium stearate. In other embodiments, magnesium stearate may be used in combination with one or more other lubricants or a surfactant, such as sodium lauryl sulfate. In particular, if needed to overcome potential hydrophobic properties of magnesium stearate, sodium lauryl sulfate may also be included when using magnesium stearate (Remington: the Science and Practice of Pharmacy, 20^{th} edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000)).

In some embodiments, the at least one binder is hydroxypropyl cellulose. In some embodiments, the at least one lubricant is magnesium stearate. In some embodiments, the at least one binder is hydroxypropyl cellulose and the at least one lubricant is magnesium stearate.

In certain embodiments, the tablet is coated. The coating may be, without limitation, a color overcoat.

The tablet may be any shape that is suitable for immediate release and allows the release of at least 85% of the APC salt contained therein within a period of less than 15 minutes after administration of the tablet to a subject. In some embodiments, the tablet maximizes surface area to volume ratio to promote rapid dissolution. In some embodiments, the tablet is oblong in shape.

The tablet may contain any amount of the APC salt suitable for administration as a unit dosage form. In some embodiments, the tablet contains the equivalent of about 1 mg to about 1000 mg of APC or any range or value therein, e.g., about 100 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

["Immediate release" as used herein, refers to a composition that releases the APC salt substantially completely into the gastrointestinal tract of the user within a period of less than about 15 minutes, usually between about 1 minute and about 15 minutes from ingestion. Such a delivery rate allows the drug to be absorbed by the gastrointestinal tract in a manner that is bioequivalent to an oral solution. Such rapid absorption will typically occur for an immediate release unit dosage form, such as a tablet, caplet or capsule, if the drug included in such dosage form dissolves in the upper portion the gastrointestinal tract.

Release rates can be measured using standard dissolution test methods. For example, the standard conditions may be those described in FDA guidance (e.g., 50 rpm, 37° C., USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel).

Immediate release formulations suitable for oral administration may comprise unit dosage forms, such as tablets, caplets or filled capsules, which can deliver a therapeutically

effective dose of the APC salt upon ingestion thereof by the patient of one or more of said dosage forms, each of which can provide a dosage of, for example, about 37.5 mg to about 75 mg, or 75 mg to about 150 mg of APC. Additionally, the immediate release dosage forms can be shaped or scored to facilitate dose adjustment through tablet splitting. For example, a 75 mg APC tablet or caplet may be scored to facilitate tablet splitting into two 37.5 mg APC doses.

The formulation and structure of an immediate release dosage form as disclosed herein can be adjusted to provide immediate release performance that suits a particular dosing need. In particular, the formulation and structure of the dosage forms as described herein can be adjusted to provide any combination of the immediate release performance characteristics described herein. In particular embodiments, for example, an immediate release dosage form as disclosed herein provides rapid onset of action, releasing more than about 85%, such as, for example, more than about 90% or 95%, of the drug contained therein within a period of time selected from less than 15 minutes, less than 12 minutes, less than 10 minutes, and less than 5 minutes after administration.

Moreover, the rate of drug release from an immediate release dosage form as disclosed herein may be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. In certain such embodiments, the total amount of the APC salt in the dosage formulation may include an equivalent dose of about 10 mg to about 300 mg APC, about 30 mg to about 300 mg APC, about 100 mg to about 300 mg APC, or about 150 mg to about 300 mg APC, about 75 to 150 mg APC, about 37.5 to about 75 mg APC, and about 37.5 to about 150 mg APC. In particular embodiments, the equivalent dose of APC in the dosage formulation is 37.5 mg, and in other particular embodiments, the equivalent dose of APC in the dosage formulation is 75 mg. In some cases, such dosage formulations may be formed (e.g., scoring) to facilitate creating more than one dose from a particular dosage form.

The immediate release formulations provided herein generally include the APC salt and some level of lubricant to facilitate processing of the formulations into a unit dosage form. In some embodiments, therefore, the formulations described herein include a combination of the APC salt and lubricant, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. In other embodiments, the immediate release formulations described herein include a combination of the APC salt, lubricant, and binder, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. Though the immediate release formulations described herein may be formulated using a combination of drug and one or more of a lubricant and binder, in certain embodiments, the compositions described herein may include one or more additional excipients selected from, for example, fillers, compression aids, diluents, disintegrants, colorants, flavorants, buffering agents, coatings, glidants, or other suitable excipients.

The immediate release formulations described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and dry powder blending. Suitable methods for the manufacture of the immediate release formulations and unit dosage forms described herein are provided, for example, in Remington, 20^{th} edition, Chapter 45 (Oral Solid Dosage Forms). It has been found that, even without the aid of binders or non-lubricating excipients, such as compression aids, wet granulation techniques can afford flowable granules with compression characteristics suitable for forming unit dosage forms as described herein. Therefore, in certain embodiments, where a drug content greater than about 85%, 90% or 95% by weight is desired for the immediate release formulation, wet granulation techniques may be used to prepare immediate release formulations as described herein. In such embodiments, as illustrated in the Examples provided herein, conventional organic or aqueous solvents may be used in the wet granulation process. Suitable wet granulation processes can be performed as fluidized bed, high shear, or low shear (wet massing) granulation techniques, as are known in the art.

In addition to one or more the APC salt, lubricant, and binder, where desired, the immediate release formulations described herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. Where a filler or compression aid is used, in certain embodiments, it may be included in the immediate release formulation in an amount ranging from about 1%-15% by weight.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a moisture barrier layer using materials and methods known in the art. For example, where the APC salt delivered by the unit dosage form is highly hygroscopic, providing a moisture barrier layer over the immediate release dosage form as disclosed herein may be desirable. For example, protection of an immediate release dosage form as disclosed herein from water during storage may be provided or enhanced by coating the tablet with a coating of a substantially water soluble or insoluble polymer. Useful water-insoluble or water-resistant coating polymers include ethyl cellulose and polyvinyl acetates. Further water-insoluble or water resistant coating polymers include polyacrylates, polymethacrylates or the like. Suitable water-soluble polymers include polyvinyl alcohol and HPMC. Further suitable water-soluble polymers include PVP, HPC, HPEC, PEG, HEC and the like.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a color overcoat or other aesthetic or functional layer using materials and methods known in the art.

The dosage forms disclosed herein can also be provided as a kit comprising, separately packaged, a container comprising a plurality of immediate release tablets, which tablets can be individually packaged, as in foil envelopes or in a blister pack. The tablets can be packaged in many conformations with or without desiccants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, e.g., sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of APC in vivo for preselected periods of time, to treat a preselected condition.

Daily Dosage and Treatment Regimens

In the methods described herein, the typical daily dose of the APC salt for subjects with normal renal function, equivalent to 75-150 mg of APC, is modified for certain renally impaired subjects. As discussed above, for a subject with an eGFR of 30-59 ml/min/1.73 m^2, i.e., a subject with moderate renal impairment, the APC salt is administered once daily at an initial dose equivalent to 37.5 mg of APC. In some cases, this daily dose may be increased after at least 7 days of the

initial dose equivalent to 75 mg of APC. Further, in some embodiments, for a subject with an eGFR of 15-29 ml/min/1.73 m^2, i.e., a subject with severe renal impairment, the APC salt is administered once daily at a maximum dose equivalent to 37.5 of APC. In some embodiments, such dosages may be used for a subject who has narcolepsy, a subject with OSA, or when reduction of toxicity of the APC salt is indicated. In particular embodiments, the APC salt is APC-HCl.

A dose is "equivalent to" a 37.5 mg or 75 mg of APC, if the weight of the APC base (the "active moiety") in the formulation is 37.5 mg or 75 mg, respectively, regardless of the weight of the APC salt. Thus, the weight of the APC salt may be greater than 37.5 mg or 75 mg, respectively, in the formulation. Where APC is provided in the form of APC-HCl salt, a dose of 37.5 mg APC is equivalent to 44.7 mg (or 44.65 mg) of APC-HCl; a dose of 75 mg APC is equivalent to 89.3 mg of APC-HCl; and a dose of 150 mg APC is equivalent to 178.5 mg of APC-HCl. An "initial dose equivalent" is the daily dose at which the subject starts the treatment regimen, corresponding to the weight of the active moiety (APC), and the initial dose may be increased at some time point, such as in a number of days (e.g., 1, 2, 3, 4, 5, 6, 7, or more days). The "maximum dose equivalent" is the largest dose, corresponding to the weight of the active moiety (APC), that the patient may be administered daily at any time point.

In general, the daily dose is administered once daily. However, in some embodiments, the daily dose may be administered at two or more different time points. Administration of the APC salt can continue for one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve weeks or longer. Alternatively, administration of the APC salt can continue for one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment, the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, the APC salt is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Such agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. In some embodiments, the APC salt is delivered to a subject concurrently with an additional therapeutic agent that is not a monoamine oxidase inhibitor. In still other embodiments, the APC salt is delivered to a subject who has not been treated with a monoamine oxidase inhibitor within the preceding 14 days. In exemplary embodiments of the invention, a subject with obstructive sleep apnea is treated with APC concurrently with adherence to a primary OSA therapy. Examples of primary OSA therapies include, without limitation, positive airway pressure (PAP), continuous positive airway pressure (CPAP), oral appliances, and surgical procedures. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302.

The APC salt can be administered at any time during the day, but in some embodiments, the APC salt is administered to the subject no later than at least 12 hours before the bedtime of the subject. Studies by the present inventors have found that that administration of the APC salt within a few of hours of waking minimizes side effects of the treatment such as insomnia. In some embodiments, the APC is administered shortly after waking, e.g., within about 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, or 3 hours of waking. In exemplary embodiments, the APC is administered at least 9 hours before the bedtime of the subject, e.g., at least 9, 10, 11, 12, 13, 14, 15, or 16 or more hours before bedtime.

Subjects

The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults and geriatric subjects. In some embodiments of the invention, the human subject is an adult.

In particular embodiments, the subject is a human subject that has excessive daytime sleepiness or another disorder amenable to treatment with the APC salt. In other embodiments, the subject used in the methods of the invention is an animal model of excessive daytime sleepiness or another disorder amenable to treatment with APC.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, is suspected of having excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, and/or is anticipated to experience excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment. Disorders amenable to treatment with APC include, without limitation, sleep-wake disorder, excessive daytime sleepiness, depression, attention deficit/hyperactivity disorder, drug addiction, bipolar disorder, fibromyalgia, fatigue, obesity, restless legs syndrome, cataplexy, and sexual dysfunction.

Specific embodiments of the invention include, without limitation, the following.

Embodiment 1: A method of providing [R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) to a renally impaired subject in need thereof according to a dose escalation regimen, said method comprising providing to the subject a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of the dose escalation regimen; and providing to the subject a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen, wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC, and wherein the renally impaired subject has an estimated glomerular filtration rate (eGFR) of about 30 m/min/1.73 m^2 to about 59 mL/min/1.73 m^2.

Embodiment 2: The method of embodiment 1, wherein the subject is provided APC-HCl for the treatment of excessive daytime sleepiness.

Embodiment 3: The method of embodiment 2, wherein the excessive daytime sleepiness is associated with narcolepsy.

Embodiment 4: The method of embodiment 2, wherein the excessive daytime sleepiness is associated with obstructive sleep apnea.

Embodiment 5: The method of embodiment 1, wherein the subject is provided the first oral daily dose in the form of about 44.7 mg APC-HCl.

Embodiment 6: The method of embodiment 1, wherein the subject is provided the second oral daily dose in the form of about 89.3 mg APC-HCl.

Embodiment 7: The method of embodiment 1, wherein the subject is provided a first oral daily dose in the form of about 44.7 mg APC-HCl and a second oral daily dose in the form of about 89.3 mg APC-HCl.

Embodiment 8: The method of embodiment 1, wherein the first oral daily dose and second oral daily dose are each administered upon the subject's awakening.

Embodiment 9: The method of embodiment 1, wherein the first oral daily dose and second oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

Embodiment 10: The method of embodiment 1, wherein the subject is a human.

Embodiment 11: The method of embodiment 1, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

Embodiment 12: The method of embodiment 1, wherein n_1 is an integer equal to or greater than 7.

Embodiment 13: A method of providing APC-HCl to a renally impaired subject with narcolepsy in need thereof, said method comprising:

providing to the subject an oral daily dose equivalent to 37.5 mg APC, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC; and wherein the renally impaired subject has an eGFR of about 15 ml/min/1.73 m^2 to about 29 ml/min/1.73 m^2.

Embodiment 14: The method of embodiment 13, wherein the oral daily dose is provided to the renally impaired subject in the form of 44.7 mg APC-HCl.

Embodiment 15: The method of embodiment 13, wherein the oral daily dose is administered upon the subject's awakening.

Embodiment 16: The method of embodiment 13, wherein the oral daily dose is administered more than nine hours in advance of the subject's bedtime.

Embodiment 17: The method of embodiment 13, wherein the subject is a human.

Embodiment 18: The method of embodiment 17, wherein the subject is an adult.

Embodiment 19: The method of embodiment 13, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

Embodiment 20: A method of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Embodiment 21: The method of embodiment 20, further comprising increasing the dose to a maximum equivalent to 75 APC once daily after at least 5 days.

Embodiment 22: The method of embodiment 21, wherein the dose is increased to a maximum equivalent to 75 mg APC once daily after at least 7 days.

Embodiment 23: A method of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Embodiment 24: A method of guiding APC therapy in a renally impaired subject with narcolepsy in need thereof, comprising

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of less than 15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 25: The method of embodiment 24, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 26: The method of embodiment 24, wherein the dose is increased from a dose equivalent to 75 mg APC to a dose equivalent to 150 mg APC after at least 3 days if the subject has mild renal impairment and the dose is increased from a dose equivalent to 37.5 mg APC to a dose equivalent to 75 mg APC after at least 7 days if the subject has moderate renal impairment.

Embodiment 27: A method of guiding APC therapy in a renally impaired subject with obstructive sleep apnea in need thereof, comprising:

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of less than 15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily;

or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 28: The method of embodiment 27, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 29: The method of embodiment 27, wherein the regimen comprises doubling the dose of APC-HCl at intervals of at least 3 days if the subject has mild renal impairment and increasing the dose from a dose equivalent to 37.5 mg APC to a dose equivalent to 75 mg APC after at least 7 days if the subject has moderate renal impairment.

Embodiment 30: A method of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily,

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Embodiment 31: The method of embodiment 30, wherein the dose is increased to a maximum equivalent to 75 mg APC once daily after at least 7 days.

Embodiment 32: A method of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Embodiment 33: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising:

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily;

increasing the daily dose to a maximum dose equivalent to 75 mg APC after at least 7 days;

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl therapy in the subject.

Embodiment 34: The method of embodiment 33, wherein the initial dose is provided in the form of about 44.7 mg APC-HCl and the maximum dose is provided in the form of about 89.3 mg APC-HCl.

Embodiment 35: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl in the subject.

Embodiment 36: The method of embodiment 35, wherein the maximum dose is provided in the form of about 44.7 mg APC-HCl.

Embodiment 37: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising:

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily after at least 3 days; or

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APCl once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 38: The method of embodiment 37, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 39: The method of embodiment 37, wherein the eGFR is calculated by the Modification of Diet in Renal Disease equation.

Embodiment 40: The method of embodiment 37, wherein the subject is a human.

Embodiment 41: The method of embodiment 40, wherein the subject is an adult.

Embodiment 42: The method of embodiment 37, wherein the APC-HCl is administered orally.

Embodiment 43: The method of embodiment 37, wherein the APC-HCl is formulated with a pharmaceutical carrier.

Embodiment 44: The method of embodiment 37, wherein the subject is being treated for excessive daytime sleepiness associated with narcolepsy.

[The present invention is explained in greater detail in the following non-limiting Examples. Each example has a self-contained list of references.

Example 1: Evaluation of the PK of Solriamfetol HCl in Participants with Renal Impairment and Those with ESRD Undergoing Hemodialysis Compared with Healthy Participants with Normal Renal Function

Methods

In healthy subjects with normal renal function, solriamfetol HCl is renally excreted ~90% unchanged within 48 hours of administration. Thus, renal impairment, as well as hemodialysis in individuals with end-stage renal disease (ESRD), could affect the PK of solriamfetol HCl. To ascertain the precise impact of renal impairment and hemodialysis on pharmacokinetics and safety of solriamfetol HCl, a Phase 1, parallel-group, open-label, single-dose study was conducted at 2 U.S. sites. The protocol was approved by the IntegReview Institutional Review Board (Austin, Texas), and the study was conducted in compliance with the protocol, the Guideline for Good Clinical Practice E6; the US Code of Federal Regulations pertaining to conduct and reporting of clinical studies; the Clinical Trials Directive of the European Medicines Agency (Directive 2001/20/EC); and the Declaration of Helsinki. Written informed consent was obtained from each subject before enrollment in the study and before performance of any study-related procedure. See, also, Zomorodi K, Chen D, Lee L, Lasseter K, Marbury T. An Open-Label, Single-Dose, Phase 1 Study of the Pharmacokinetics and Safety of JZP-110 in Subjects With Normal or Impaired Renal Function and With End-Stage Renal Disease Requiring Hemodialysis [abstract]. *Sleep*. 2017; 40 (suppl):A382-383.

Eligible participants were men and non-pregnant, non-lactating women between the ages of 18 and 80 years, with a body mass index (BMI)<35 kg/m^2. Women of childbearing

potential were required to have used a medically accepted method of birth control for at least 2 months prior to the first dose of study drug, with continued use throughout the study period and for 30 days after study completion. Participants were excluded if they had a clinically significant medical abnormality (other than renal impairment or its underlying causes), or any unstable conditions including neurological or psychiatric disorder, hepatic, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease, or any other abnormality that could interfere with the PK evaluation of the study drug or the participant's completion of the trial.

Eligible participants were assigned to 1 of 5 groups according to renal disease status as measured by the estimated glomerular filtration rate (eGFR) on the day prior to dosing, calculated using the Modification in Diet in Renal Disease equation. Group 1 consisted of healthy participants with normal renal function (eGFR>90 mL/min/1.73 m^2) and served as the control group. Groups 2, 3, and 4 had mild, moderate, and severe renal impairment based on eGFRs of 60-89, 30-59, and <30 mL/min/1.73 m^2, respectively. Group 5 consisted of participants with ESRD who required ≥3 hemodialysis treatments per week for the preceding 3 months. Every effort was made to ensure that the groups were comparable with respect to age, sex, and body mass index (BMI). Group 1 was enrolled last to facilitate matching the mean age, BMI, and sex distribution of Groups 2-5.

Among participants with impaired renal function, continued use of medications necessary for treatment of renal function and/or coexisting disease was allowed, with the exception of monoamine oxidase inhibitors and medications with known risk for torsade de pointes.

Groups 1-4 received one dose of solriamfetol HCl (89.3 mg; equivalent to 75-mg solriamfetol) on day 1; Group 5 received one dose equivalent to 75-mg dose on day 1 followed by 4-hour hemodialysis (designated Group 5.2), and one dose equivalent to 75-mg solriamfetol on day 8 without hemodialysis (designated Group 5.1). All doses were administered on an empty stomach following an overnight fast except for participants in Group 5, who received a standardized snack on day 7 and breakfast early on day 8 before starting an 8-hour fast. Participants remained fasting for 4 hours after administration, with water allowed except for 1 hour before and after dosing.

In this study, 75 mg solriamfetol was selected as the dose for administration in participants with renal impairment as it was considered sufficiently low and potentially safe for this population. The 75-mg dose was expected to result in plasma concentrations of solriamfetol that were above the assay detection level at time points sufficient to characterize the PK profile.

Serial blood samples of approximately 4 mL were collected within 30 minutes prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-dose in Groups 1-3, with continued sampling at 60 and 72 hours post-dose in Groups 4 and 5. All blood samples were collected into labeled K_2EDTA tubes by direct venipuncture or indwelling catheter and kept on ice until the samples were centrifuged within 30 minutes of collection at approximately 2500 rpm (1315×g) at 4° C. for 10 minutes. The plasma was transferred into polypropylene tubes for freezing and storage at −70° C. until analysis.

Urine samples were collected predose and for the time intervals of 0-4, 4-8, 8-12, 12-24, and 24-48 hours in Groups 1-3, with additional collection for the 48-72 hour time interval in Groups 4 and 5. During the hemodialysis period on day 1 for Group 5, dialysate samples and pre- and post-dialyzer paired blood samples were collected at pre-dialysis (2 hours), and at 3, 4, 5, and 6 hours following dosing. Urine and dialysate samples were aliquoted into polypropylene tubes for freezing and storage at −70° C. until analysis. All blood, urine, and dialysate samples were shipped on dry ice to a central bioanalytical laboratory.

Bioanalytical analyses were performed by a central laboratory (KCAS, LLC, Shawnee, Kansas) using validated proprietary methods that included extraction/derivatization and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Measurement of solriamfetol was over the linear range of 8.42 to 4,210 ng/mL in plasma, 0.21 to 84.2 μg/mL in urine, and 1.68 to 842 ng/mL in dialysate. Solriamfetol was removed from dialysate samples with use of the Fresenius Optiflux F180NR dialyzer (Fresenius Medical Care, Waltham, Massachusetts). Assay performance was monitored by spiking blank interference free human plasma with positive controls and internal standards to generate standard curve and quality control samples. After derivatization, samples were chromatographed on a C8 reversed phase analytical HPLC (high-performance liquid chromatography) column, with subsequent monitoring using an API4000 LC-MS/MS unit (Sciex, Framingham, Massachusetts). Quantification was based on setting a calibration graph using the internal standard method. Coefficients of variation (CVs) for quality control samples were 3.2% to 6.0% for the plasma samples, 1.6% to 5.6% for the urine samples, and 3.5% to 7.1% for the dialysate samples.

The following plasma PK parameters were evaluated using non-compartmental analysis in Phoenix® WinNonlin® Version 6.3: C_{max}; time to reach C_{max} following drug administration (t_{max}); $t_{1/2}$; area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_t); AUC from time zero to infinity (AUC_∞); apparent total clearance of the drug from plasma after oral administration (CL/F); and apparent volume of distribution (V_d/F). The PK parameters for solriamfetol in urine included the amount of unchanged drug excreted in urine (A_e) over 48 or 72 hours; the fraction of the dose excreted unchanged in urine (F_e); and renal clearance of the drug (CL_R). For participants on hemodialysis (Group 5), the additional PK parameters included the amount of solriamfetol cleared by the 4-hour hemodialysis (A_{dial}); the fraction of dose removed by the 4-hour hemodialysis (F_{dial}); and hemodialysis clearance (CL_{dial}) calculated as $CL_{dial}=A_{dial}/AUC_{dial}$ where AUC_{dial} is the area under the pre-dialyzer plasma concentration-time curve during the hemodialysis period.

PK parameters were summarized by group using descriptive statistics. To assess differences in PK between each level of renal impairment (Groups 2-5) versus participants with normal renal function (Group 1), a linear effects model was used to compare natural log-transformed PK parameters (C_{max}, AUC_t, and AUC_∞). For Group 5, the participants without dialysis on day 8 (Group 5.1) and the participants who received dialysis on day 1 (Group 5.2) were analyzed and compared separately.

Point estimates and 90% confidence intervals (CIs) for differences on the natural log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. The 90% CIs around the geometric means ratios were presented for each pairwise comparison and expressed as a percentage relative to the geometric means of the reference group (Group 1). The inter-participant CV was estimated. To evaluate effects of dialysis on PK parameters for Group 5, an analysis of variance model was used that included "Day" as a fixed effect and measurements within the participant as a repeated measure. Day 8 was used as the

reference for comparison. In addition, nonparametric analysis was conducted for t_{max} as appropriate.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of the 31 participants who were enrolled and received treatment (6 participants in each of Groups 1 through 4 and 7 participants in Group 5), 30 participants (97%) completed the study. One participant from Group 5 discontinued due to adverse events. Participant demographics (Table 1) show that most participants in Groups 1-4 were white; however, most participants in Group 5 were black. There were at least 2 participants per sex in each group, and mean age for Groups 1, 2, 3, and 4 were comparable with an overlap in the range; the age range in Group 5 was lower than in the other groups. Mean BMI for Groups 1, 2, 3, 4, and 5 were comparable, with an overlap in the range. Furthermore, all participants in Group 1 matched the mean age (±10 years) and BMI (±20%) of participants in Groups 2-5.

TABLE 1

Demographic Characteristics of the Study Population

Variable	Group 1 Normal renal function (n = 6)	Group 2 Mild renal impairment (n = 6)	Group 3 Moderate renal impairment (n = 6)	Group 4 Severe renal impairment (n = 6)	Group 5 End-stage renal disease (n = 7)
Sex, n (%)					
Female	3 (50)	4 (67)	2 (33)	2 (33)	2 (29)
Male	3 (50)	2 (33)	4 (67)	4 (67)	5 (71)
Race, n (%)					
White	5 (83)	5 (83)	4 (67)	5 (83)	1 (14)
Black	1 (17)	1 (17)	2 (33)	1 (17)	6 (86)
Ethnicity, n (%)					
Non-Hispanic or Latino	0	3 (50)	2 (33)	3 (50)	6 (86)
Hispanic or Latino	6 (100)	3 (50)	4 (67)	3 (50)	1 (14)
Age, mean (SD), y	55.8 (3.9)	67.8 (7.4)	70.2 (7.7)	59.7 (15.6)	42.0 (7.6)
Weight, mean (SD), kg	73.1 (6.8)	67.1 (14.2)	76.8 (11.5)	85.5 (16.4)	88.2 (10.5)
BMI, mean (SD), kg/m2	28.1 (2.7)	25.1 (4.1)	28.8 (1.9)	29.3 (3.0)	29.9 (3.0)
eGFR, mean (SD), mL/min/1.73 m2	111.8 (32.3)	78.5 (8.4)	44.2 (6.2)	16.2 (5.8)	7.4 (4.8)

BMI = body mass index

For all study groups, mean PK parameters are summarized in Table 2 and mean plasma solriamfetol concentration-time profiles are shown in FIGS. **1**A and **1**B.

TABLE 2

Solriamfetol Pharmacokinetic Parameters by Level of Renal Function

	Mean ± standard deviation (% coefficient of variation)					
					End-stage renal disease (Group 5)	
	Normal renal	Renal impairment			Group 5.1	Group 5.2
Variable	function Group 1 (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Without hemodialysis[a] (n = 6)	With hemodialysis (n = 7)[b]
C_{max}, ng/mL	499.0 ± 142.4 (28.5)	521.8 ± 118.8 (22.8)	517.3 ± 131.6 (25.4)	552.8 ± 154.4 (27.9)	474.1 ± 79.0 (16.7)	396.4 ± 75.4 (19.0)
t_{max},[c] h	1.3 (0.5, 2.0)	1.5 (0.5, 2.0)	1.5 (1.0, 2.5)	2.0 (0.5, 3.0)	3.3 (1.0, 24.0)	1.5 (1.5, 10.0)
$t_{1/2}$, h	7.6 ± 5.1 (67.7)	9.1 ± 1.6 (18.1)	14.3 ± 4.5 (31.4)	29.6 ± 14.4 (48.7)	100.5 ± 78.8 (78.4)[d]	164.7 ± 81.4 (49.4)[e]
AUC_t, ng · h/mL[f]	4849 ± 3454 (71.2)	6613 ± 1574 (23.8)	9230 ± 2538 (27.5)	17 500 ± 9267 (52.9)	25 580 ± 4544 (17.8)	18 920 ± 3131 (16.5)
AUC_∞, ng · h/mL	5273 ± 4104 (77.8)	6836 ± 1730 (25.3)	10 470 ± 3642 (34.8)	23 650 ± 16 776 (70.9)	64 560 ± 35 962 (55.7)[d]	76 770 ± 41 993 (54.7)[e]
CL/F, L/h	19.8 ± 10.1 (50.9)	11.5 ± 2.5 (22.1)	7.8 ± 2.4 (30.5)	4.7 ± 2.8 (59.4)	1.6 ± 1.1 (72.3)[d]	1.5 ± 1.3 (91.0)[e]

TABLE 2-continued

Solriamfetol Pharmacokinetic Parameters by Level of Renal Function

Mean ± standard deviation (% coefficient of variation)

Variable	Normal renal function Group 1 (n = 6)	Renal impairment Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	End-stage renal disease (Group 5) Group 5.1 Without hemodialysis[a] (n = 6)	Group 5.2 With hemodialysis (n = 7)[b]
V_d/F, L	163.9 ± 23.8 (14.5)	147.2 ± 29.1 (19.8)	152.0 ± 32.6 (21.4)	157.2 ± 41.2 (26.2)	153.6 ± 45.6 (29.7)[d]	231.4 ± 28.5 (12.3)[e]

[a]Baseline adjusted to remove the impact of the day 1 dose on the day 8 concentration profile.
[b]Excluding 2 concentration values: 1 participant at predose, and 1 participant at 24 hours.
[c]For t_{max}, median (min, max) is presented.
[d]n = 3.
[e]n = 6.
[f]Over 48 h for normal, mild, and moderate, and over 72 h for severe.

In general, mean C_{max} and t_{max} were not substantially affected by renal impairment across Groups 1-4 (Table 2). However, solriamfetol AUC and $t_{1/2}$ values increased with increasing levels of renal impairment. Solriamfetol mean±SD overall exposure (AUC_∞) increased from 5273+4104 ng·h/mL in participants with normal renal function to 6836 ng·h/mL+1730 in Group 2 (mild impairment), 10,470±3642 in Group 3 (moderate impairment), and 23,650±16,776 in Group 4 (severe impairment) (Table 2). Similarly, solriamfetol mean±SD $t_{1/2}$ was 7.6±5.1 hours in participants with normal renal function and increased with greater levels of renal impairment: 9.1±1.6, 14.3±4.5, and 29.6±14.4 hours in Groups 2, 3, and 4, respectively (Table 2). While CL/F decreased with greater levels of renal impairment, there were no substantial changes in V_d/IF (Table 2). A plot of solriamfetol CL/F versus day −1 eGFR for Groups 1-4 is presented in FIG. **2**. This relationship is best described by the equation: solriamfetol CL/F (L/h)= 0.63184±0.16463×eGFR (mL/min/1.73 m^2).

Among participants with ESRD (Group 5), overall exposure (AUC_t) was approximately 5-fold higher for participants without dialysis on day 8 (Group 5.1; 25 580±4544 ng·h/mL) and about 4-fold higher among participants with dialysis on day 1 (Group 5.2; 18 920±3131) relative to Group 1 (4849±3454) (Table 2). Mean $t_{1/2}$ values exceeded 100 hours in both Group 5.1 (100.5 hours) and Group 5.2 (164.7 hours) (Table 2), and compared with Group 1, C_{max} values were slightly lower and t_{max} values differed significantly (P≤0.05 for both).

Ratios of geometric means and their associated 90% CIs for the pairwise comparisons of solriamfetol plasma PK parameters for Groups 2 through 5 versus Group 1 are presented in Table 3.

TABLE 3

Comparisons of Solriamfetol Plasma PK Parameters

PK parameter	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)[a]
			Geometric LS mean			
Cmax, ng/mL	482.3	510.5	503.2	533.0	468.8	389.9
AUCt, ng · h/mLb	4087.3	6469.6	8960.2	15 549	25 253	18 689
AUC∞, ng · h/mL	4363.9	6672.4	10002	19 140	56 319[c]	65 306[d]
			Percent ratio (90% confidence interval) of geometic mean relative to Group 1			
Cmax	—	105.9 (80.6, 139.0)	104.3 (78.4, 138.9)	110.5 (81.1, 150.6)	97.2 (76.1, 124.1)	80.9 (63.4, 103.1)
AUCt	—	158.3 (97.5, 256.9)	219.2 (133.7, 359.6)	380.4 (208.4, 694.4)	617.8 (385.3, 990.8)	457.2 (296.6, 704.9)

TABLE 3-continued

Comparisons of Solriamfetol Plasma PK Parameters

PK parameter	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)[a]
AUC∞	—	152.9 (92.9, 251.7)	229.2 (135.6, 387.4)	438.6 (217.3, 885.3)	1290.6 (542.78, 3068.5)	1496.5 (748.7, 2991.2)

Notes:

Parameters were ln-transformed prior to analysis. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the analysis of variance. % mean ratio = 100*(test/reference).

[a]Excluding 2 concentration values: 1 participant at predose, and 1 participant at 24 hours.

[b]Over 48 hours for Groups 1-3 and over 72 hours for Groups 4 and 5.

[c]n = 3.

[d]n = 6.

As shown, small increases were observed in C_{max}, which was approximately 6%, 4%, and 11% higher in Groups 2, 3, and 4, respectively, versus Group 1. However, total solriamfetol exposure (AUC_{∞}) in Groups 2, 3, and 4 was 53%, 129%, and 339% higher, respectively, relative to Group 1. In participants with ESRD, C_{max} was approximately 3% and 19% lower in groups 5.1 (ESRD without hemodialysis) and 5.2 (ESRD with hemodialysis), respectively, versus Group 1, and exposure was approximately 518% and 357% higher in the 2 groups versus Group 1.

Renal clearance (CL_R) and the cumulative amount of solriamfetol excreted in urine decreased as renal impairment increased (Table 4).

TABLE 4

Urinary Excretion of Solriamfetol

	Mean ± standard deviation (% coefficient of variation)			
PK parameter	Group 1 Normal renal function (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)
$F_{e(0\text{-}48)}$, %	85.8 ± 7.7 (9.0)	80.0 ± 9.0 (11.2)	66.4 ± 12.8 (19.2)	57.1 ± 18.6 (32.5)
CL_R, L/h	17.0 ± 7.7 (45.4)	9.3 ± 1.6 (17.1)	5.8 ± 2.0 (34.1)	3.8 ± 2.6 (68.0)

CL_R, renal clearance;

$F_{e(0\text{-}48)}$, fraction of the dose excreted unchanged in urine in 48 hours.

In Group 1, the mean±SD percentage of solriamfetol recovered unchanged in urine over 48 hours was 85.8%±7.7% and decreased to 80.0%±9.0%, 66.4%±12.8%, and 57.1%±18.6% in Groups 2, 3, and 4, respectively. Mean solriamfetol renal clearance also decreased with renal impairment, from 17.0±7.7 L/h in the normal renal function group to 9.3±1.6 L/h in Group 2, 5.8±2.0 L/h in Group 3, and 3.8±2.6 L/h in Group 4. Only 1 participant made urine and was able to provide data in Group 5, and the cumulative amount of solriamfetol excreted in urine was lower with hemodialysis, 42.1%, compared with 52.9% without hemodialysis.

Over the 4-hour hemodialysis period on day 1 for participants with ESRD, the mean±SD cumulative fraction of the 75-mg solriamfetol dose removed was 20.6%±1.7% (range 19.2% to 24.1%), and the hemodialysis clearance was 12.4 L/h±1.5 L/h (range 11.3 to 15.9 L/h).

There were no deaths or other serious AEs during this study. A total of 4 participants (13%), 1 each in Groups 2 and 3, and 2 in Group 5 (1 with and 1 without hemodialysis), reported 5 treatment-emergent adverse events (TEAEs; Table 5). This includes single events of nausea, skin abrasion, and headache in 1 participant each, and an increase in alanine aminotransferase (ALT; to 144 IU/L; reference range 8-54 IU/L) and aspartate aminotransferase (AST; to 66 IU/L; reference range 8-40 IU/L) observed 6 days after dosing in 1 participant that led to discontinuation. All TEAEs were considered by the investigator to be mild, and all but the skin abrasion were considered to be related to study drug. All TEAEs resolved, including the increased ALT and AST, which resolved on day 11. No other abnormal laboratory findings were considered clinically meaningful. No clinically significant abnormal findings were observed in vital sign and ECG measurements.

TABLE 5

Number (%) of Participants with Treatment-Emergent Adverse Events (TEAEs)

	Normal renal function	Renal impairment			End-stage renal disease (Group 5)	
Adverse event	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)
Any TEAE	0	1 (17%)	1 (17%)	0	1 (17%)	1 (14%)
Nausea	0	0	0	0	1 (17%)	0
Skin abrasion	0	1 (17%)	0	0	0	0

TABLE 5-continued

Number (%) of Participants with Treatment-Emergent Adverse Events (TEAEs)						
	Normal renal function	Renal impairment			End-stage renal disease (Group 5)	
					Group 5.1	Group 5.2
Adverse event	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Without hemodialysis (n = 6)	With hemodialysis (n = 7)
ALT increased	0	0	0	0	0	1 (14%)
AST increased	0	0	0	0	0	1 (14%)
Headache	0	0	1 (17%)	0	0	0

[a]One participant from Group 5 discontinued the study before day 8 due to adverse events of mild elevated ALT and AST.
ALT, alanine aminotransferase; AST aspartate aminotransferase; TEAE, treatment-emergent adverse event.

This study showed that renal impairment increases overall exposure to solriamfetol, with the magnitude of the increase reflecting the level of impairment. The incremental decreases in CL/F with worsening renal function resulted in corresponding increases in overall solriamfetol exposure that was 53% for mild, 129% for moderate, and 339% for severe impairment relative to normal renal function. Increasing renal impairment was also associated with decreasing cumulative percent of solriamfetol excreted in urine. The mean percentage of solriamfetol dose recovered in urine as unchanged drug over 48 hours was 85.8%, 80.0%, 66.4% and 64.0% (over 72 hours) for subjects with normal renal function and for subjects with mild, moderate, and severe renal impairment, respectively. Additionally, since there were no substantial changes in V_d/F, the decreases in solriamfetol CL/F resulted in increased $t_{1/2}$ by approximately 1.2-, 1.9-, and 3.9-fold in participants with mild, moderate, and severe renal impairment, respectively, compared with participants with normal renal function. In this regard, it should also be noted that while C_{max} values were not substantially affected by renal impairment, the observed increases in $t_{1/2}$ associated with renal impairment are expected to translate to changes in steady-state C_{max} that are not fully accounted for by the single-dose regimen evaluated in this clinical study, due to accumulation. AUC and t½ values increased with increasing levels of renal impairment. Solriamfetol $AUC_{0\text{-}inf}$ was higher by approximately 53% (1.53-fold), 129% (2.29-fold), and 339% (4.39-fold) compared with subjects with normal renal function.

Consistent with the inability of ESRD participants requiring hemodialysis to eliminate solriamfetol via renal excretion, these participants had increased overall exposure to solriamfetol (≥4-fold), longer $t_{1/2}$ values (≥13-fold), and slightly lower C_{max} values (≤19%), relative to participants with normal renal function. Furthermore, ESRD participants had lower solriamfetol C_{max} and AUC_t values after undergoing a 4-hour hemodialysis session, with 20.6% of the solriamfetol dose removed as unchanged drug. Notably, the solriamfetol hemodialysis clearance of 12.4 L/h estimated from solriamfetol recovered in the dialysate was approximately 30% lower than solriamfetol renal clearance in participants with normal renal function.

Example 2: Simulations of Solriamfetol Exposure in Patients with Renal Impairment

Methods

A population PK model was developed based on data collected in clinical studies. The population PK model provides a unified characterization of solriamfetol and of its sources of variability across studies and sub-populations of subjects. The population PK analysis examined the influence of potential covariates that have not been evaluated in clinical trials, such as potential differences between narcolepsy and OSA patients, as well as healthy subjects and narcolepsy/OSA patients, and investigated other factors such as age, gender, body weight, race/ethnicity, and formulation effects.

The following thorough evaluation of the source data was performed: (1) Visual inspection of individual plasma concentration-time profiles of solriamfetol relative to actual dosing history (e.g., spaghetti plots for rich concentration-time profiles, mean profiles); (2) Evaluation of potential outliers based on preliminary population PK runs (e.g., using a one compartment model without covariate); and (3) Review of demographic data and baseline characteristics for each study.

The dataset included actual time of observation (sampling and dosing) and main demographic characteristics (covariates) such as age, weight, height, body mass index (BMI), gender, race and markers of renal and liver functions. Extrinsic covariates were also included. The following main variables were included in the analysis dataset.

- NMID (unique individual identifier)
- STUDY (study identifier)
- SUBJ (subject ID used in the study)
- DATE (date of the event MM/DD/YYYY)
- TIME (time of the event HH:MM)
- DV (plasma concentration of solriamfetol, ng/mL)
- AMT (actual dose of solriamfetol in mg, calculated based on free base weight)
- EVID (event identification for PK observations only: 0=non-below the limit of quantification [BLQ] PK observation, 1=dose administration, 2=other-type event [BLQ PK records])
- MDV (missing data code: 0=non-missing, 1=missing data or excluded data)
- BLQ (1=BLQ concentration, 0=non-BLQ concentration or dosing event)
- FAST (fasted status during administration: 1=fasted; 0=fed)
- FORM (formulation: 0=drug substance in capsule; 1=tablet; 2=over-encapsulated tablet)

Daily dose (actual dose of solriamfetol in mg, calculated based on free base weight)
DS (disease status: 0=healthy subjects, 1=subjects with narcolepsy; 2=subjects with OSA)
WT (body weight at screening in kg)
Age at baseline (age in years)
Age as a categorical covariate (i.e., non-elderly vs. elderly≥65 years old)
Race (White, Black, Asian, Native Hawaiian or other Pacific Islander, Hispanic, Oriental, other)
Ethnicity (1=Hispanic or Latino, 0=non-Hispanic or Latino)
Gender (0=female, 1=male)
TAD (time after previous dose in h)
VISIT (visit number)
NTIME (nominal time after the dose in hours)
CRCL at baseline (creatinine clearance in mL/min calculated by Cockcroft-Gault formula) (Cockcroft D W, Gault M H: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41)
eGFR at baseline
Renal impairment status based on Food and Drug Administration (FDA) guidance 10:
Normal: eGFR≥90 mL/min/1.73 m^2
Mild: eGFR 60-89 mL/min/1.73 m^2 (i.e., ≥60 to <90)
Moderate: eGFR 30-59 mL/min/1.73 m^2 (i.e., ≥30 to <60)
Severe: eGFR 15-29 mL/min/1.73 m^2 (i.e., ≥15 to <30) and not on hemodialysis
End-stage renal disease (ESRD): eGFR<15 mL/min/1.73 m^2 and not on hemodialysis or patients on hemodialysis
HT (height in m)
BMI at baseline (body mass index in kg/m^2)
BSA at baseline (body surface area, calculated by Dubois and Dubois formula) (DuBois D; DuBois EF: A formula to estimate the approximate surface area if height and weight be known. Arch Int Med 1916 17:863-71)
ALT at baseline (alanine aminotransferase in U/L)
AST at baseline (aspartate aminotransferase in U/L)
ALB at baseline (albumin in g/L)
Bioanalytical method (High performance liquid chromatography [HPLC] or Liquid chromatography-tandem mass spectrometry [LC-MS/MS]).

Base Population PK Model Buildup

In a first step, compartmental PK models without covariates were evaluated to assess the PK of solriamfetol. One and two-compartment models with linear disposition were tested to assess the concentration-time profiles of solriamfetol.

Model Buildup

The population PK model included the following.

1. A structural component describing the relationships between plasma concentration and time using the following equation:

$$C_{pij}=C(D_i,t_j,\theta_i)\cdot(1+\varepsilon_{p,ij})+\varepsilon_{a,ij}$$

$$\theta_i=(\theta_{i1},\ldots\theta_{ip})$$

wherein C_{pij} is the concentration at the j^{th} collection time t^j for subject i, Di represents dosing history for subject i, ϑ_i is the vector of p different PK parameters for subject i, and $\varepsilon_{p,ij}$ and $\varepsilon_{a,ij}$ are the proportional and additive random residual error terms, respectively, associated with jth concentration for subject i. ε_p and ε_a are normally distributed with mean 0 and variances σ_p^2 and σ_a^2, respectively.

2. A variance component characterizing between-subject variability (BSV) and, if required, inter-occasion variability (IOV) in model parameters.

$$\theta_{ink}=(\theta_{TV,n}e^{(\eta_{in}\rightarrow\omega_{ink})})$$

$$(\eta_1,\ldots\eta_p)=MVN(0,\Omega)$$

$$\omega_{nk}=N(0,\Phi_n)$$

where θ_{ink} is the value of the n_{th} PK parameter of the ith individual on the kth occasion, $\theta_{TV,n}$ is the typical value of the nth PK parameter in the population, η_{in} is the random inter-individual deviation from the typical value $\theta_{TV,n}$ for subject i, and ψ_{ink} is the random inter-occasion subject deviation from the value of the nth parameter for subject i on occasion k. Inter-individual random effects ($\eta_1,\ldots,\eta_m$), also known as ETAs, are multivariate normally distributed with mean 0 and estimated variance ω_n^2 included in the variance-covariance OMEGA (Ω) matrix. Inter-occasion random effects for the nth parameter ψ_{nk} are normally distributed with mean 0 and variance Φ_n, with all $\psi_{n1},\ldots,\psi_{nm}$ sharing the same variance, where m is the number of occasions.

The evaluation of the BSV/IOV models included possible addition of BSV terms (ETAs) to the model parameters, evaluation of the most appropriate form of the ETAs, and evaluation of pair-wise plots of the ETAs for any correlations. Covariance between ETA terms was estimated in the model where correlations between ETAs were deemed probable based on these diagnostic plots. Models with shared ETA were also considered.

3. Error models describing residual unexplained variability in the form of additive, proportional or additive and proportional models:

$$y_{ij}=\hat{y}_{ij}*(1+\varepsilon_{1ij})+\varepsilon_{2ij}$$

where y_{ij} and $\hat{y}_{ij}$ represent the jth observed and predicted plasma drug concentration for the ith participant and ε is the random residual variability. Each ε (ε_1 and ε_2) is normally distributed with mean 0 and variance σ^2. An allometric function accounting for body weight effect on clearance (CL/F) and volume of distribution (V/F) was included in the model. In addition, the effect of creatinine clearance was added on CL/F since the drug was previously demonstrated to undergo important renal excretion.

Model Evaluation

Consistent with the FDA/EMA Guidance for Industry, evaluation of the models was based on the following.

Standard model diagnostics and standard statistical criteria of goodness-of-fit criteria such as the log-likelihood difference between alternative models (e.g., a decrease in the objective function value [OFV])
Successful model convergence
Examining pertinent graphical representations of goodness-of-fit:
Observed data versus population predicted data (DV vs. PRED) and individual predicted data (DV vs. IPRED) with a line of unity and a trend line, on linear and log scales
Observed Data versus time after the 1st dose and after the previous dose (DV vs. time and DV vs. TAD) with trend lines of DV and PRED, on linear and log scales
Conditional weighted residuals versus predicted data (CWRES vs. PRED) with zero line and a trend line

Conditional weighted residuals versus time after the 1st dose and previous dose [CWRES vs. time and CWRES vs. TAD] with zero line and a trend line

Quantile-quantile plot of CWRES (QQ plot)

Estimating shrinkage of the empirical Bayesian estimates (EBEs) of the model parameters was evaluated for diagnostic purpose. The shrinkage magnitude for a structural parameter 0 (η-shrinkage) was calculated as follow:

$$sh_\theta = 1 - \frac{SD(\eta_{EBE,P})}{\omega_\theta}$$

where $SD(\eta_{EBE,P})$ is the standard deviation of the individual EBEs for parameter P, ω_P is the model estimate of the standard deviation associated with parameter P. If no shrinkage in parameter P is present, the ratio between $SD(\eta_{EBE,P})$ and ω_P is unity, and shP becomes zero. Shrinkage reflects the degree of information available in the data to estimate the random effects independently, where a shrinkage of 100% reflects a case where there is no information at all on the random effect and all individual parameters revert back to the population estimate. Covariate effects may be interpreted with caution for PK parameters associated with high shrinkage (e.g., >30%), as the individual random effect estimates are expected to shrink towards zero.

Incorporation of Assay Conversion Factor

All plasma samples were assayed using an LC-MS/MS or an HPLC method. Exploratory analyses were performed to investigate potential differences in concentrations determined using the two different methods, and were used to guide further steps in model development, and whether or not an effect of assay was to be included as part of the base population PK model or the residual error model. As a consequence of the observed differences in concentrations due to use of the two different assay methodologies, an assay conversion factor (CF) was incorporated into the model to scale solriamfetol concentrations from HPLC assay to LC-MS/MS as per the following linear and nonlinear models:

$$C_{LC\text{-}MS/MS}=(C_{HPLC})\times CF \quad \text{Linear CF}$$

$$C_{LC\text{-}MS/MS}=(C_{HPLC})^{CF} \quad \text{Nonlinear CF}$$

In addition, different error models were considered for each assay. The CF was tested in the additive and proportional components of the error models. The selection of the final CF model was based on quality-of-fit using standard graphical representations of goodness-of-fit, including the diagnostic plots.

Sources of Variability and Covariate Analysis

The relationships between PK parameters and covariates were explored graphically to identify the covariates likely to affect the PK of solriamfetol. Scatter plots of the relationships between the random effect of PK parameters and continuous variables included LOESS lines, Pearson correlation coefficients, and the corresponding p-value for each relationship. Box plots were used to describe the relationship for categorical covariates. The investigated intrinsic factors included the following.

Age at baseline (as a continuous covariate in years and/or categorical covariate [i.e., non-elderly (18-64) vs. elderly (>65 years old)]). Covariate was tested on CL/F, V/F and Ka.

Gender. Covariate was tested on CL/F and V/F.

Measures of body size at baseline (i.e., body weight): Included in the base model on CL/F and V/F.

Ethnic origin/Race. Covariates were tested on CL/F and V/F.

Markers of renal function at baseline (based on creatinine clearance): Included in the base model on CL/F.

Markers of liver function at baseline (ALB, ALT and AST). Covariates were tested on CL/F and V/F.

The investigated extrinsic factors included:

Nominal dose levels of JZP-110. Covariate was tested on CL/F, V/F and Ka.

Formulation (Over-encapsulated Tablet vs. Tablet vs. drug substance in Capsule). Covariate was tested on CL/F, V/F and Ka.

Fasted status (i.e., fed vs. fasted). Covariate was tested on Tlag and Ka.

Disease status. Covariate was tested on CL/F and V/F.

Healthy subjects

Subjects with narcolepsy

Subjects with OSA

In the next step, the most relevant covariates were formally evaluated within the population PK model using a stepwise forward additive approach using a p-value of 0.01 (ΔOFV=6.63, for one degree of freedom [df]) and a backward elimination approach using a p-value of 0.001 (ΔOFV=10.83, for one df).

In addition, a nonparametric bootstrap resampling analysis was performed. The bootstrap technique involves repeatedly drawing random samples from the original data, with replacement. The bootstrap was used to reduce the model by removing covariates for which the 95% prediction interval (PI) included the null value relative to the reference population. Statistically significant covariates identified during the covariate analysis were displayed graphically in a forest plot. See, Menon-Andersen D, Yu B, Madabushi R, Bhattaram V, Hao W, Uppoor R S, Mehta M, Lesko L, Temple R, Stockbridge N, Laughren T, Gobburu J V. Essential pharmacokinetic information for drug dosage decisions: a concise visual presentation in the drug label. Clin Pharmacol Ther. 2011 September; 90(3):471-4.

Final Model

The final population PK model was evaluated using visual predictive check (VPC). Based on the estimates of the final model, concentration-time profiles were simulated using 1000 replicates. Observed and simulated data were separated into distinct bins. Within each bin, a 95% confidence interval of the 5th, 50^{th} and 95th prediction intervals was obtained by simulation. The confidence intervals give an indication of the uncertainty of the predictions. The 5th, 50th and 95th percentiles of observed concentrations were compared to the 95% confidence intervals.

The final population PK model was used to simulate rich concentration-time profiles of solriamfetol in adult subjects with renal impairment (mild, moderate, severe, and ESRD) and in pediatric patients following administration of different dosing regimens.

The final population PK model was used to perform simulations in 10000 narcolepsy/OSA patients for each dose level of solriamfetol tablet formulation (37.5, 75, 150, and 300 mg), and exposure parameters (AUCtau, Cmax, Cmin, C14 h and t1/2) were derived.

Descriptive statistics of exposure parameters for each dose level and according to each renal impairment category are presented in Tables 6-10. Boxplots of exposure parameters for each dose level and according to each renal impairment category are presented in FIGS. **3-7**. Simulated concentration-time profiles for each dose level and according to each renal impairment category are presented in Table 8.

TABLE 6

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Normal Renal Function

	Dose (mg) - Solriamfetol			
Parameters	37.5 (n = 10000)	75 (n = 10000)	150 (n = 10000)	300 (n = 10000)
	AUC_{tau} (ng · h/mL)			
Mean (CV%)	1931 (34.4%)	4139 (34.4%)	8874 (34.4%)	19024 (34.4%)
Median	1822	3906	8382	17952
[Min, Max]	[471, 7671]	[1010, 16473]	[2165, 35375]	[4641, 75968]
Geom. Mean (Geom.CV %)	1825 (34.6%)	3912 (34.6%)	8387 (34.6%)	17980 (34.6%)
	C_{max} (ng/mL)			
Mean (CV %)	202 (24.5%)	410 (24.6%)	835 (24.8%)	1702 (25.0%)
Median	197	399	811	1654
[Min, Max]	[79.1, 494]	[160, 1004]	[323, 2086]	[656, 4370]
Geom. Mean (Geom.CV %)	196 (24.5%)	398 (24.6%)	810 (24.8%)	1651 (25.0%)
	C_{min} (ng/mL)			
Mean (CV %)	19.6 (78.9%)	46.7 (75.0%)	110 (71.5%)	259 (68.4%)
Median	15.8	38.3	92.2	219
[Min, Max]	[0.0290, 194]	[0.104, 432]	[0.362, 961]	[1.21, 2132]
Geom. Mean (Geom.CV %)	14.3 (108%)	35.0 (99.2%)	84.9 (92.1%)	204 (85.9%)
	$C_{14\ h}$ (ng/mL)			
Mean (CV %)	53.6 (50.3%)	120 (48.5%)	268 (46.9%)	595 (45.5%)
Median	49.1	111	248	552
[Min, Max]	[1.21, 296]	[3.39, 642]	[9.32, 1390]	[25.1, 3007]
Geom. Mean (Geom.CV %)	47.1 (57.7%)	106 (54.7%)	240 (52.2%)	536 (50.0%)
	Half-life (h)			
Mean (CV %)	6.35 (30.7%)	6.81 (30.7%)	7.30 (30.7%)	7.82 (30.7%)
Median	6.08	6.52	6.99	7.50
[Min, Max]	[1.71, 21.4]	[1.83, 22.9]	[1.96, 24.5]	[2.10, 26.3]
Geom. Mean (Geom.CV %)	6.08 (30.5%)	6.51 (30.4%)	6.98 (30.4%)	7.48 (30.5%)

AUC_{tau}: Area under the concentration-time curve at steady state;

$C_{14\ h}$: concentration at 14 h post-dose at steady state;

C_{max}: maximum concentration at steady state;

C_{min}: concentration at 24 h post-dose at steady state;

CV %: coefficient of variation;

Min: minimum;

Max: maximum;

n: number of subjects.

TABLE 7

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Mild Renal Impairment

	Reference (Adult, Dose = 150 mg, Normal	Dose			
Parameters	Renal Function)	37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
	AUC_{tau} (ng · h/mL)				
Mean (CV %)	8874 (34.4%)	2624 (34.3%)	5626 (34.2%)	12059 (34.2%)	25853 (34.2%)
Median	8382	2479	5320	11395	24428
[Min, Max]	[2165, 35375]	[721, 9598]	[1548, 20619]	[3321, 44294]	[7124, 95152]
Geom. Mean (Geom. CV %)	8387 (34.6%)	2482 (34.4%)	5321 (34.3%)	11407 (34.3%)	24453 (34.3%)
	C_{max} (ng/mL)				
Mean (CV %)	835 (24.8%)	225 (24.8%)	461 (25.1%)	946 (25.3%)	1945 (25.6%)
Median	811	219	448	919	1890
[Min, Max]	[323, 2086]	[82.4, 550]	[167, 1158]	[338, 2444]	[686, 5171]

TABLE 7-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Mild Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
Geom. Mean (Geom. CV %)	810 (24.8%)	218 (24.8%)	447 (25.1%)	917 (25.3%)	1884 (25.6%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	39.8 (64.5%)	91.8 (61.9%)	211 (59.5%)	482 (57.4%)
Median	92.2	34.3	80.1	186	428
[Min, Max]	[0.362, 961]	[0.677, 289]	[2.06, 636]	[6.09, 1396]	[17.5, 3062]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	32.2 (77.9%)	75.7 (73.3%)	177 (69.3%)	409 (65.8%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	84.9 (43.8%)	187 (42.6%)	411 (41.6%)	902 (40.8%)
Median	248	79.1	175	384	845
[Min, Max]	[9.32, 1390]	[8.46, 385]	[21.3, 830]	[52.6, 1791]	[128, 3861]
Geom. Mean (Geom. CV %)	240 (52.2%)	77.2 (47.2%)	171 (45.6%)	378 (44.1%)	831 (42.9%)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	8.67 (30.8%)	9.29 (30.7%)	9.96 (30.7%)	10.7 (30.7%)
Median	6.99	8.26	8.85	9.48	10.2
[Min, Max]	[1.96, 24.5]	[2.69, 26.1]	[2.88, 28.0]	[3.09, 30.0]	[3.31, 32.2]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	8.29 (30.4%)	8.89 (30.4%)	9.53 (30.4%)	10.2 (30.4%)

AUC_{tau}: Area under the concentration-time curve at steady state;
$C_{14\ h}$: concentration at 14 h post-dose at steady state;
C_{max}: maximum concentration at steady state;
C_{min}: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

TABLE 8

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Moderate Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
		AUC_{tau} (ng · h/mL)			
Mean (CV %)	8874 (34.4%)	3743 (36.6%)	8024 (36.6%)	17201 (36.5%)	36875 (36.5%)
Median	8382	3518	7539	16157	34617
[Min, Max]	[2165, 35375]	[777, 14484]	[1666, 31285]	[3570, 67577]	[7652, 145970]
Geom. Mean (Geom. CV %)	8387 (34.6%)	3517 (36.4%)	7540 (36.4%)	16164 (36.3%)	34651 (36.3%)
		C_{max} (ng/mL)			
Mean (CV %)	835 (24.8%)	266 (26.8%)	550 (27.2%)	1139 (27.6%)	2366 (28.0%)
Median	811	255	527	1093	2267
[Min, Max]	[323, 2086]	[87.6, 810]	[179, 1712]	[365, 3624]	[748, 7684]
Geom. Mean (Geom. CV %)	810 (24.8%)	257 (26.4%)	531 (26.8%)	1099 (27.2%)	2280 (27.6%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	78.3 (57.9%)	177 (56.1%)	397 (54.5%)	888 (53.0%)
Median	92.2	69.6	158	356	801
[Min, Max]	[0.362, 961]	[1.00, 434]	[2.86, 961]	[7.96, 2126	[21.7, 4695]

TABLE 8-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Moderate Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
Geom. Mean (Geom. CV %)	84.9 (92.1%)	66.4 (65.6%)	151 (62.8%)	343 (60.2%)	774 (58.0%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	135 (4.24%)	293 (41.7%)	638 (41.1%)	1385 (40.5%)
Median	248	125	273	594	1294
[Min, Max]	[9.32, 1390]	[9.10, 573]	[22.4, 1243]	[54.3, 2699]	[130, 5855]
Geom. Mean (Geom. CV %)	240 (52.2%)	123 (44.1%)	270 (43.1%)	588 (42.3%)	1281 (41.5%)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	12.4 (32.6%)	13.2 (32.5%)	14.2 (32.5%)	15.2 (32.5%)
Median	6.99	11.8	12.6	13.5	14.5
[Min, Max]	[1.96, 24.5]	[3.14, 40.3]	[3.37, 43.2]	[3.61, 46.3]	[3.87, 49.7]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	11.8 (32.4%)	12.6 (32.4%)	13.5 (32.4%)	14.5 (32.4%)

AUC_{tau}: Area under the concentration-time curve at steady state;
$C_{14\ h}$: concentration at 14 h post-dose at steady state;
C_{max}: maximum concentration at steady state;
C_{min}: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

TABLE 9

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Severe Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
		AUC_{tau} (ng · h/mL)			
Mean (CV %)	8874 (34.4%)	5967 (36.9%)	12790 (36.8%)	27416 (36.8%)	58772 (36.8%)
Median	8382	5608	12026	25790	55249
[Min, Max]	[2165, 35375]	[1448, 20711]	[3129, 44391]	[6762, 95179]	[14323, 205161]
Geom. Mean (Geom. CV %)	8387 (34.6%)	5602 (36.6%)	12009 (36.6%)	25744 (36.6%)	55188 (36.5%)
		C_{max} (ng/mL)			
Mean (CV %)	835 (24.8%)	353 (29.3%)	738 (29.7%)	1546 (30.1%)	3243 (30.5%)
Median	811	338	705	1475	3089
[Min, Max]	[323, 2086]	[116, 1014]	[240, 2150]	[496, 4561]	[1029, 9681]
Geom. Mean (Geom. CV %)	810 (24.8%)	339 (28.8%)	708 (29.2%)	1482 (29.6%)	3105 (30.0%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	163 (49.6%)	360 (48.6%)	794 (47.6%)	1748 (46.8%)
Median	92.2	149	330	728	1608
[Min, Max]	[0.362, 961]	[15.8, 737]	[37.9, 1606]	[90.0, 3498]	[212, 7613]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	145 (52.5%)	322 (51.0%)	713 (49.7%)	1576 (48.6%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	231 (39.7%)	498 (39.4%)	1076 (39.0%)	2322 (38.8%)
Median	248	216	468	1010	2178
[Min, Max]	[9.32, 1390]	[45.4, 841]	[101, 1816]	[226, 3919]	[498, 8460]

TABLE 9-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Severe Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
Geom. Mean (Geom. CV %)	240 (52.2%)	214 (40.1%)	464 (39.7%)	1002 (39.3%)	2164 (38.9%)
Half-life (h)					
Mean (CV %)	7.30 (30.7%)	19.7 (33.1%)	21.1 (33.0%)	22.6 (33.0%)	24.2 (33.0%)
Median	6.99	18.7	20.0	21.5	23.0
[Min, Max]	[1.96, 24.5]	[5.21, 70.6]	[5.57, 75.7]	[5.96, 81.1]	[6.37, 86.9]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	18.7 (32.9%)	20.0 (32.9%)	21.5 (32.8%)	23.0 (32.8%)

AUC_{tau}: Area under the concentration-time curve at steady state;
$C_{14\ h}$: concentration at 14 h post-dose at steady state;
C_{max}: maximum concentration at steady state;
C_{min}: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

TABLE 10

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with ESRD

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
AUC_{tau} (ng · h/mL)					
Mean (CV %)	8874 (34.4%)	25371 (42.5%)	54399 (42.6%)	116645 (42.7%)	250132 (42.7%)
Median	8382	23288	49948	107070	229500
[Min, Max]	[2165, 35375]	[5989, 136885]	[12737, 292530]	[27087, 625152]	[57605, 1335983]
Geom. Mean Geom. CV %)	8387 (34.6%)	23394 (41.7%)	50152 (41.8%)	107514 (41.8%)	230486 (41.9%)
C_{max} (ng/mL)					
Mean (CV %)	835 (24.8%)	1153 (39.8%)	2456 (40.0%)	5234 (40.3%)	11162 (40.5%)
Median	811	1065	2267	4827	10282
[Min, Max]	[323, 2086]	[290, 5893]	[617, 12563]	[1310, 26789]	[2786, 57133]
Geom. Mean (Geom. CV %)	810 (24.8%)	1074 (38.6%)	2286 (38.9%)	4868 (39.1%)	10373 (39.4%)
C_{min} (ng/mL)					
Mean (CV %)	110 (71.5%)	961 (45.7%)	2075 (45.6%)	4476 (45.4%)	9655 (45.3%)
Median	92.2	876	1891	4084	8816
[Min, Max]	[0.362, 961]	[183, 5509]	[398, 11801]	[862, 25275]	[1866, 54124]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	875 (45.6%)	1889 (45.3%)	4079 (45.1%)	8803 (45.0%)
$C_{14\ h}$ (ng/mL)					
Mean (CV %)	268 (46.9%)	1045 (43.0%)	2243 (43.0%)	4814 (43.0%)	10333 (43.1%)
Median	248	958	2056	4413	9473
[Min, Max]	[9.32, 1390]	[236, 5689]	[505, 12161]	[1079, 25995]	[2304, 55566]
Geom. Mean (Geom. CV %)	240 (52.2%)	962 (42.3%)	2064 (42.2%)	4430 (42.3%)	9509 (42.3%)
Half-life (h)					
Mean (CV %)	7.30 (30.7%)	83.6 (38.1%)	89.7 (38.2%)	96.1 (38.3%)	103 (38.4%)
Median	6.99	77.9	83.4	89.6	95.9
[Min, Max]	[1.96, 24.5]	[20.8, 337]	[22.3, 363]	[23.9, 392]	[25.5, 422]

TABLE 10-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with ESRD

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
Geom. Mean (Geom. CV %)	6.98 (30.4%)	78.1 (38.1%)	83.7 (38.2%)	89.8 (38.2%)	96.2 (38.3%)

AUC_{tau}: Area under the concentration-time curve at steady state;
$C_{14\ h}$: concentration at 14 h post-dose at steady state;
C_{max}: maximum concentration at steady state;
C_{min}: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

Ratios were generated to facilitate the comparison across populations of patients with renal impairment in order to optimally match the exposure of the reference dose in adult patients with normal renal function (i.e., 150 mg). Ratios of AUC_{tau}, C_{max}, C_{min}, C_{14h} and $t_{1/2}$ are presented in Table 11.

TABLE 11

Ratio of Mean Steady State PK Parameters of Solriamfetol in Patients with Renal Impairment (at different doses) Relative to Patients with Normal Renal Function (at 150 mg dose)

Sub-Population	Dose (mg)	Ratio Relative to Typical Patient with Normal Renal Function AUCtau	Cmax	C14 h	Cmin	t1/2
Mild Renal Impairment	300	2.91	2.33	3.37	4.38	1.47
	150	1.36	1.13	1.53	1.92	1.36
	75	0.63	0.55	0.70	0.83	1.27
	37.5	0.30	0.27	0.32	0.36	1.19
Moderate Renal Impairment	300	4.16	2.83	5.17	8.07	2.08
	150	1.94	1.36	2.38	3.61	1.95
	75	0.90	0.66	1.09	1.61	1.81
	37.5	0.42	0.32	0.50	0.71	1.70
Severe Renal Impairment	300	6.62	3.88	8.66	15.89	3.32
	150	3.09	1.85	4.01	7.22	3.10
	75	1.44	0.88	1.86	3.27	2.89
	37.5	0.67	0.42	0.86	1.48	2.70
ESRD	300	28.19	13.37	36.56	87.77	14.11
	150	13.1	6.27	18.0	40.7	13.2
	75	6.13	2.94	8.37	18.9	12.3
	37.5	2.86	1.38	3.90	8.74	11.5

AUCtau: Area under the concentration-time curve at steady state;
Cmax: maximum concentration at steady state;
C14 h: concentration at 14 h post-dose at steady state;
Cmin: concentration at 24 h post-dose at steady state;
t1/2: elimination half-life.

Based on the inventor's analyses of solriamfetol's pharmacokinetics and safety profile together with population PK simulations, it was discovered that, in patients with mild renal impairment, an equivalent dose used in patients with normal renal function was associated with comparable exposures. A 150 mg dose in patients with mild renal impairment is associated with AUC_{tau} and C_{max} values 36% and 13% higher than those observed in patients with normal renal function for the same dose. Typical C_{14h} and C_{min} values in a patient with mild renal impairment are expected to be approximately 1.5- and 2-fold higher than that observed in patients with normal renal function due to the longer $t_{1/2}$. Therefore, no dosage adjustments should be needed in patients with mild renal impairment and this subgroup of renally impaired patients can be safety administered at an initial daily dose equivalent to 75 mg of solriamfetol and escalating to a maximum daily dose equivalent to 150 mg of solriamfetol after at least 3 days, based on soiriamfetol's elimination half-life.

In patients with moderate renal impairment, one-half of the dose used in patients with normal renal function was associated with comparable exposures. A 75 mg dose in patients with moderate renal impairment is associated with AUC_{tau} and C_{max} values 10% and 34% lower than those observed in patients with normal renal function at a 150 mg dose. Typical C_{14h} and C_{min} values in a patient with moderate renal impairment is expected to be approximately 9% and 61% higher than that observed in patients with normal renal function due to the longer $t_{1/2}$. Therefore, dosing adjustments are warranted in patients with moderate renal impairment. The appropriate dose escalation regimen for this subgroup of renally impaired patients was determined by the present inventor to be an initial daily dose equivalent to 37.5 mg solriamfetol and escalating to a maximum daily dose equivalent to 75 mg solriamfetol after at least five days to at least seven days, based on solriamfetol's elimination half-life.

In patients with severe renal impairment, one-quarter of the dose used in patients with normal renal function was associated with comparable exposures. A 75 mg dose in patients with severe renal impairment was associated with AUC_{tau} and C_{max} values 44% higher and 12% lower than those in patients with normal renal function at a 150 mg dose. Typical C_{14h} and C_{min} following a 75 mg dose in patients with severe renal impairment is expected to be approximately 1.9- and 3-fold higher than that in patients with normal renal function. Therefore, it was determined that a 75 mg dose would not be appropriate for patients with severe renal impairment. Therefore, dosing adjustment is warranted in patients with severe renal impairment. A 37.5 mg dose in patients with severe renal impairment was associated with AUC_{tau} and C_{max} values 33% lower and 58% lower than those in patients with normal renal function at a 150 mg dose. Typical C_{14h} and C_{min} values following a 37.5 mg dose in a patient with severe renal impairment are expected to be 14% lower and 48% higher than that in patients with normal renal function. Therefore, dosing adjustments is warranted in patients with severe renal

impairment. The appropriate dose escalation regimen for this subgroup of renally impaired patients was determined by the present inventor to be a daily maximum dose equivalent to 37.5 mg of solriamfetol.

Based on the substantial increase in solriamfetol exposure in patients with ESRD, use of solriamfetol in this subpopulation should be avoided.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A method of treating a human subject with [R]-2-amino-3-phenylpropylcarbamate (APC) in need thereof having a history of bipolar disorders, said method comprising:

determining if the patient has moderate or severe renal impairment based on the estimated glomerular filtration rate (eGFR) of the subject, and

(a) providing to a subject having an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2:

a first oral daily dose equivalent to 37.5 mg APC from day one to day n_1 of a dose escalation regimen, and

a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen,

wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1,

wherein the subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC; and

(b) providing to a subject having an eGFR of about 15 mL/min/1.73 m^2 to about 29 mL/min/1.73 m^2:

an oral daily dose equivalent to 37.5 mg APC,

wherein the subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC.

2. The method of claim **1**, wherein the subject has excessive daytime sleepiness.

3. The method of claim **2**, wherein the excessive daytime sleepiness is due to obstructive sleep apnea.

4. The method of claim **2**, wherein the excessive daytime sleepiness is due to narcolepsy.

5. The method of claim **2**, wherein the excessive daytime sleepiness is due to shift work disorder.

6. The method of claim **1**, wherein the subject has attention deficit hyperactivity disorder.

7. The method of claim **1**, wherein the subject has binge eating disorder.

8. The method of claim **1**, wherein the subject experiences a reduced risk of psychiatric adverse reactions.

9. The method of claim **8**, wherein the psychiatric adverse reaction is anxiety.

10. The method of claim **8**, wherein the psychiatric adverse reaction is insomnia.

11. The method of claim **1**, wherein the subject is provided said first oral daily dose or said oral daily dose in the form of about 44.7 mg APC-HCl.

12. The method of claim **1**, wherein the subject is provided said second oral daily dose in the form of about 89.3 mg APC-HCl.

13. The method of claim **1**, wherein the subject is provided said first oral daily dose in the form of about 44.7 mg APC-HCl and said second oral daily dose in the form of about 89.3 mg APC-HCl.

14. The method of claim **1**, wherein said first oral daily dose, said second oral daily dose, and said oral daily dose are each administered upon the subject's awakening.

15. The method of claim **1**, wherein said first oral daily dose, said second oral daily dose, and said oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

16. The method of claim **1**, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

17. The method of claim **1**, wherein n_1 is an integer equal to or greater than 7.

18. The method of claim **2**, wherein the excessive daytime sleepiness is due to depression.

* * * * *

EXHIBIT B

US011986454B1

(12) **United States Patent**
Zomorodi

(10) **Patent No.: US 11,986,454 B1**
(45) **Date of Patent: *May 21, 2024**

(54) **METHODS OF PROVIDING SOLRIAMFETOL THERAPY TO SUBJECTS WITH IMPAIRED RENAL FUNCTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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A61B 5/20	(2006.01)

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(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to methods for decreasing adverse effects associated with solriamfetol ([R]-2-amino-3-phenylpropylcarbamate) therapy in subjects with impaired renal function. In particular, the invention provides an optimized dose escalation scheme for subjects with moderate renal impairment which results in the subjects having increased tolerance to adverse effects associated with the administration of solriamfetol. The invention also provides adjusted dosing for safe therapeutic use of solriamfetol in subjects having severe renal impairment.

23 Claims, 9 Drawing Sheets

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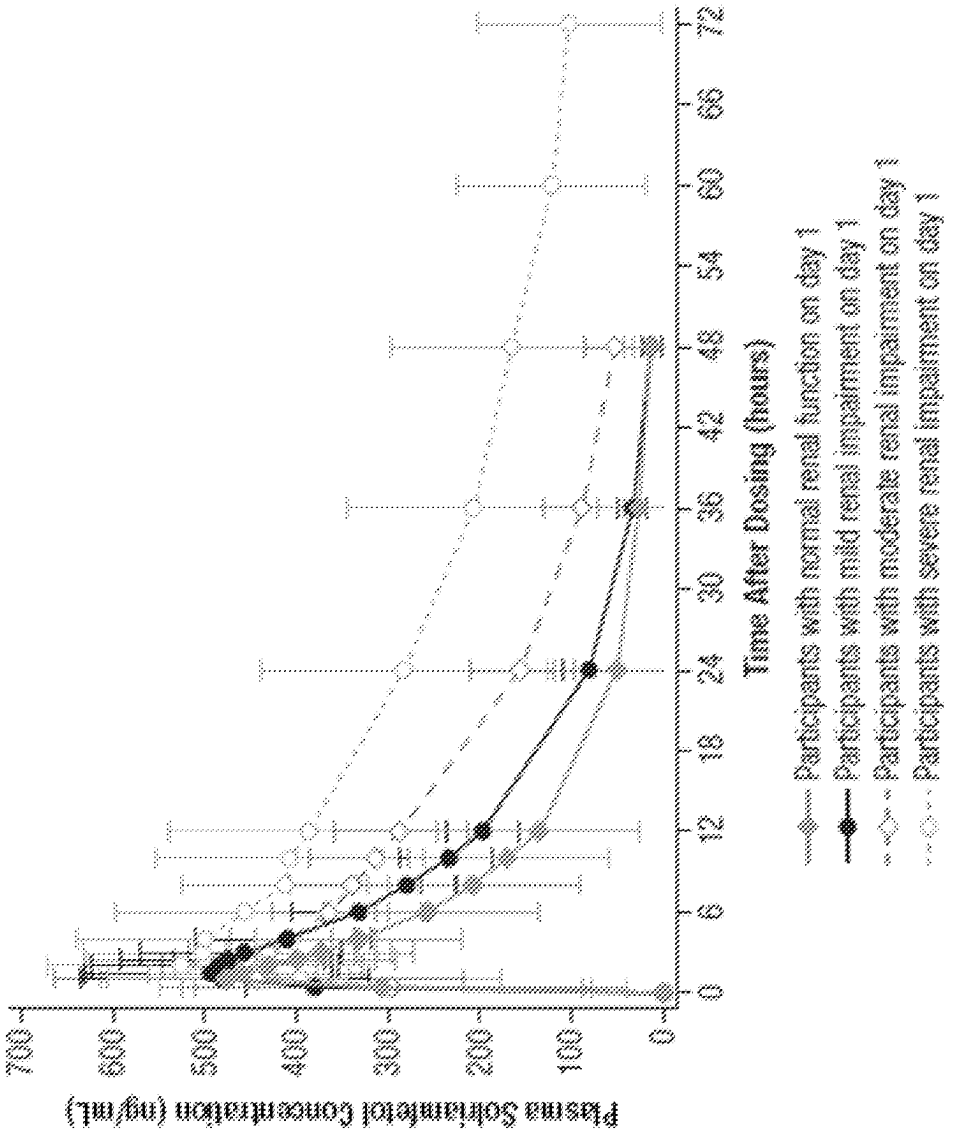

Plasma Soltrianbetol Concentration (ng/mL)
700
600
500
400
300
200
100
0
0
6
12
18
24
30
36
42
48
54
60
66
72
Time After Dosing (hours)
Participants with normal renal function on day 1
Participants with mild renal impairment on day 1
Participants with moderate renal impairment on day 1
Participants with severe renal impairment on day 1

FIG. 1A

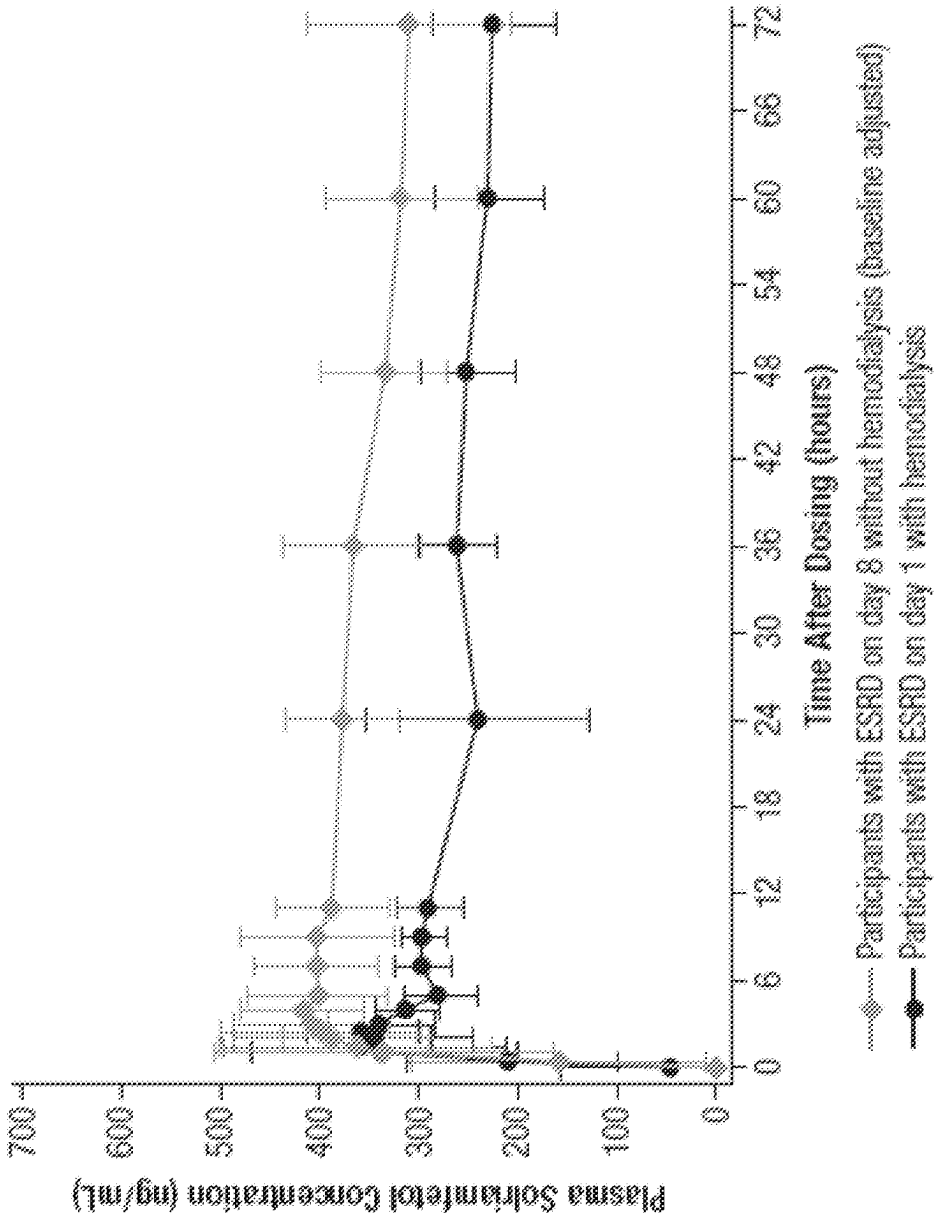
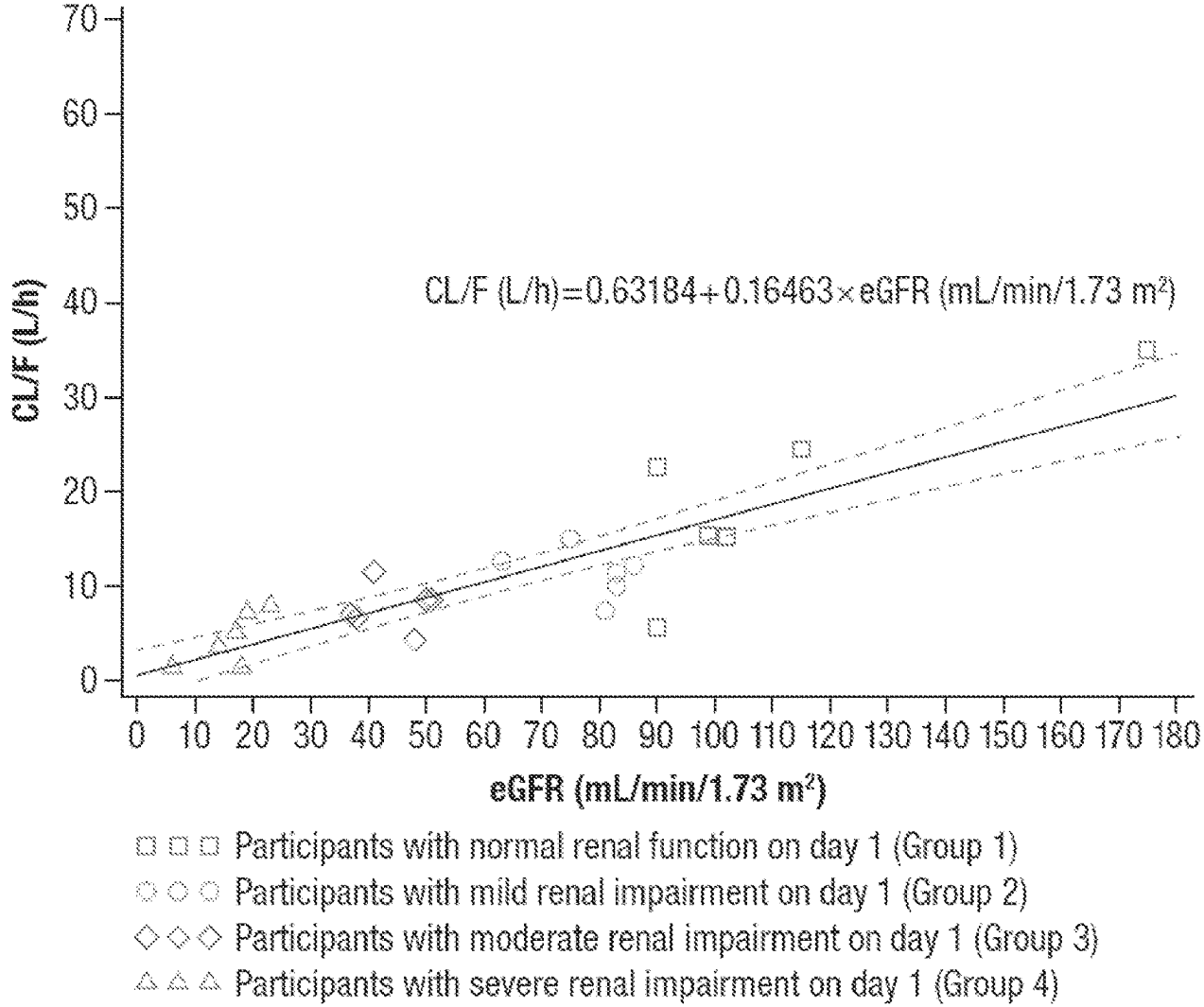

Plasma Sotrimetol Concentration (ng/mL)
700
600
500
400
300
200
100
0
0
6
12
18
24
30
36
42
48
54
60
66
72
Time After Dosing (hours)
Participants with ESRD on day 8 without hemodialysis (baseline adjusted)
Participants with ESRD on day 1 with hemodialysis

FIG. 1B

FIG. 2


CL/F (L/h)=0.63184+0.16463×eGFR (mL/min/1.73 m²)
CL/F (L/h)
eGFR (mL/min/1.73 m²)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
0 10 20 30 40 50 60 70
Participants with normal renal function on day 1 (Group 1)
Participants with mild renal impairment on day 1 (Group 2)
Participants with moderate renal impairment on day 1 (Group 3)
Participants with severe renal impairment on day 1 (Group 4)

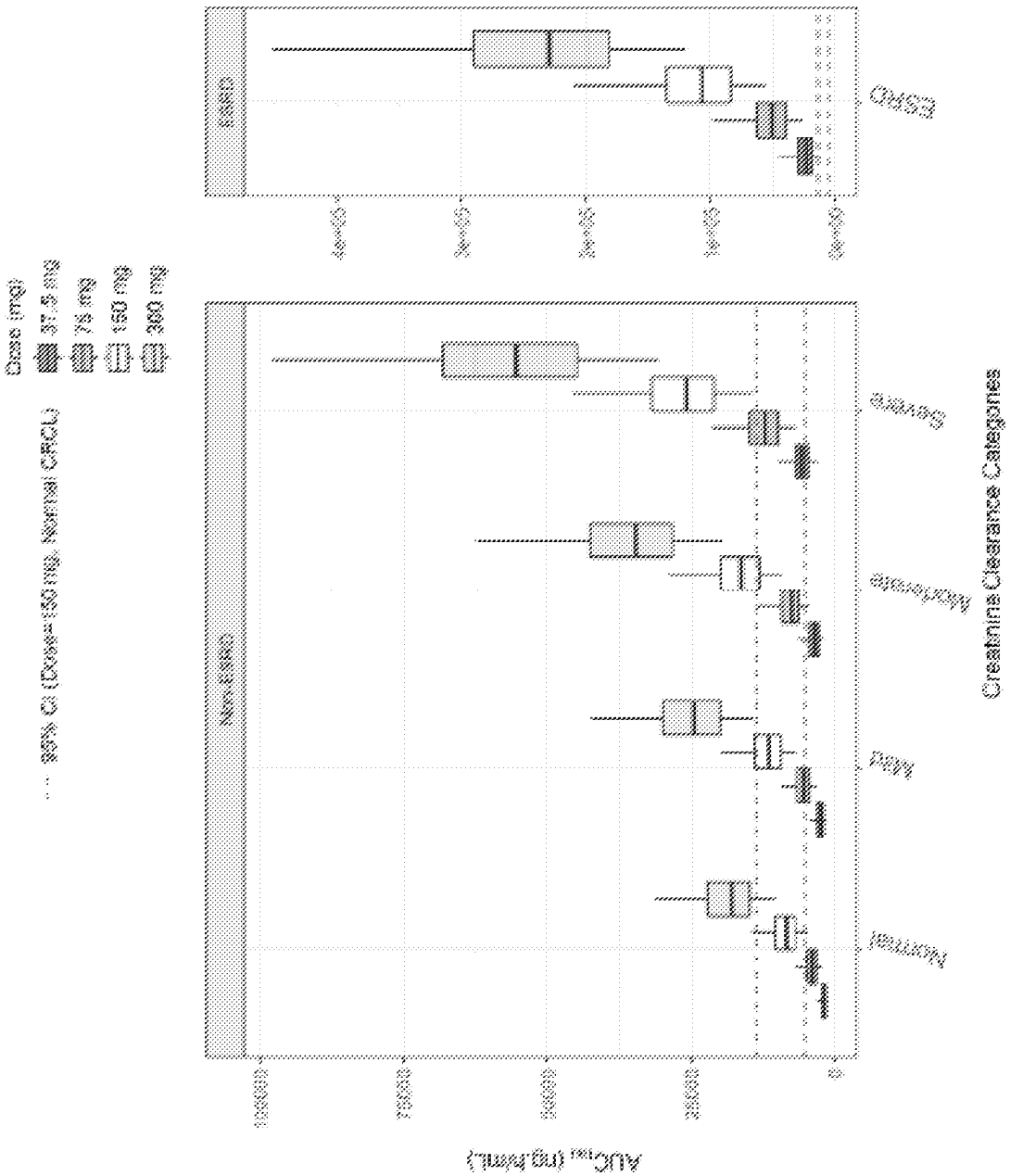

Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
90% CI (Dose-150 mg, Normal CRCL)
Severe
Moderate
Mild
Normal
Creatinine Clearance Categories
AUC$_{tau}$ (ng h/mL)

FIG. 3

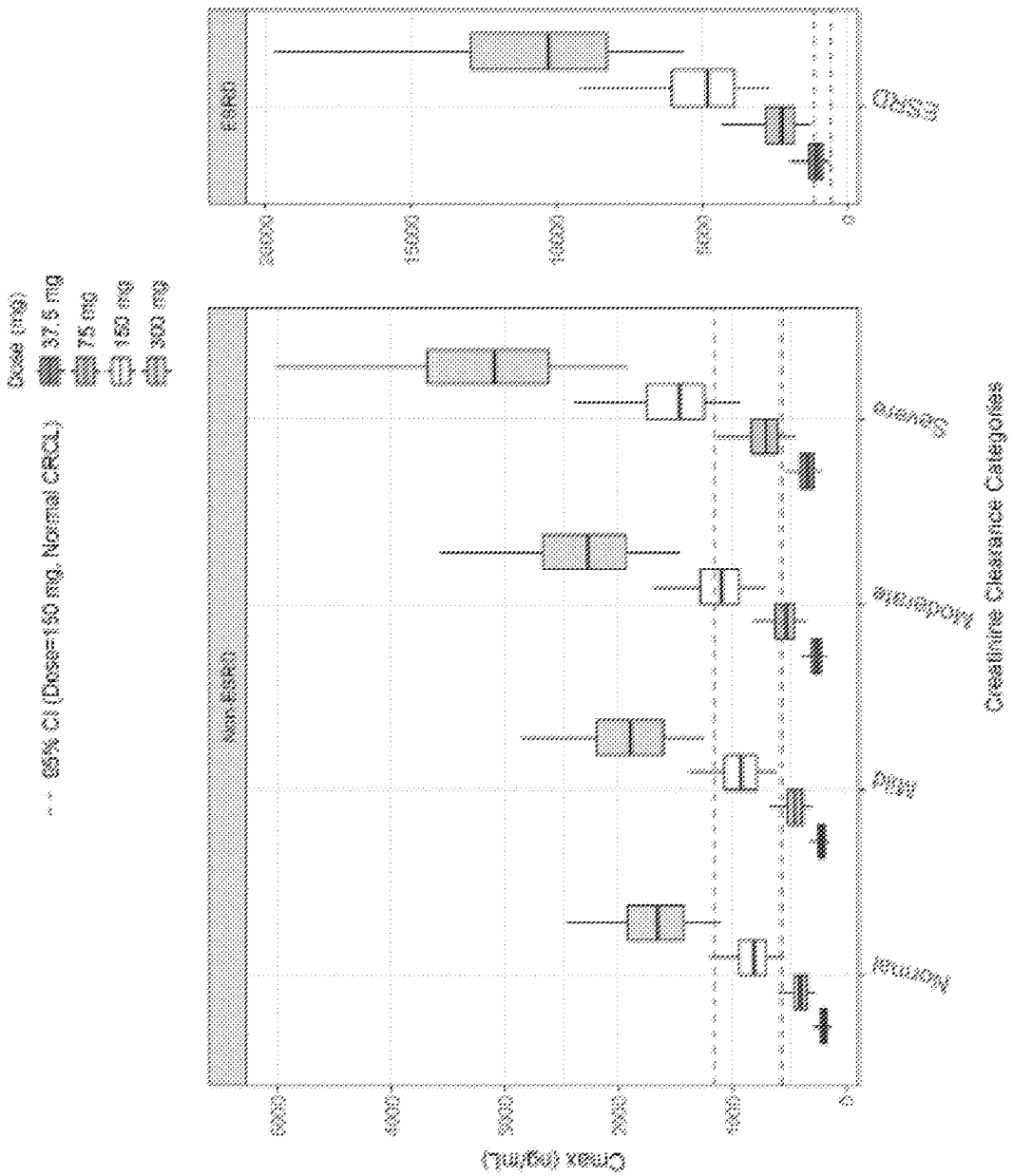

ESRD
Non-ESRD
Cmax (ng/mL)
Creatinine Clearance Categories
Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)

FIG. 4

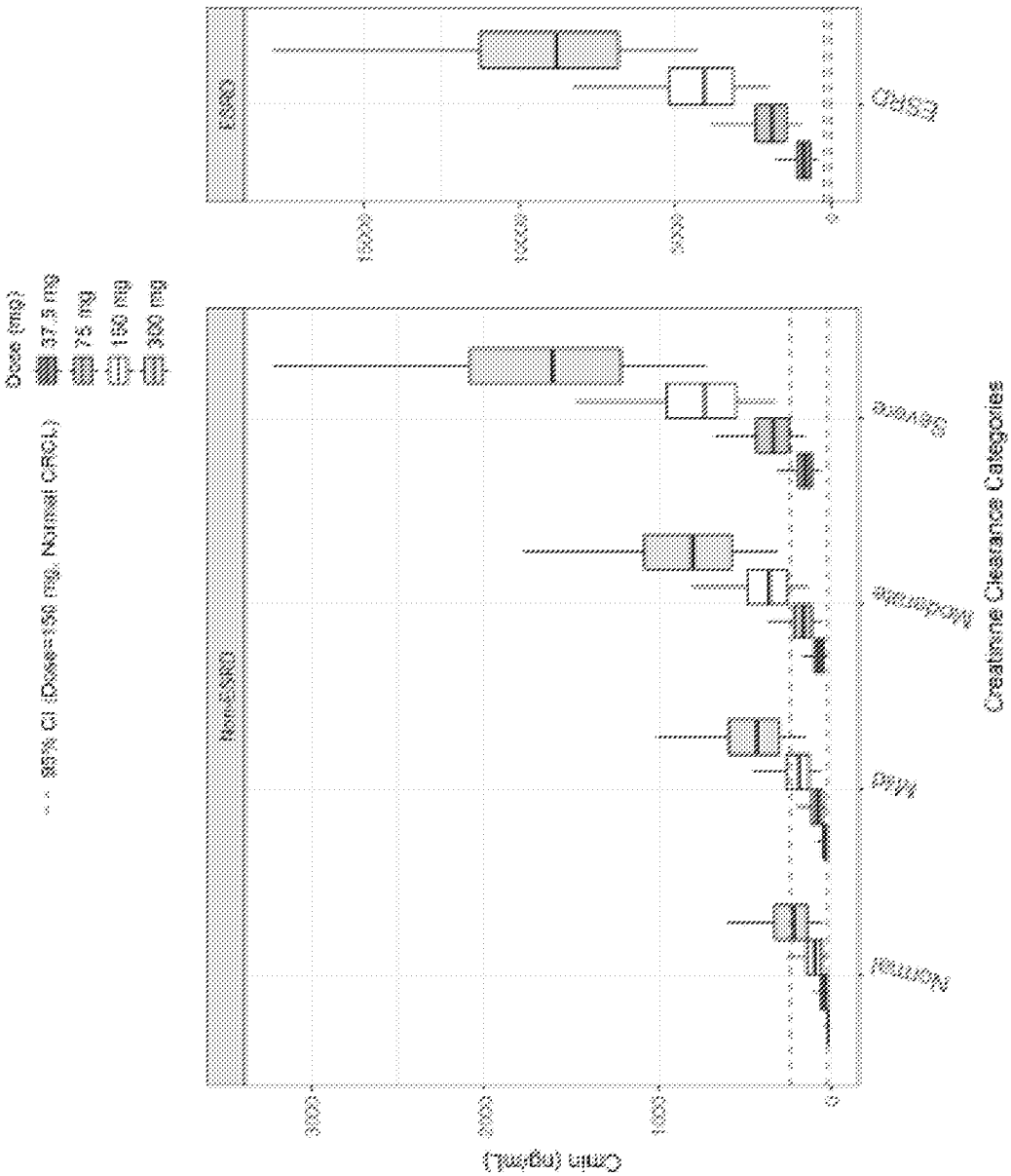

Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)
Cmin (ng/mL)
Creatinine Clearance Categories
Normal
Mild
Moderate
Severe
ESRD

FIG. 5

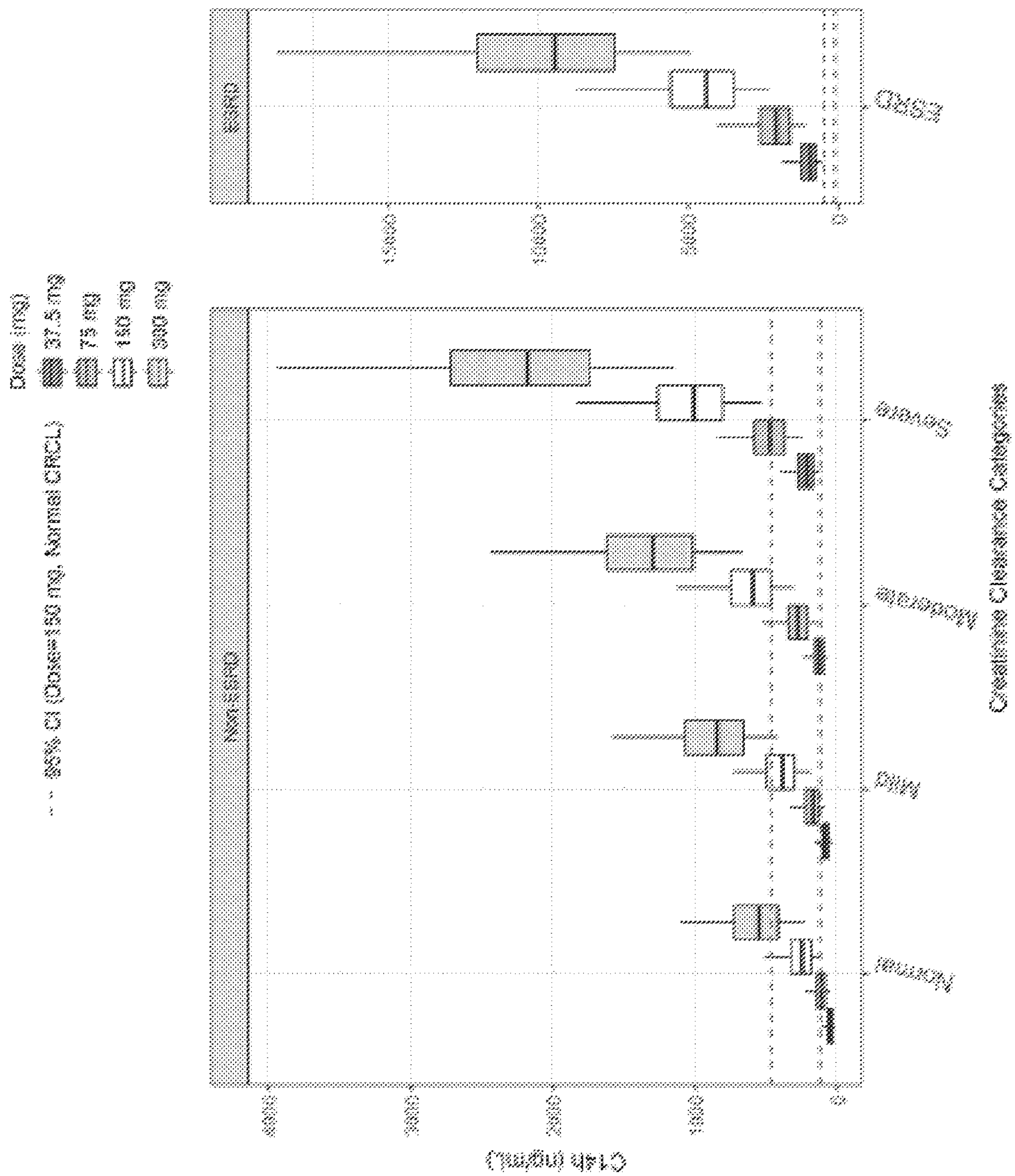

ESRD
Non ESRD
Normal
Mild
Moderate
Severe
Creatinine Clearance Categories
Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)

FIG. 6

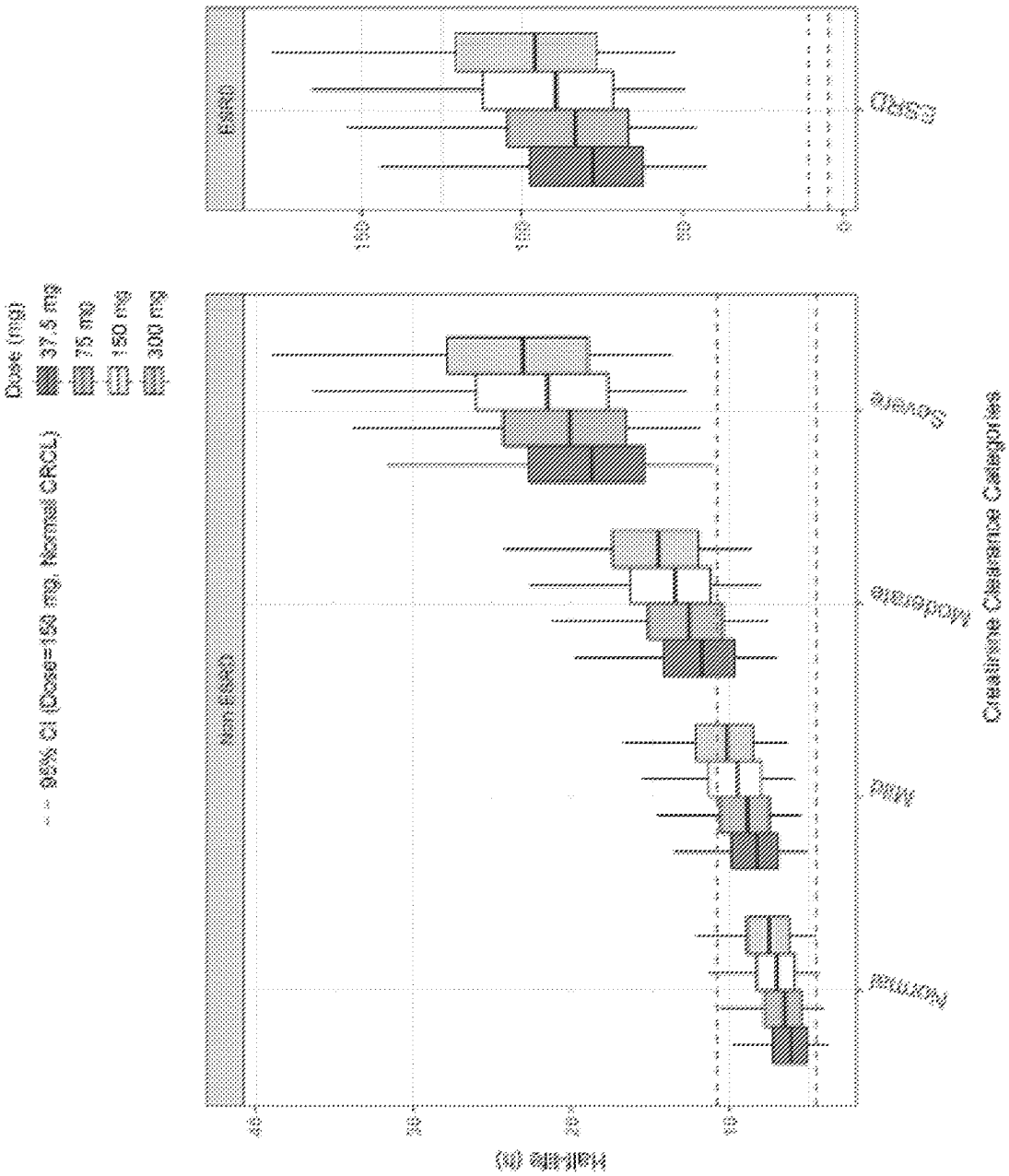

Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)
Creatinine Clearance Categories
Severe
Moderate
Mild
Normal
Half-life (h)

FIG. 7

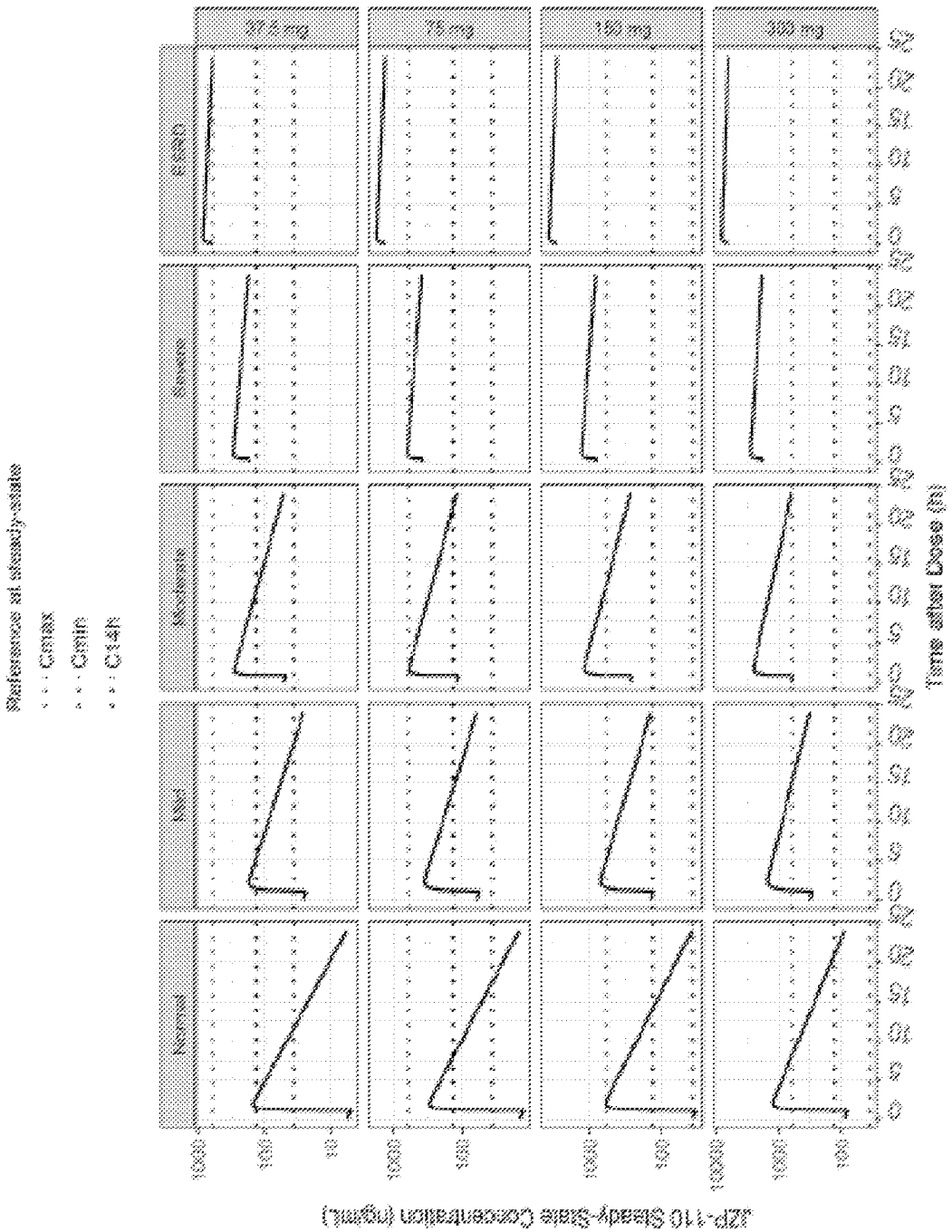

37.5 mg
75 mg
150 mg
300 mg
Normal
Mild
Moderate
Severe
ESRD
Time after Dose (h)
JZP-110 Steady-State Concentration (ng/mL)
Reference at steady-state
Cmax
Cmin
C24h

FIG. 8

METHODS OF PROVIDING SOLRIAMFETOL THERAPY TO SUBJECTS WITH IMPAIRED RENAL FUNCTION

STATEMENT OF PRIORITY

This application is a continuation of and claims priority to U.S. patent application Ser. No. 17/479,121, filed Sep. 20, 2021, which is a continuation of and claims priority to U.S. Patent application Ser. No. 17/149,406, filed Jan. 14, 2021, now U.S. Pat. No. 11,160,779, which is a continuation of and claims priority to U.S. patent application Ser. No. 16/824,560, filed Mar. 19, 2020, now U.S. Pat. No. 10,940,133, the entire contents of each of which is incorporated by reference herein in its entirety.

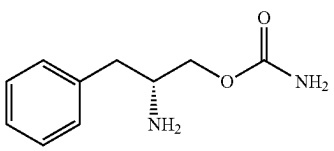
FIELD OF THE INVENTION

The invention relates to methods for decreasing adverse effects associated with solriamfetol ([R]-2-amino-3-phenylpropylcarbamate) therapy in subjects with impaired renal function. In particular, the invention provides an optimized dose escalation scheme for subjects with moderate renal impairment which results in the subjects having increased tolerance to adverse effects associated with the administration of solriamfetol. The invention also provides adjusted dosing for safe therapeutic use of solriamfetol in subjects having severe renal impairment.

BACKGROUND OF THE INVENTION

APC and its phenylalanine analogs have demonstrated application in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, attention deficit/hyperactivity disorder and others. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; 9,359,290; and 9,610,274 and U.S. Publication No. 2015/0018414. The structure of the free base of APC is given below as Formula I.

(I)



Those of skill in the art will appreciate that methods for producing APC (which also has other names) and related compounds can be found in U.S. Pat. Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817.

[R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) is a selective dopamine and norepinephrine reuptake inhibitor. At micromolar concentrations, APC-HCl can selectively bind and inhibit reuptake at dopamine and norepinephrine transporters without promoting monoamine release (See, Carter L, Baladi M, Black J, JZP-110: a dopamine-norepinephrine reuptake inhibitor (DNRI) with robust wake-promoting effects and low abuse potential. Poster presented at: Winter Conference on Brain Research; Jan. 23-28, 2016; Breckenridge, Colorado. Poster #Su23, 2016; and Baladi M G, Forster M J, Gatch M B, et al., Characterization of the neurochemical and behavioral

effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther.* 2018; 366:367-376).

As those of skill may recognize, APC-HCl (also referred to as solriamfetol HCl) has been approved by the FDA and EMA as a wake-promoting agent for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea (OSA). Phase 3 trials conducted with APC-HCl on patients having narcolepsy and OSA demonstrated statistically significant reductions in excessive daytime sleepiness measured on the patient-reported Epworth Sleepiness Scale and improvement in objective assessment of wakefulness using the Maintenance of Wakefulness Test. Significantly higher percentages of participants treated with APC-HCl in these trials also reported improvement on the Patient Global Improvement of Change scale relative to placebo at all evaluated time points. See, Johns M W, A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14(6):540-545); Thorpy M J, Dauvilliers Y, Shapiro C, et al., A randomized, placebo-controlled, phase 3 study of the safety and efficacy of JZP-110 for the treatment of excessive sleepiness in patients with narcolepsy, *Sleep,* 2017; 40 (suppl): A250; Schweitzer P K, Rosenberg R, Zammit G K, et al., Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial, *Am J Respir Crit Care Med.* 2018; December 6; and Strollo P J, Jr., Hedner J, Collop N, et al., Solriamfetol for the treatment of excessive sleepiness in obstructive sleep apnea: A placebo-controlled randomized-withdrawal study. *Chest.* 2018; November 21.

The most common adverse reactions or effects associated with APC-HCl therapy include headache, nausea, decreased appetite, anxiety, nervousness, panic attack, dry mouth, and diarrhea. Many of these effects can interfere with everyday activities and quality of life. Data from 12-week placebo-controlled clinical trials comparing various doses of solriamfetol support the conclusion that these adverse effects are dose-dependent and that they are exacerbated when APC-HCl is administered at higher doses. Additionally, solriamfetol has been shown to rely on renal excretion of unchanged drug as its primary route of elimination. The fact that the mean renal clearance of APC-HCl is 3 times the glomerular filtration rate suggest that its renal clearance is most likely attributed to a combination of passive diffusion and active renal tubular secretion by multiple cation transporters working in concert, with minimal tubular reabsorption. Therefore, administration of APC-HCl to patients with impaired renal function (which entails reduced passive diffusion and active renal tubular secretion) would be expected to result in higher APC-HCl exposure in this patient population. Prior to the present inventor's discovery however, it was not known what dose, if any, or escalation of APC-HCl would be safe for the renally impaired given the drug's unique pharmacological profile.

SUMMARY OF THE INVENTION

The present invention addresses an unmet medical need by providing methods of administering APC-HCl to renally impaired subjects in a manner that minimizes adverse effects. Of the methods provided is a dose escalation scheme for administering APC-HCl to patients with mild renal impairment, which involves an initial daily dose equivalent to 75 mg APC and waiting until after at least 3 days to reach the maximum daily dose equivalent to 150 mg APC. In another aspect of the invention, the dose escalation scheme of the present invention provides APC-HCl to patients with

moderate renal impairment at an initial daily dose equivalent to 37.5 mg APC and in a manner such that maximum dosage is not reached until after at least five days (in some embodiments of the invention, at least seven days); the method allows for a maximum dosage equivalent to 75 mg APC per day to be administered to a patient so as to reduce the incidence of adverse effects associated with the administration of APC-HCl by tailoring dose escalation to account for tolerance development in the patient. For patients with severe renal impairment (who have further reduced passive diffusion and active renal tubular secretion as compared with moderately impaired patients), the invention provides an alternative dosing regimen involving a daily maximum dose equivalent to 37.5 mg APC. The present inventor, based on analyses of the pharmacokinetics and safety profile of APC-HCl in conjunction with population PK simulations, has additionally discovered that use of APC-HCl should be avoided for patients with end-stage renal disease (with or without hemodialysis).

As such, provided according to embodiments of the present invention are methods of providing APC-HCl to a renally impaired subject in need thereof according to a dose escalation regimen, the method comprising providing to the subject a first oral daily dose equivalent to 37.5 mg APC from day one to day n_1 of the dose escalation regimen; and providing to the subject a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen, wherein n is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC, and wherein the renally impaired subject has an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2.

Further provided according to embodiments of the invention are methods of providing APC-HCl to a renally impaired subject with narcolepsy in need thereof, the method comprising providing to the subject an oral daily dose equivalent to 37.5 mg APC, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent 37.5 mg APC; and wherein the renally impaired subject has an eGFR of about 15 ml/min/1.73 m^2 to about 29 ml/min/1.73 m^2.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of guiding APC therapy in a renally impaired subject with narcolepsy in need thereof, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Further provided according to embodiments of the invention are methods of guiding APC therapy in a renally impaired subject with obstructive sleep apnea in need thereof, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising: administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; increasing the daily dose to a maximum dose equivalent to 75 mg APC after at least 7 days; wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl therapy in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising administering to the

subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of <15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily after at least 3 days; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease. In some embodiments of the invention, the subject is being treated with the above dosing regimen for excessive daytime sleepiness associated with narcolepsy.

In other embodiments of the invention, methods of reducing toxicity of APC-HCl therapy in a renally impaired subject with obstructive sleep apnea comprise: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of <15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 37.5 mg APC once daily and doubling the dose at intervals of at least 3 days to a maximum dose equivalent to 150 mg APC; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

The present invention is explained in greater detail in the drawings herein and the specification set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows the mean (SD) plasma of APC-HCl concentration-time profiles following a single dose equivalent to 75-mg APC for participants with normal renal function and mild-to-severe renal impairment.

FIG. **1**B shows the mean (SD) plasma APC-HCl concentration-time profiles following a single dose equivalent to 75-mg APC for participants with end-stage renal disease with and without hemodialysis.

FIG. **2** shows the apparent oral clearance (CL/F) versus day-1 estimated glomerular filtration rate (eGFR) for Groups 1-4. The broken lines represent the 90% confidence intervals.

FIG. **3** shows results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (narcolepsy/OSA, tablet, fasting conditions) by renal function—AUCtau.

FIG. **4** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—Cmax.

FIG. **5** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—Cmin.

FIG. **6** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—C14h.

FIG. **7** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—half-life.

FIG. **8** shows the results of simulations to support dosing in sub-populations—adult patients (Narcolepsy/OSA, tablet, fasting conditions)—individual PK profile (Semi-Log Scale).

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. For example, features illustrated with respect to one embodiment can be incorporated into other embodiments, and features illustrated with respect to a particular embodiment can be deleted from that embodiment. In addition, numerous variations and additions to the embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety for all purposes.

As used herein, "a," "an," or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even 0.1% of the specified amount.

The term "consists essentially of" (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition. The term "materially altered," as applied to a composition, refers to an increase or decrease in the therapeutic effectiveness of the composition of at least about 20% or more as compared to the effectiveness of a composition consisting of the recited components.

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, prevention or delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Treat" or "treating" or "treatment" refers to any type of action that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art.

"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., *Remington's Pharmaceutical Science;* 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

The compound [R]-2-amino-3-phenylpropylcarbamate (APC) or solriamfetol is also named (R)-(beta-amino-benzenepropyl) carbamate or O-carbamoyl-(D)-phenylalaninol and has alternatively been called ADX-N05, SKL-N05, SK-N05, YKP10A, and R228060. The hydrochloride salt of the compound is named [R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) or solriamfetol HCl.

A "disorder or condition amenable to treatment" refers to any disorder or condition in which administration of APC to a subject results in the treatment of one or more symptoms of the disorder in the subject. Disorders amenable to treatment with APC include, without limitation, excessive daytime sleepiness, fatigue, drug addiction, sexual dysfunction, depression, fibromyalgia syndrome, attention deficit/hyperactivity disorder, restless legs syndrome, bipolar disorder, cataplexy, obesity, and smoking cessation.

In some embodiments, APC may be used to treat and/or prevent excessive daytime sleepiness (EDS). See U.S. Pat. Nos. 8,440,715; 8,877,806; 9,604,917; and 10,351,517; incorporated by reference herein in their entirety. EDS may be due to, without limitation, a central nervous system (CNS) pathologic abnormality, stroke, narcolepsy, idiopathic CNS hypersomnia, sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder, Alzheimer's disorder, bipolar disorder, cardiac ischemia, misalignments of the body's circadian pacemaker with the environment, or jet lag; or a subject doing shift work or taking sedating drugs.

In some embodiments, APC may be used to treat and/or prevent fatigue. See U.S. Pat. Nos. 8,741,950; 9,464,041; 9,999,609; and 10,507,192; incorporated by reference herein in their entirety. Fatigue may be due to, without limitation, a disease, disorder or condition such as depression, cancer, multiple sclerosis, Parkinson's disease, Alzheimer's disease, chronic fatigue syndrome, fibromyalgia, chronic pain, traumatic brain injury, AIDS, and osteoarthritis. Fatigue may be due to, without limitation, a treatment or medication such as chemotherapy, radiation therapy, bone marrow transplant, and anti-depressant treatment.

In some embodiments, APC may be used to treat drug addiction. See U.S. Pat. No. 8,232,315, incorporated by reference in its entirety. In some embodiments, the addicted drug may be nicotine, opioid, cocaine, amphetamine, methamphetamine, ethanol, heroin, morphine, phencyclidine (PCP), and methylenedioxymethamphetamine (MDMA).

In some embodiments, APC may be used to treat sexual dysfunction. See U.S. Pat. No. 8,552,060, incorporated by reference herein in its entirety. In some embodiments, the treatment may increase interest in sex and/or the ability to have an orgasm. In some embodiments, the sexual dysfunction may be due to treatment with a therapeutic agent, including without limitation, selective serotonin reuptake inhibitors (SSRIs); selective serotonin and norepinephrine reuptake inhibitors (SNRIs); older tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAO-inhibitors), reversible inhibitors of monoamine oxidase (RIMAs), ter-

tiary amine tricyclics and secondary amine tricyclic antidepressants, e.g., therapeutic agents such as fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, 5-MCA-NAT, lithium carbonate, isocarboxazid, phenelzine, tranylcypromine, selegiline, moclobemide, kappa opioid receptor antagonists; selective neurokinin antagonists, corticotropin releasing factor (CRF) antagonists, antagonists of tachykinins, α-adrenoreceptor antagonists, amitriptyline, clomipramine, doxepin, imipramine, venlafaxine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

In some embodiments, APC may be used as an adjunctive therapy to treat depression. See U.S. Pat. No. 8,729,120, incorporated by reference herein in its entirety. In some embodiments, APC is administered to a subject in conjunction with an antidepressant such as, without limitation, fluoxetine, amitriptyline, clomipramine, doxepin, imipramine, trimipramine or a pharmaceutically acceptable salt thereof.

In some embodiments, APC may be used to treat fibromyalgia syndrome. See U.S. Pat. Nos. 8,927,602 and 9,688,620; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to treat attention deficit/hyperactivity disorder (ADHD) or diminish symptoms associated with ADHD. See U.S. Pat. Nos. 8,895,609; 9,663,455; and 10,202,335; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to treat restless legs syndrome. See U.S. Pat. No. 8,623,913, incorporated by reference herein in its entirety.

In some embodiments, APC may be used to treat bipolar disorder. See U.S. Pat. Nos. 9,610,274 and 9,907,777; incorporated by reference herein in their entirety. In some embodiments, APC may be used to diminish manic symptoms in a subject suffering from bipolar disorder.

In some embodiments, APC may be used to treat cataplexy. See U.S. Pat. Nos. 9,359,290; 9,585,863; and 10,259,780; incorporated by reference herein in their entirety. In some embodiments, the cataplexy is secondary to a condition that lowers hypocretin levels in a subject, such as a brain tumor, astrocytoma, glioblastoma, glioma, subependynoma, craniopharyngioma, arterio-venous malformations, ischemic events, multiple sclerosis, head injury, brain surgery, paraneoplastic syndromes, Neimann-Pick type C disease, or encephalitis.

In some embodiments, APC may be used to treat obesity, reduce body weight, reduce or prevent body weight gain, reduce food intake, or treat pathological eating. See U.S. Pat. Nos. 9,226,910; 9,649,291; and 10,105,341; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to promote cessation or reduction in the smoking and/or chewing of tobacco or nicotine-containing products and/or to prevent relapse of the same. See US Publication No. 2015/0018414, incorporated by reference herein in its entirety.

Methods of Treating Excessive Daytime Sleepiness

Provided according to embodiments of the present invention are methods of treating excessive daytime sleepiness in a renally impaired subject in need thereof, comprising administering to the subject an APC salt, such as APC-HCl. In some embodiments, such methods comprise administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject. In particular embodiments, such methods further include increasing the dose to a maximum equivalent of 75 mg APC once daily after at least 7 days. In some embodiments of the invention, the subject has narcolepsy, OSA, or both.

Further provided according to some embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject in need thereof that comprise administering to the subject an APC salt, such as APC-HCl, at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of guiding the treatment of excessive daytime sleepiness in a renally impaired subject in need thereof, comprising:

(a) determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

(b) administering to the subject the dose of an APC salt (e.g., APC-HCl) recommended for subjects without renal impairment if the subject has mild renal impairment; or administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject an APC salt if the subject has end stage renal disease.

In some embodiments, the methods further comprise measuring the eGFR in the subject prior to step (a).

Also provided according to other embodiments of the present invention are methods of reducing toxicity of an APC salt (e.g., APC-HCl) in a renally impaired subject, comprising administering to the subject the APC salt at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of the APC salt. In particular embodiments, such methods further include increasing the dose to a maximum equivalent of 75 mg APC once daily after at least 7 days. "Reducing toxicity," as used herein, refers to reducing the number and/or severity of adverse reactions or effects associated with APC-HCl therapy relative to the number and/or severity of adverse reactions or effects in the absence of the methods of the invention.

Provided according to some embodiments of the present invention are methods of reducing toxicity of an APC salt (e.g., APC-HCl) in a renally impaired subject, such methods comprising administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby reducing the toxicity of the APC salt in the subject.

Further, provided according to embodiments of the present invention are methods of reducing toxicity of an APC salt in a renally impaired subject, comprising:

(a) determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

(b) administering to the subject the dose of an APC salt recommended for subjects without renal impairment if

the subject has mild renal impairment; or administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject an APC salt if the subject has end stage renal disease. In some embodiments, the methods further comprise measuring the estimated glomerular filtration rate in the subject prior to step (a).

The methods of the invention may be used to treat any disorder or condition amenable to treatment with APC. Disorders amenable to treatment with APC include, without limitation, excessive daytime sleepiness, fatigue, sleep apnea, drug addiction, sexual dysfunction, depression, fibromyalgia syndrome, attention deficit/hyperactivity disorder, restless legs syndrome, bipolar disorder, cataplexy, obesity, as well as induction of smoking cessation.

Excessive Daytime Sleepiness

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift.

In some embodiments of the invention, treating excessive daytime sleepiness in a subject in need thereof may result in the decrease the subject's score on the Epworth Sleepiness Scale (ESS) by 5 or more points, e.g., by 10 or more points, e.g., by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more points or any range therein. In some embodiments, the amount of APC salt administered is sufficient to decrease the subject's score on the ESS to a level that is considered normal, e.g., 10 or less. In certain embodiments, at least about 5% of the treated subjects achieve the specified score, e.g., at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

The ESS is a subjective sleepiness test that is well known in the art and routinely used to measure the sleepiness level of a subject. The scale is intended to measure daytime sleepiness through the use of a short questionnaire that asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives. The scores for the eight questions are added together to obtain a single number that estimates the subject's average sleep propensity (ASP). A number in the 0-10 range is considered to be normal while 11-12 indicates mild excessive sleepiness, 13-15 indicates moderate excessive sleepiness, and 16 or higher indicates severe excessive sleepiness. Narcolepsy patients have an average score of about 17. Obstructive sleep apnea (OSA) patients with excessive sleepiness have an average score of about 15.

In some cases, treating excessive daytime sleepiness in a subject in need thereof results in an increase the subject's score on the maintenance of wakefulness test (MWT) by at least 5 minutes, e.g., at least 10 minutes or 15 minutes, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 minutes or more or any range therein. In certain embodiments, at least about 5% of the treated subjects achieve the specified score, e.g., at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

The MWT is an objective test used to measure how alert a subject is during the day. The test consists of four sleep trials with two hours in between the trials. The first trial is performed 1.5-3 hours after the subject's normal wake-up time. Sensors are placed on the head, face, and chin to detect when the subject is asleep and awake during the test. The subject sits quietly in bed with his or her back and head supported by a pillow and is asked to sit still and look straight ahead while trying to stay awake as long as possible. Each trial lasts 40 minutes or until the subject is asleep for 90 seconds. Between trials, the subject stays out of bed and occupies himself or herself to remain awake. Falling asleep in an average of less than eight minutes is considered abnormal. About 40-60% of subjects with normal sleep stay awake for the entire 40 minutes of all four trials.

The baseline measurement for determining a change in test results, such as ESS and MWT, may be performed before the subject has been administered APC or at a timepoint during a course of treatment of APC at which a baseline determination is desired. One or more subsequent determinations of test results may be made at any time after administration of one or more doses of APC. For example, determination of a change in test results may be made 1, 2, 3, 4, 5, or 6 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks after the administration of APC has begun or after the baseline determination was made.

The methods of the invention may be effective no matter the cause of the EDS, but in some embodiments of the invention, the EDS is associated with narcolepsy or obstructive sleep apnea (OSA). In other embodiments, the cause of the EDS may be, without limitation, central nervous system (CNS) pathologic abnormalities, stroke, idiopathic CNS hypersomnia; sleep deficiency, other sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder (ADHD), Alzheimer's disorder, major depression, bipolar disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work, or sedating drugs.

The methods of the invention may also be used to increase wakefulness and/or alertness in a subject in need thereof.

Renal Impairment

In embodiments of the present invention, the renal status of the subject may be determined by measuring the "estimated glomerular filtration rate" or "eGFR" of the individual. The eGFR in mL/min/1.73 m^2 is calculated by the Modification of Diet in Renal Disease [MDRD] equation:

$$(\text{eGFR in mL/min})/1.73\ m^2 = 175 \times (\text{serum creatinine in } mg/dL)^{-1.154} \times \text{Age}^{-0.203} \times 0.742(\text{if female}) \times 1.212(\text{if black}).$$

Further details regarding the calculation of the eGFR may be found in, e.g., Levey A S, Coresh J, Greene T, Marsh J, Stevens L A, Kusek J W, Van Lente F: Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Ann Intern Med. 2009; 150(9):604-12.

Renal impairment status based on Food and Drug Administration (FDA) guidance is as follows.

Normal: eGFR≥90 mL/min/1.73 m^2

Mild: eGFR 60-89 mL/min/1.73 m^2 (i.e., ≥60 to <90)

Moderate: eGFR 30-59 mL/min/1.73 m^2 (i.e., ≥30 to <60)

Severe: eGFR 15-29 mL/min/1.73 m^2 (i.e., ≥15 to <30) and not on hemodialysis

End-stage renal disease (ESRD): eGFR <15 mL/min/1.73 m^2 and not on hemodialysis or on hemodialysis

See, Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis and Impact on Dosing and Labeling. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) February 2010. As used herein, a "renally impaired subject" may have mild, moderate, or severe renal impairment, or may have ESRD.

APC Salts

The methods of the present invention may be carried out using compounds, formulations and unit dosage forms provided herein. In some embodiments, the formulations and dosage forms may include pharmaceutically acceptable salts of APC ("APC salt"), which also includes hydrates, solvates, clathrates, inclusion compounds, and complexes thereof.

In some embodiments of the invention, the APC salt is a hydrochloride salt (APC-HCl). However, suitable salts of APC also include, without limitation, acetate, adipate, alginate, aspartate, benzoate, butyrate, citrate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, hydroxynapthoate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, can be employed in the preparation of salts useful as intermediates in obtaining the compound of the invention and their pharmaceutically acceptable acid addition salts. APC salts include those having quaternization of any basic nitrogen-containing group therein.

The discussion herein is, for simplicity, provided without reference to the addition of deuterium atoms, but the APC salts may further include non-ordinary isotopes. Those skilled in the art will appreciate that the APC salt can contain one or more asymmetric centers and thus occur as racemates and racemic mixtures and single optical isomers. In embodiments of the present invention, the APC salt stereoisomer is preferred, but formulations according to embodiments of the invention may include both (R) and (S) isomers in a racemic mixture, or in any ratio of the isomers. In particular embodiments, the (R)-2-amino-3-phenylpropyl carbamate salt stereoisomer is present at a greater concentration than the (S)-2-amino-3-phenylpropyl carbamate salt stereoisomer, and in some embodiments, the formulation includes the 2-amino-3-phenylpropyl carbamate salt as a substantially enantiomerically pure (R)-2-amino-3-phenylpropyl carbamate salt stereoisomer such as having an enantiomeric excess of greater than 80%, 90%, 95%, or 99%. In some embodiments, the (R)-2-amino-3-phenylpropyl carbamate salt is enantiomerically pure, and in some cases is enantiomerically pure (R)-2-amino-3-phenylpropyl carbamate hydrochloride. When the (R)-2-amino-3-phenylpropyl carbamate salt is referenced specifically, it is understood that the dosage (e.g., 37.5 mg or 75 mg) refers to the equivalent weight of the (R) enantiomer only.

The APC salt(s) may be obtained or synthesized by methods known in the art and as described herein. Details of reaction schemes for synthesizing APC have been described in U.S. Pat. Nos. 5,705,640; 5,756,817; 5,955,499; and 6,140,532, all incorporated herein by reference in their entirety.

APC Salt Formulations

Any suitable dosage form comprising the APC salts may be used in the methods of the invention. In some embodiments, the dosage formulation comprises the APC salt (which is pharmaceutically acceptable) and a pharmaceutically acceptable carrier. In some embodiments, the dosage form is an oral dosage form, e.g., a tablet or a capsule, e.g., an immediate release dosage form.

In some embodiments, the dosage form is an immediate release tablet that releases at least 85%, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99%, of the APC salt contained therein within a period of less than 15 minutes after administration of the tablet to a subject. See, for example, U.S. Pat. No. 10,195,151, incorporated herein by reference in its entirety.

Formulations of the APC salt, including immediate release formulations, may be processed into unit dosage forms suitable for oral administration, such as for example, filled capsules, compressed tablets or caplets, or other dosage form suitable for oral administration using conventional techniques. Immediate release dosage forms prepared as described may be adapted for oral administration, so as to attain and maintain a therapeutic level of the compound over a preselected interval. In certain embodiments, an immediate release dosage form as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or polygonal. In one such embodiment, the surfaces of the immediate release dosage form may be flat, round, concave, or convex. In some embodiments, the shape may be selected to maximize surface area, e.g., to increase the rate of dissolution of the dosage form.

In particular, when the immediate release formulations are prepared as a tablet, the immediate release tablets may contain a relatively large percentage and absolute amount of the compound and so may be expected to improve patient compliance and convenience by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets as described herein can be administered, by oral ingestion, e.g., closely spaced, in order to provide a therapeutically effective dose of the compound to the subject in a relatively short period of time.

Where desired or necessary, the outer surface of an immediate release dosage form may be coated, e.g., with a color coat or with a moisture barrier layer using materials and methods known in the art.

In some embodiments, the dosage formulation is an immediate release compressed tablet, the tablet comprising: the APC salt thereof in an amount of about 90-98% by weight of the tablet; at least one binder in an amount of about 1-5% by weight of the tablet; and at least one lubricant in an amount of about 0.1-2% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises: the APC salt thereof in an amount of about 91-95% by weight of the tablet; at least one binder in an amount of about 2-3% by weight of the tablet; at least one lubricant in an amount of about 0.1-1% by weight of the tablet; and optionally, a cosmetic film coat in an amount of about 3-4% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained

therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises: the APC salt thereof in an amount of about 93.22% by weight of the tablet; at least one binder (e.g., hydroxypropylcellulose) in an amount of about 2.87% by weight of the tablet; at least one lubricant (e.g., magnesium stearate) in an amount of about 0.52% by weight of the tablet; and optionally, a cosmetic film coat (e.g., Opadry® II yellow) in an amount of about 3-4% by weight of the tablet; wherein the tablet releases at least 85% of the APC salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In some embodiments, the composition is an immediate release oral dosage form of an APC salt, the oral dosage form comprising: the APC salt thereof in an amount of about 90-98% by weight of the oral dosage form; at least one binder in an amount of about 1-5% by weight of the oral dosage form; and at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form; wherein the oral dosage form releases at least 85% of the APC salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject.

In certain embodiments, the tablet does not comprise a disintegrant. The term "disintegrant," as used herein, refers to an agent added to a tablet to promote the breakup of the tablet in an aqueous environment. The tablets of the present invention are advantageous in that they dissolve rather than disintegrate. In the present invention the presence of disintegrant in the formulation may actually slow down release of APC.

In certain embodiments, the APC salt is present in an amount of about 90%, 90.5%, 91%, 91.5%, 92%, 92.5%, 93%, 93.5%, 94%, 94.5%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, or 98% by weight of the tablet or any value or range therein. In certain embodiments, the APC salt thereof is present in an amount of about 90% to about 98%, about 92% to about 98%, about 94% to about 98%, about 96% to about 98%, about 90% to about 92%, about 90% to about 94%, about 90% to about 96%, about 92% to about 94%, about 92% to about 96%, or about 94% to about 96%.

In certain embodiments, the at least one binder is present in an amount of about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the tablet or any value or range therein. In certain embodiments, the at least one binder is present in an amount of about 1% to about 5%, about 2% to about 5%, about 3% to about 5%, about 4% to about 5%, about 1% to about 2%, about 1% to about 3%, about 1% to about 4%, about 2% to about 3%, about 2% to about 4%, or about 3% to about 4%. The tablet may comprise at least one binder, e.g., 1, 2, 3, 4, 5, or more binders.

In certain embodiments, the at least one binder is selected from at least one of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, sodium carboxymethylcellulose, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate or any combination thereof. In some embodiments, the at least one binder is hydroxypropyl cellulose.

In certain embodiments, the at least one lubricant is present in an amount of about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, or 2.0% by weight of the tablet or any value or range therein. In certain embodiments, the at least one lubricant is present in an amount of about 0.1% to about 2.0%, about 0.5% to about 2.0%, about 1.0% to about 2.0%, about 1.5% to about 2.0%, about 0.1% to about 0.5%, about 0.1% to about 1.0%, about 0.1% to about 1.5%, about 0.5% to about 1.0%, about 0.5% to about 1.5%, or about 1.0% to about 1.5%. The tablet may comprise at least one lubricant, e.g., 1, 2, 3, 4, 5, or more lubricants. Where the immediate release formulation is provided as a tableted dosage form, still lower lubricant levels may be achieved with use of a "puffer" system during tableting. Such systems are known in the art, commercially available and apply lubricant directly to the punch and die surfaces rather than throughout the formulation.

In certain embodiments, the at least one lubricant is selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate or any combination thereof. In some embodiments, the at least one lubricant is magnesium stearate. In other embodiments, magnesium stearate may be used in combination with one or more other lubricants or a surfactant, such as sodium lauryl sulfate. In particular, if needed to overcome potential hydrophobic properties of magnesium stearate, sodium lauryl sulfate may also be included when using magnesium stearate (Remington: the Science and Practice of Pharmacy, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000)).

In some embodiments, the at least one binder is hydroxypropyl cellulose. In some embodiments, the at least one lubricant is magnesium stearate. In some embodiments, the at least one binder is hydroxypropyl cellulose and the at least one lubricant is magnesium stearate.

In certain embodiments, the tablet is coated. The coating may be, without limitation, a color overcoat.

The tablet may be any shape that is suitable for immediate release and allows the release of at least 85% of the APC salt contained therein within a period of less than 15 minutes after administration of the tablet to a subject. In some embodiments, the tablet maximizes surface area to volume ratio to promote rapid dissolution. In some embodiments, the tablet is oblong in shape.

The tablet may contain any amount of the APC salt suitable for administration as a unit dosage form. In some embodiments, the tablet contains the equivalent of about 1 mg to about 1000 mg of APC or any range or value therein, e.g., about 100 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

["Immediate release" as used herein, refers to a composition that releases the APC salt substantially completely into the gastrointestinal tract of the user within a period of less than about 15 minutes, usually between about 1 minute and about 15 minutes from ingestion. Such a delivery rate allows the drug to be absorbed by the gastrointestinal tract in a manner that is bioequivalent to an oral solution. Such rapid absorption will typically occur for an immediate release unit dosage form, such as a tablet, caplet or capsule, if the drug included in such dosage form dissolves in the upper portion the gastrointestinal tract.

Release rates can be measured using standard dissolution test methods. For example, the standard conditions may be those described in FDA guidance (e.g., 50 rpm, 37° C., USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel).

Immediate release formulations suitable for oral administration may comprise unit dosage forms, such as tablets, caplets or filled capsules, which can deliver a therapeutically

effective dose of the APC salt upon ingestion thereof by the patient of one or more of said dosage forms, each of which can provide a dosage of, for example, about 37.5 mg to about 75 mg, or 75 mg to about 150 mg of APC. Additionally, the immediate release dosage forms can be shaped or scored to facilitate dose adjustment through tablet splitting. For example, a 75 mg APC tablet or caplet may be scored to facilitate tablet splitting into two 37.5 mg APC doses.

The formulation and structure of an immediate release dosage form as disclosed herein can be adjusted to provide immediate release performance that suits a particular dosing need. In particular, the formulation and structure of the dosage forms as described herein can be adjusted to provide any combination of the immediate release performance characteristics described herein. In particular embodiments, for example, an immediate release dosage form as disclosed herein provides rapid onset of action, releasing more than about 85%, such as, for example, more than about 90% or 95%, of the drug contained therein within a period of time selected from less than 15 minutes, less than 12 minutes, less than 10 minutes, and less than 5 minutes after administration.

Moreover, the rate of drug release from an immediate release dosage form as disclosed herein may be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. In certain such embodiments, the total amount of the APC salt in the dosage formulation may include an equivalent dose of about 10 mg to about 300 mg APC, about 30 mg to about 300 mg APC, about 100 mg to about 300 mg APC, or about 150 mg to about 300 mg APC, about 75 to 150 mg APC, about 37.5 to about 75 mg APC, and about 37.5 to about 150 mg APC. In particular embodiments, the equivalent dose of APC in the dosage formulation is 37.5 mg, and in other particular embodiments, the equivalent dose of APC in the dosage formulation is 75 mg. In some cases, such dosage formulations may be formed (e.g., scoring) to facilitate creating more than one dose from a particular dosage form.

The immediate release formulations provided herein generally include the APC salt and some level of lubricant to facilitate processing of the formulations into a unit dosage form. In some embodiments, therefore, the formulations described herein include a combination of the APC salt and lubricant, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. In other embodiments, the immediate release formulations described herein include a combination of the APC salt, lubricant, and binder, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. Though the immediate release formulations described herein may be formulated using a combination of drug and one or more of a lubricant and binder, in certain embodiments, the compositions described herein may include one or more additional excipients selected from, for example, fillers, compression aids, diluents, disintegrants, colorants, flavorants, buffering agents, coatings, glidants, or other suitable excipients.

The immediate release formulations described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and dry powder blending. Suitable methods for the manufacture of the immediate release formulations and unit dosage forms described herein are provided, for example, in Remington, 20^{th} edition, Chapter 45 (Oral Solid Dosage Forms). It has been found that, even without the aid of binders or non-lubricating excipients, such as compression aids, wet granulation techniques can afford flowable granules with compression characteristics suitable for forming unit dosage forms as described herein. Therefore, in certain embodiments, where a drug content greater than about 85%, 90% or 95% by weight is desired for the immediate release formulation, wet granulation techniques may be used to prepare immediate release formulations as described herein. In such embodiments, as illustrated in the Examples provided herein, conventional organic or aqueous solvents may be used in the wet granulation process. Suitable wet granulation processes can be performed as fluidized bed, high shear, or low shear (wet massing) granulation techniques, as are known in the art.

In addition to one or more the APC salt, lubricant, and binder, where desired, the immediate release formulations described herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. Where a filler or compression aid is used, in certain embodiments, it may be included in the immediate release formulation in an amount ranging from about 1%-15% by weight.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a moisture barrier layer using materials and methods known in the art. For example, where the APC salt delivered by the unit dosage form is highly hygroscopic, providing a moisture barrier layer over the immediate release dosage form as disclosed herein may be desirable. For example, protection of an immediate release dosage form as disclosed herein from water during storage may be provided or enhanced by coating the tablet with a coating of a substantially water soluble or insoluble polymer. Useful water-insoluble or water-resistant coating polymers include ethyl cellulose and polyvinyl acetates. Further water-insoluble or water resistant coating polymers include polyacrylates, polymethacrylates or the like. Suitable water-soluble polymers include polyvinyl alcohol and HPMC. Further suitable water-soluble polymers include PVP, HPC, HPEC, PEG, HEC and the like.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a color overcoat or other aesthetic or functional layer using materials and methods known in the art.

The dosage forms disclosed herein can also be provided as a kit comprising, separately packaged, a container comprising a plurality of immediate release tablets, which tablets can be individually packaged, as in foil envelopes or in a blister pack. The tablets can be packaged in many conformations with or without desiccants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, e.g., sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of APC in vivo for preselected periods of time, to treat a preselected condition.

Daily Dosage and Treatment Regimens

In the methods described herein, the typical daily dose of the APC salt for subjects with normal renal function, equivalent to 75-150 mg of APC, is modified for certain renally impaired subjects. As discussed above, for a subject with an eGFR of 30-59 ml/min/1.73 m^2, i.e., a subject with moderate renal impairment, the APC salt is administered once daily at an initial dose equivalent to 37.5 mg of APC. In some cases, this daily dose may be increased after at least 7 days of the

initial dose equivalent to 75 mg of APC. Further, in some embodiments, for a subject with an eGFR of 15-29 ml/min/1.73 m^2, i.e., a subject with severe renal impairment, the APC salt is administered once daily at a maximum dose equivalent to 37.5 of APC. In some embodiments, such dosages may be used for a subject who has narcolepsy, a subject with OSA, or when reduction of toxicity of the APC salt is indicated. In particular embodiments, the APC salt is APC-HCl.

A dose is "equivalent to" a 37.5 mg or 75 mg of APC, if the weight of the APC base (the "active moiety") in the formulation is 37.5 mg or 75 mg, respectively, regardless of the weight of the APC salt. Thus, the weight of the APC salt may be greater than 37.5 mg or 75 mg, respectively, in the formulation. Where APC is provided in the form of APC-HCl salt, a dose of 37.5 mg APC is equivalent to 44.7 mg (or 44.65 mg) of APC-HCl; a dose of 75 mg APC is equivalent to 89.3 mg of APC-HCl; and a dose of 150 mg APC is equivalent to 178.5 mg of APC-HCl. An "initial dose equivalent" is the daily dose at which the subject starts the treatment regimen, corresponding to the weight of the active moiety (APC), and the initial dose may be increased at some time point, such as in a number of days (e.g., 1, 2, 3, 4, 5, 6, 7, or more days). The "maximum dose equivalent" is the largest dose, corresponding to the weight of the active moiety (APC), that the patient may be administered daily at any time point.

In general, the daily dose is administered once daily. However, in some embodiments, the daily dose may be administered at two or more different time points. Administration of the APC salt can continue for one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve weeks or longer. Alternatively, administration of the APC salt can continue for one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment, the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, the APC salt is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Such agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. In some embodiments, the APC salt is delivered to a subject concurrently with an additional therapeutic agent that is not a monoamine oxidase inhibitor. In still other embodiments, the APC salt is delivered to a subject who has not been treated with a monoamine oxidase inhibitor within the preceding 14 days. In exemplary embodiments of the invention, a subject with obstructive sleep apnea is treated with APC concurrently with adherence to a primary OSA therapy. Examples of primary OSA therapies include, without limitation, positive airway pressure (PAP), continuous positive airway pressure (CPAP), oral appliances, and surgical procedures. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302.

The APC salt can be administered at any time during the day, but in some embodiments, the APC salt is administered to the subject no later than at least 12 hours before the bedtime of the subject. Studies by the present inventors have found that that administration of the APC salt within a few of hours of waking minimizes side effects of the treatment such as insomnia. In some embodiments, the APC is administered shortly after waking, e.g., within about 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, or 3 hours of waking. In exemplary embodiments, the APC is administered at least 9 hours before the bedtime of the subject, e.g., at least 9, 10, 11, 12, 13, 14, 15, or 16 or more hours before bedtime.

Subjects

The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults and geriatric subjects. In some embodiments of the invention, the human subject is an adult.

In particular embodiments, the subject is a human subject that has excessive daytime sleepiness or another disorder amenable to treatment with the APC salt. In other embodiments, the subject used in the methods of the invention is an animal model of excessive daytime sleepiness or another disorder amenable to treatment with APC.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, is suspected of having excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, and/or is anticipated to experience excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment. Disorders amenable to treatment with APC include, without limitation, sleep-wake disorder, excessive daytime sleepiness, depression, attention deficit/hyperactivity disorder, drug addiction, bipolar disorder, fibromyalgia, fatigue, obesity, restless legs syndrome, cataplexy, and sexual dysfunction.

Specific embodiments of the invention include, without limitation, the following.

Embodiment 1: A method of providing [R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) to a renally impaired subject in need thereof according to a dose escalation regimen, said method comprising providing to the subject a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of the dose escalation regimen; and providing to the subject a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen, wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC, and wherein the renally impaired subject has an estimated glomerular filtration rate (eGFR) of about 30 m/min/1.73 m^2 to about 59 mL/min/1.73 m^2.

Embodiment 2: The method of embodiment 1, wherein the subject is provided APC-HCl for the treatment of excessive daytime sleepiness.

Embodiment 3: The method of embodiment 2, wherein the excessive daytime sleepiness is associated with narcolepsy.

Embodiment 4: The method of embodiment 2, wherein the excessive daytime sleepiness is associated with obstructive sleep apnea.

Embodiment 5: The method of embodiment 1, wherein the subject is provided the first oral daily dose in the form of about 44.7 mg APC-HCl.

Embodiment 6: The method of embodiment 1, wherein the subject is provided the second oral daily dose in the form of about 89.3 mg APC-HCl.

Embodiment 7: The method of embodiment 1, wherein the subject is provided a first oral daily dose in the form of about 44.7 mg APC-HCl and a second oral daily dose in the form of about 89.3 mg APC-HCl.

Embodiment 8: The method of embodiment 1, wherein the first oral daily dose and second oral daily dose are each administered upon the subject's awakening.

Embodiment 9: The method of embodiment 1, wherein the first oral daily dose and second oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

Embodiment 10: The method of embodiment 1, wherein the subject is a human.

Embodiment 11: The method of embodiment 1, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

Embodiment 12: The method of embodiment 1, wherein n_1 is an integer equal to or greater than 7.

Embodiment 13: A method of providing APC-HCl to a renally impaired subject with narcolepsy in need thereof, said method comprising:

providing to the subject an oral daily dose equivalent to 37.5 mg APC, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC; and wherein the renally impaired subject has an eGFR of about 15 ml/min/1.73 m^2 to about 29 ml/min/1.73 m^2.

Embodiment 14: The method of embodiment 13, wherein the oral daily dose is provided to the renally impaired subject in the form of 44.7 mg APC-HCl.

Embodiment 15: The method of embodiment 13, wherein the oral daily dose is administered upon the subject's awakening.

Embodiment 16: The method of embodiment 13, wherein the oral daily dose is administered more than nine hours in advance of the subject's bedtime.

Embodiment 17: The method of embodiment 13, wherein the subject is a human.

Embodiment 18: The method of embodiment 17, wherein the subject is an adult.

Embodiment 19: The method of embodiment 13, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

Embodiment 20: A method of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2;

thereby treating excessive daytime sleepiness in the subject.

Embodiment 21: The method of embodiment 20, further comprising increasing the dose to a maximum equivalent to 75 APC once daily after at least 5 days.

Embodiment 22: The method of embodiment 21, wherein the dose is increased to a maximum equivalent to 75 mg APC once daily after at least 7 days.

Embodiment 23: A method of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2;

thereby treating excessive daytime sleepiness in the subject.

Embodiment 24: A method of guiding APC therapy in a renally impaired subject with narcolepsy in need thereof, comprising

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of less than 15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 25: The method of embodiment 24, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 26: The method of embodiment 24, wherein the dose is increased from a dose equivalent to 75 mg APC to a dose equivalent to 150 mg APC after at least 3 days if the subject has mild renal impairment and the dose is increased from a dose equivalent to 37.5 mg APC to a dose equivalent to 75 mg APC after at least 7 days if the subject has moderate renal impairment.

Embodiment 27: A method of guiding APC therapy in a renally impaired subject with obstructive sleep apnea in need thereof, comprising:

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of less than 15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily;

or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 28: The method of embodiment 27, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 29: The method of embodiment 27, wherein the regimen comprises doubling the dose of APC-HCl at intervals of at least 3 days if the subject has mild renal impairment and increasing the dose from a dose equivalent to 37.5 mg APC to a dose equivalent to 75 mg APC after at least 7 days if the subject has moderate renal impairment.

Embodiment 30: A method of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Embodiment 31: The method of embodiment 30, wherein the dose is increased to a maximum equivalent to 75 mg APC once daily after at least 7 days.

Embodiment 32: A method of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Embodiment 33: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising:

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; increasing the daily dose to a maximum dose equivalent to 75 mg APC after at least 7 days; wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl therapy in the subject.

Embodiment 34: The method of embodiment 33, wherein the initial dose is provided in the form of about 44.7 mg APC-HCl and the maximum dose is provided in the form of about 89.3 mg APC-HCl.

Embodiment 35: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl in the subject.

Embodiment 36: The method of embodiment 35, wherein the maximum dose is provided in the form of about 44.7 mg APC-HCl.

Embodiment 37: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising:

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily after at least 3 days; or

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APCl once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 38: The method of embodiment 37, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 39: The method of embodiment 37, wherein the eGFR is calculated by the Modification of Diet in Renal Disease equation.

Embodiment 40: The method of embodiment 37, wherein the subject is a human.

Embodiment 41: The method of embodiment 40, wherein the subject is an adult.

Embodiment 42: The method of embodiment 37, wherein the APC-HCl is administered orally.

Embodiment 43: The method of embodiment 37, wherein the APC-HCl is formulated with a pharmaceutical carrier.

Embodiment 44: The method of embodiment 37, wherein the subject is being treated for excessive daytime sleepiness associated with narcolepsy.

[The present invention is explained in greater detail in the following non-limiting Examples. Each example has a self-contained list of references.

EXAMPLE 1: Evaluation of the PK of Solriamfetol HCl in Participants with Renal Impairment and Those with ESRD Undergoing Hemodialysis Compared with Healthy Participants with Normal Renal Function

Methods

In healthy subjects with normal renal function, solriamfetol HCl is renally excreted ~90% unchanged within 48 hours of administration. Thus, renal impairment, as well as hemodialysis in individuals with end-stage renal disease (ESRD), could affect the PK of solriamfetol HCl. To ascertain the precise impact of renal impairment and hemodialysis on pharmacokinetics and safety of solriamfetol HCl, a Phase 1, parallel-group, open-label, single-dose study was conducted at 2 U.S. sites. The protocol was approved by the IntegReview Institutional Review Board (Austin, Texas), and the study was conducted in compliance with the protocol, the Guideline for Good Clinical Practice E6; the US Code of Federal Regulations pertaining to conduct and reporting of clinical studies; the Clinical Trials Directive of the European Medicines Agency (Directive 2001/20/EC); and the Declaration of Helsinki. Written informed consent was obtained from each subject before enrollment in the study and before performance of any study-related procedure. See, also, Zomorodi K, Chen D, Lee L, Lasseter K, Marbury T. An Open-Label, Single-Dose, Phase 1 Study of the Pharmacokinetics and Safety of JZP-110 in Subjects With Normal or Impaired Renal Function and With End-Stage Renal Disease Requiring Hemodialysis [abstract]. *Sleep.* 2017; 40 (suppl):A382-383.

Eligible participants were men and non-pregnant, non-lactating women between the ages of 18 and 80 years, with a body mass index (BMI)≤35 kg/m^2. Women of childbearing potential were required to have used a medically accepted method of birth control for at least 2 months prior to the first dose of study drug, with continued use throughout the study period and for 30 days after study completion. Participants were excluded if they had a clinically significant medical abnormality (other than renal impairment or its underlying causes), or any unstable conditions including neurological or psychiatric disorder, hepatic, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease, or any other

abnormality that could interfere with the PK evaluation of the study drug or the participant's completion of the trial.

Eligible participants were assigned to 1 of 5 groups according to renal disease status as measured by the estimated glomerular filtration rate (eGFR) on the day prior to dosing, calculated using the Modification in Diet in Renal Disease equation. Group 1 consisted of healthy participants with normal renal function (eGFR >90 mL/min/1.73 m^2) and served as the control group. Groups 2, 3, and 4 had mild, moderate, and severe renal impairment based on eGFRs of 60-89, 30-59, and <30 mL/min/1.73 m^2, respectively. Group 5 consisted of participants with ESRD who required >3 hemodialysis treatments per week for the preceding 3 months. Every effort was made to ensure that the groups were comparable with respect to age, sex, and body mass index (BMI). Group 1 was enrolled last to facilitate matching the mean age, BMI, and sex distribution of Groups 2-5.

Among participants with impaired renal function, continued use of medications necessary for treatment of renal function and/or coexisting disease was allowed, with the exception of monoamine oxidase inhibitors and medications with known risk for torsade de pointes.

Groups 1-4 received one dose of solriamfetol HCl (89.3 mg; equivalent to 75-mg solriamfetol) on day 1; Group 5 received one dose equivalent to 75-mg dose on day 1 followed by 4-hour hemodialysis (designated Group 5.2), and one dose equivalent to 75-mg solriamfetol on day 8 without hemodialysis (designated Group 5.1). All doses were administered on an empty stomach following an overnight fast except for participants in Group 5, who received a standardized snack on day 7 and breakfast early on day 8 before starting an 8-hour fast. Participants remained fasting for 4 hours after administration, with water allowed except for 1 hour before and after dosing.

In this study, 75 mg solriamfetol was selected as the dose for administration in participants with renal impairment as it was considered sufficiently low and potentially safe for this population. The 75-mg dose was expected to result in plasma concentrations of solriamfetol that were above the assay detection level at time points sufficient to characterize the PK profile.

Serial blood samples of approximately 4 mL were collected within 30 minutes prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-dose in Groups 1-3, with continued sampling at 60 and 72 hours post-dose in Groups 4 and 5. All blood samples were collected into labeled K_2EDTA tubes by direct venipuncture or indwelling catheter and kept on ice until the samples were centrifuged within 30 minutes of collection at approximately 2500 rpm (1315×g) at 4° C. for 10 minutes. The plasma was transferred into polypropylene tubes for freezing and storage at −70° C. until analysis.

Urine samples were collected predose and for the time intervals of 0-4, 4-8, 8-12, 12-24, and 24-48 hours in Groups 1-3, with additional collection for the 48-72 hour time interval in Groups 4 and 5. During the hemodialysis period on day 1 for Group 5, dialysate samples and pre- and post-dialyzer paired blood samples were collected at predialysis (2 hours), and at 3, 4, 5, and 6 hours following dosing. Urine and dialysate samples were aliquoted into polypropylene tubes for freezing and storage at −70° C. until analysis. All blood, urine, and dialysate samples were shipped on dry ice to a central bioanalytical laboratory.

Bioanalytical analyses were performed by a central laboratory (KCAS, LLC, Shawnee, Kansas) using validated proprietary methods that included extraction/derivatization and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Measurement of solriamfetol was over the linear range of 8.42 to 4,210 ng/mL in plasma, 0.21 to 84.2 μg/mL in urine, and 1.68 to 842 ng/mL in dialysate. Solriamfetol was removed from dialysate samples with use of the Fresenius Optiflux F180NR dialyzer (Fresenius Medical Care, Waltham, Massachusetts). Assay performance was monitored by spiking blank interference free human plasma with positive controls and internal standards to generate standard curve and quality control samples. After derivatization, samples were chromatographed on a C8 reversed phase analytical HPLC (high-performance liquid chromatography) column, with subsequent monitoring using an API4000 LC-MS/MS unit (Sciex, Framingham, Massachusetts). Quantification was based on setting a calibration graph using the internal standard method. Coefficients of variation (CVs) for quality control samples were 3.2% to 6.0% for the plasma samples, 1.6% to 5.6% for the urine samples, and 3.5% to 7.1% for the dialysate samples.

The following plasma PK parameters were evaluated using non-compartmental analysis in Phoenix® WinNonlin® Version 6.3: C_{max}; time to reach C_{max} following drug administration (tmax); tv2; area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_t); AUC from time zero to infinity (AUC_∞); apparent total clearance of the drug from plasma after oral administration (CL/F); and apparent volume of distribution (V_d/F). The PK parameters for solriamfetol in urine included the amount of unchanged drug excreted in urine (Ae) over 48 or 72 hours; the fraction of the dose excreted unchanged in urine (Fe); and renal clearance of the drug (CLR). For participants on hemodialysis (Group 5), the additional PK parameters included the amount of solriamfetol cleared by the 4-hour hemodialysis (A_{dial}); the fraction of dose removed by the 4-hour hemodialysis (F_{dial}); and hemodialysis clearance (CL_{dial}) calculated as $CL_{dial}=A_{dial}/AUC_{dial}$ where AUC_{dial} is the area under the pre-dialyzer plasma concentration-time curve during the hemodialysis period.

PK parameters were summarized by group using descriptive statistics. To assess differences in PK between each level of renal impairment (Groups 2-5) versus participants with normal renal function (Group 1), a linear effects model was used to compare natural log-transformed PK parameters (C_{max}, AUC_t, and AUC_∞). For Group 5, the participants without dialysis on day 8 (Group 5.1) and the participants who received dialysis on day 1 (Group 5.2) were analyzed and compared separately.

Point estimates and 90% confidence intervals (CIs) for differences on the natural log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. The 90% CIs around the geometric means ratios were presented for each pairwise comparison and expressed as a percentage relative to the geometric means of the reference group (Group 1). The inter-participant CV was estimated. To evaluate effects of dialysis on PK parameters for Group 5, an analysis of variance model was used that included "Day" as a fixed effect and measurements within the participant as a repeated measure. Day 8 was used as the reference for comparison. In addition, nonparametric analysis was conducted for tmax as appropriate.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of the 31 participants who were enrolled and received treatment (6 participants in each of Groups 1 through 4 and

7 participants in Group 5), 30 participants (97%) completed the study. One participant from Group 5 discontinued due to adverse events. Participant demographics (Table 1) show that most participants in Groups 1-4 were white; however, most participants in Group 5 were black. There were at least 2 participants per sex in each group, and mean age for Groups 1, 2, 3, and 4 were comparable with an overlap in the range; the age range in Group 5 was lower than in the other groups. Mean BMI for Groups 1, 2, 3, 4, and 5 were comparable, with an overlap in the range. Furthermore, all participants in Group 1 matched the mean age (±10 years) and BMI (±20%) of participants in Groups 2-5.

TABLE 1

Demographic Characteristics of the Study Population

Variable	Group 1 Normal renal function (n = 6)	Group 2 Mild renal impairment (n = 6)	Group 3 Moderate renal impairment (n = 6)	Group 4 Severe renal impairment (n = 6)	Group 5 End-stage renal disease (n = 7)
Sex, n (%)					
Female	3 (50)	4 (67)	2 (33)	2 (33)	2 (29)
Male	3 (50)	2 (33)	4 (67)	4 (67)	5 (71)
Race, n (%)					
White	5 (83)	5 (83)	4 (67)	5 (83)	1 (14)
Black	1 (17)	1 (17)	2 (33)	1 (17)	6 (86)
Ethnicity, n (%)					
Non-Hispanic or Latino	0	3 (50)	2 (33)	3 (50)	6 (86)
Hispanic or Latino	6 (100)	3 (50)	4 (67)	3 (50)	1 (14)
Age, mean (SD), y	55.8 (3.9)	67.8 (7.4)	70.2 (7.7)	59.7 (15.6)	42.0 (7.6)
Weight, mean (SD), kg	73.1 (6.8)	67.1 (14.2)	76.8 (11.5)	85.5 (16.4)	88.2 (10.5)
BMI, mean (SD), kg/m2	28.1 (2.7)	25.1 (4.1)	28.8 (1.9)	29.3 (3.0)	29.9 (3.0)
eGFR, mean (SD), mL/min/1.73 m2	111.8 (32.3)	78.5 (8.4)	44.2 (6.2)	16.2 (5.8)	7.4 (4.8)

BMI = body mass index

For all study groups, mean PK parameters are summarized in Table 2 and mean plasma solriamfetol concentration-time profiles are shown in FIGS. **1**A and **1**B.

TABLE 2

Solriamfetol Pharmacokinetic Parameters by Level of Renal Function

	Mean ± standard deviation (% coefficient of variation)					
	Normal renal function	Renal impairment			End-stage renal disease (Group 5)	
					Group 5.1	Group 5.2
Variable	Group 1 (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Without hemodialysis[a] (n = 6)	With hemodialysis (n = 7)[b]
C_{max}, ng/ml	499.0 ± 142.4 (28.5)	521.8 ± 118.8 (22.8)	517.3 ± 131.6 (25.4)	552.8 ± 154.4 (27.9)	474.1 ± 79.0 (16.7)	396.4 ± 75.4 (19.0)
t_{max},[c] h	1.3 (0.5, 2.0)	1.5 (0.5, 2.0)	1.5 (1.0, 2.5)	2.0 (0.5, 3.0)	3.3 (1.0, 24.0)	1.5 (1.5, 10.0)
$t_{1/2}$, h	7.6 ± 5.1 (67.7)	9.1 ± 1.6 (18.1)	14.3 ± 4.5 (31.4)	29.6 ± 14.4 (48.7)	100.5 ± 78.8 (78.4)[d]	164.7 ± 81.4 (49.4)[e]
AUC_t, ng · h/mL[f]	4849 ± 3454 (71.2)	6613 ± 1574 (23.8)	9230 ± 2538 (27.5)	17 500 ± 9267 (52.9)	25 580 ± 4544 (17.8)	18 920 ± 3131 (16.5)
AUC_∞, ng · h/mL	5273 ± 4104 (77.8)	6836 ± 1730 (25.3)	10 470 ± 3642 (34.8)	23 650 ± 16 776 (70.9)	64 560 ± 35 962 (55.7)[d]	76 770 ± 41 993 (54.7)[e]
CL/F, L/h	19.8 ± 10.1 (50.9)	11.5 ± 2.5 (22.1)	7.8 ± 2.4 (30.5)	4.7 ± 2.8 (59.4)	1.6 ± 1.1 (72.3)[d]	1.5 ± 1.3 (91.0)[e]
V_d/F, L	163.9 ± 23.8 (14.5)	147.2 ± 29.1 (19.8)	152.0 ± 32.6 (21.4)	157.2 ± 41.2 (26.2)	153.6 ± 45.6 (29.7)[d]	231.4 ± 28.5 (12.3)[e]

[a]Baseline adjusted to remove the impact of the day 1 dose on the day 8 concentration profile.
[b]Excluding 2 concentration values: 1 participant at predose, and 1 participant at 24 hours.
[c]For t_{max}, median (min, max) is presented.
[d]n = 3.
[e]n = 6.
[f]Over 48 h for normal, mild, and moderate, and over 72 h for severe.

In general, mean C_{max} and tmax were not substantially affected by renal impairment across Groups 1-4 (Table 2). However, solriamfetol AUC and $t_{1/2}$ values increased with increasing levels of renal impairment. Solriamfetol mean±SD overall exposure (AUC_∞) increased from 5273+4104 ng·h/mL in participants with normal renal function to 6836 ng·h/mL+1730 in Group 2 (mild impairment), 10,470±3642 in Group 3 (moderate impairment), and 23,650±16,776 in Group 4 (severe impairment) (Table 2). Similarly, solriamfetol mean±SD $t_{1/2}$ was 7.6±5.1 hours in participants with normal renal function and increased with greater levels of renal impairment: 9.1±1.6, 14.3±4.5, and 29.6±14.4 hours in Groups 2, 3, and 4, respectively (Table 2). While CL/F decreased with greater levels of renal impairment, there were no substantial changes in V_d/F (Table 2). A plot of solriamfetol CL/F versus day −1 eGFR for Groups 1-4 is presented in FIG. **2**. This relationship is best described by the equation: solriamfetol CL/F (L/h) =0.63184+0.16463×eGFR (mL/min/1.73 m^2).

Among participants with ESRD (Group 5), overall exposure (AUC_t) was approximately 5-fold higher for participants without dialysis on day 8 (Group 5.1; 25 580+4544 ng·h/mL) and about 4-fold higher among participants with dialysis on day 1 (Group 5.2; 18 920±3131) relative to Group 1 (4849±3454) (Table 2). Mean $t_{1/2}$ values exceeded 100 hours in both Group 5.1 (100.5 hours) and Group 5.2 (164.7 hours) (Table 2), and compared with Group 1, C_{max} values were slightly lower and tmax values differed significantly ($P \leq 0.05$ for both).

Ratios of geometric means and their associated 90% CIs for the pairwise comparisons of solriamfetol plasma PK parameters for Groups 2 through 5 versus Group 1 are presented in Table 3.

TABLE 3

Comparisons of Solriamfetol Plasma PK Parameters

PK parameter	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)[a]
Geometric LS mean						
Cmax, ng/ml	482.3	510.5	503.2	533.0	468.8	389.9
AUCt, ng · h/mL[b]	4087.3	6469.6	8960.2	15 549	25 253	18 689
AUC∞, ng · h/mL	4363.9	6672.4	10002	19 140	56 319[c]	65 306[d]
Percent ratio (90% confidence interval) of geometric mean relative to Group 1						
Cmax	—	105.9 (80.6, 139.0)	104.3 (78.4, 138.9)	110.5 (81.1, 150.6)	97.2 (76.1, 124.1)	80.9 (63.4, 103.1)
AUCt	—	158.3 (97.5, 256.9)	219.2 (133.7, 359.6)	380.4 (208.4, 694.4)	617.8 (385.3, 990.8)	457.2 (296.6, 704.9)
AUC∞	—	152.9 (92.9, 251.7)	229.2 (135.6, 387.4)	438.6 (217.3, 885.3)	1290.6 (542.78, 3068.5)	1496.5 (748.7, 2991.2)

Notes:

Parameters were ln-transformed prior to analysis. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the analysis of variance. % mean ratio = 100*(test/reference).

[a]Excluding 2 concentration values: 1 participant at predose, and 1 participant at 24 hours.

[b]Over 48 hours for Groups 1-3 and over 72 hours for Groups 4 and 5.

[c]n = 3.

[d]n = 6.

As shown, small increases were observed in C_{max}, which was approximately 6%, 4%, and 11% higher in Groups 2, 3, and 4, respectively, versus Group 1. However, total solriamfetol exposure (AUC_∞) in Groups 2, 3, and 4 was 53%, 129%, and 339% higher, respectively, relative to Group 1. In participants with ESRD, C_{max} was approximately 3% and 19% lower in groups 5.1 (ESRD without hemodialysis) and 5.2 (ESRD with hemodialysis), respectively, versus Group 1, and exposure was approximately 518% and 357% higher in the 2 groups versus Group 1.

Renal clearance (CLR) and the cumulative amount of solriamfetol excreted in urine decreased as renal impairment increased (Table 4).

TABLE 4

Urinary Excretion of Solriamfetol

PK parameter	Group 1 Normal renal function (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)
	Mean ± standard deviation (% coefficient of variation)			
$F_{e(0-48)}$, %	85.8 ± 7.7 (9.0)	80.0 ± 9.0 (11.2)	66.4 ± 12.8 (19.2)	57.1 ± 18.6 (32.5)
CL_R, L/h	17.0 ± 7.7 (45.4)	9.3 ± 1.6 (17.1)	5.8 ± 2.0 (34.1)	3.8 ± 2.6 (68.0)

CL_R, renal clearance; $F_{e(0-48)}$, fraction of the dose excreted unchanged in urine in 48 hours.

In Group 1, the mean±SD percentage of solriamfetol recovered unchanged in urine over 48 hours was 85.8%±7.7% and decreased to 80.0%±9.0%, 66.4%±12.8%, and 57.1%±18.6% in Groups 2, 3, and 4, respectively. Mean solriamfetol renal clearance also decreased with renal impairment, from 17.0±7.7 L/h in the normal renal function group to 9.3±1.6 L/h in Group 2, 5.8±2.0 L/h in Group 3, and 3.8±2.6 L/h in Group 4. Only 1 participant made urine and

was able to provide data in Group 5, and the cumulative amount of solriamfetol excreted in urine was lower with hemodialysis, 42.1%, compared with 52.9% without hemodialysis.

Over the 4-hour hemodialysis period on day 1 for participants with ESRD, the mean±SD cumulative fraction of the 75-mg solriamfetol dose removed was 20.6%±1.7% (range 19.2% to 24.1%), and the hemodialysis clearance was 12.4 L/h±1.5 L/h (range 11.3 to 15.9 L/h).

There were no deaths or other serious AEs during this study. A total of 4 participants (13%), 1 each in Groups 2 and 3, and 2 in Group 5 (1 with and 1 without hemodialysis), reported 5 treatment-emergent adverse events (TEAEs; Table 5). This includes single events of nausea, skin abrasion, and headache in 1 participant each, and an increase in alanine aminotransferase (ALT; to 144 IU/L; reference range 8-54 IU/L) and aspartate aminotransferase (AST; to 66 IU/L; reference range 8-40 IU/L) observed 6 days after dosing in 1 participant that led to discontinuation. All TEAEs were considered by the investigator to be mild, and all but the skin abrasion were considered to be related to study drug. All TEAEs resolved, including the increased ALT and AST, which resolved on day 11. No other abnormal laboratory findings were considered clinically meaningful. No clinically significant abnormal findings were observed in vital sign and ECG measurements.

TABLE 5

Number (%) of Participants with Treatment-Emergent Adverse Events (TEAEs)

	Normal renal function	Renal impairment			End-stage renal disease (Group 5)	
					Group 5.1	Group 5.2
Adverse event	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Without hemodialysis (n = 6)	With hemodialysis (n = 7)
Any TEAE	0	1 (17%)	1 (17%)	0	1 (17%)	1 (14%)
Nausea	0	0	0	0	1 (17%)	0
Skin abrasion	0	1 (17%)	0	0	0	0
ALT increased	0	0	0	0	0	1 (14%)
AST increased	0	0	0	0	0	1 (14%)
Headache	0	0	1 (17%)	0	0	0

[a]One participant from Group 5 discontinued the study before day 8 due to adverse events of mild elevated ALT and AST.

ALT, alanine aminotransferase;

AST, aspartate aminotransferase;

TEAE, treatment-emergent adverse event.

This study showed that renal impairment increases overall exposure to solriamfetol, with the magnitude of the increase reflecting the level of impairment. The incremental decreases in CL/F with worsening renal function resulted in corresponding increases in overall solriamfetol exposure that was 53% for mild, 129% for moderate, and 339% for severe impairment relative to normal renal function. Increasing renal impairment was also associated with decreasing cumulative percent of solriamfetol excreted in urine. The mean percentage of solriamfetol dose recovered in urine as unchanged drug over 48 hours was 85.8%, 80.0%, 66.4% and 64.0% (over 72 hours) for subjects with normal renal function and for subjects with mild, moderate, and severe renal impairment, respectively. Additionally, since there were no substantial changes in V_d/F, the decreases in solriamfetol CL/F resulted in increased $t_{1/2}$ by approximately 1.2-, 1.9-, and 3.9-fold in participants with mild, moderate, and severe renal impairment, respectively, compared with participants with normal renal function. In this regard, it should also be noted that while C_{max} values were not substantially affected by renal impairment, the observed increases in $t_{1/2}$ associated with renal impairment are expected to translate to changes in steady-state C_{max} that are not fully accounted for by the single-dose regimen evaluated in this clinical study, due to accumulation. AUC and $t_{1/2}$ values increased with increasing levels of renal impairment. Solriamfetol $AUC_{0\text{-}inf}$ was higher by approximately 53% (1.53-fold), 129% (2.29-fold), and 339% (4.39-fold) compared with subjects with normal renal function.

Consistent with the inability of ESRD participants requiring hemodialysis to eliminate solriamfetol via renal excretion, these participants had increased overall exposure to solriamfetol (≥4-fold), longer $t_{1/2}$ values (≥13-fold), and slightly lower C_{max} values (≤19%), relative to participants with normal renal function. Furthermore, ESRD participants had lower solriamfetol C_{max} and AUC_t values after undergoing a 4-hour hemodialysis session, with 20.6% of the solriamfetol dose removed as unchanged drug. Notably, the solriamfetol hemodialysis clearance of 12.4 L/h estimated from solriamfetol recovered in the dialysate was approximately 30% lower than solriamfetol renal clearance in participants with normal renal function.

Example 2: Simulations of Solriamfetol Exposure in Patients with Renal Impairment

Methods

A population PK model was developed based on data collected in clinical studies. The population PK model provides a unified characterization of solriamfetol and of its sources of variability across studies and sub-populations of subjects. The population PK analysis examined the influence of potential covariates that have not been evaluated in clinical trials, such as potential differences between narco-

lepsy and OSA patients, as well as healthy subjects and narcolepsy/OSA patients, and investigated other factors such as age, gender, body weight, race/ethnicity, and formulation effects.

The following thorough evaluation of the source data was performed: (1) Visual inspection of individual plasma concentration-time profiles of solriamfetol relative to actual dosing history (e.g., spaghetti plots for rich concentration-time profiles, mean profiles); (2) Evaluation of potential outliers based on preliminary population PK runs (e.g., using a one compartment model without covariate); and (3) Review of demographic data and baseline characteristics for each study.

The dataset included actual time of observation (sampling and dosing) and main demographic characteristics (covariates) such as age, weight, height, body mass index (BMI), gender, race and markers of renal and liver functions. Extrinsic covariates were also included. The following main variables were included in the analysis dataset.

- NMID (unique individual identifier)
- STUDY (study identifier)
- SUBJ (subject ID used in the study)
- DATE (date of the event MM/DD/YYYY)
- TIME (time of the event HH:MM)
- DV (plasma concentration of solriamfetol, ng/mL)
- AMT (actual dose of solriamfetol in mg, calculated based on free base weight)
- EVID (event identification for PK observations only: 0=non-below the limit of quantification [BLQ] PK observation, 1=dose administration, 2=other-type event [BLQ PK records])
- MDV (missing data code: 0=non-missing, 1=missing data or excluded data)
- BLQ (1=BLQ concentration, 0=non-BLQ concentration or dosing event)
- FAST (fasted status during administration: 1=fasted; 0=fed)
- FORM (formulation: 0=drug substance in capsule; 1=tablet; 2=over-encapsulated tablet)
- Daily dose (actual dose of solriamfetol in mg, calculated based on free base weight)
- DS (disease status: 0=healthy subjects, 1=subjects with narcolepsy; 2=subjects with OSA)
- WT (body weight at screening in kg)
- Age at baseline (age in years)
- Age as a categorical covariate (i.e., non-elderly vs. elderly ≥65 years old)
- Race (White, Black, Asian, Native Hawaiian or other Pacific Islander, Hispanic, Oriental, other)
- Ethnicity (1=Hispanic or Latino, 0=non-Hispanic or Latino)
- Gender (0=female, 1=male)
- TAD (time after previous dose in h)
- VISIT (visit number)
- NTIME (nominal time after the dose in hours)
- CRCL at baseline (creatinine clearance in m/min calculated by Cockcroft-Gault formula) (Cockcroft D W, Gault M H: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41)
- eGFR at baseline
- Renal impairment status based on Food and Drug Administration (FDA) guidance10:
  - Normal: eGFR ≥90 mL/min/1.73 m^2
  - Mild: eGFR 60-89 mL/min/1.73 m^2 (i.e., ≥60 to <90)
  - Moderate: eGFR 30-59 mL/min/1.73 m^2 (i.e., ≥30 to <60)
  - Severe: eGFR 15-29 mL/min/1.73 m^2 (i.e., ≥15 to <30) and not on hemodialysis
  - End-stage renal disease (ESRD): eGFR <15 mL/min/1.73 m^2 and not on hemodialysis or patients on hemodialysis
- HT (height in m)
- BMI at baseline (body mass index in kg/m^2)
- BSA at baseline (body surface area, calculated by Dubois and Dubois formula) (DuBois D; DuBois
  - EF: A formula to estimate the approximate surface area if height and weight be known. Arch Int Med 1916 17:863-71)
- ALT at baseline (alanine aminotransferase in U/L)
- AST at baseline (aspartate aminotransferase in U/L)
- ALB at baseline (albumin in g/L)
- Bioanalytical method (High performance liquid chromatography [HPLC] or Liquid chromatography-tandem mass spectrometry [LC-MS/MS]).

Base Population PK Model Buildup

In a first step, compartmental PK models without covariates were evaluated to assess the PK of solriamfetol. One and two-compartment models with linear disposition were tested to assess the concentration-time profiles of solriamfetol.

Model Buildup

The population PK model included the following.

1. A structural component describing the relationships between plasma concentration and time using the following equation:

$$Cp_{ij}=C(D_i,t_j,\theta_i)\cdot(1+\varepsilon_{p,ij})+\varepsilon_{\alpha,ij}$$

$$\theta_i=(\theta_{i1},\ldots,\theta_{ip})$$

wherein Cp_{ij} is the concentration at the j^{th} collection time t; for subject i, Di represents dosing history for subject i, ϑ_i is the vector of p different PK parameters for subject i, and $\varepsilon_{p,ij}$ and $\varepsilon_{\alpha,ij}$ are the proportional and additive random residual error terms, respectively, associated with jth concentration for subject i. ε_p and ε_a are normally distributed with mean 0 and variances $\sigma_p 2$ and $\sigma_\alpha{}^2$, respectively.

2. A variance component characterizing between-subject variability (BSV) and, if required, inter-occasion variability (IOV) in model parameters.

$$\theta_{ink}=(\theta_{TV,n}e^{(\eta_{lin}+\psi_{ink})})$$

$$(\eta_1,\ldots,\eta_p)=MVN(0,\Omega)$$

$$\psi_{nk}=N(0,\Phi_n)$$

where θ_{ink} is the value of the n^{th} PK parameter of the ith individual on the kth occasion, $\theta_{TV,n}$ is the typical value of the nth PK parameter in the population, r/in is the random inter-individual deviation from the typical value $\theta_{TV,n}$ for subject i, and «$_{ink}$ is the random inter-occasion subject deviation from the value of the nth parameter for subject i on occasion k. Inter-individual random effects (η_1, . . . , η_m), also known as ETAs, are multivariate normally distributed with mean 0 and estimated variance $\omega_n{}^2$ included in the variance-covariance OMEGA (Ω) matrix. Inter-occasion random effects for the nth parameter ψ_{nk} are normally distributed with mean 0 and variance Φ_n, with all ψ_{n1}, . . . , ψ_{nm} sharing the same variance, where m is the number of occasions.

The evaluation of the BSV/IOV models included possible addition of BSV terms (ETAs) to the model parameters, evaluation of the most appropriate form of the ETAs, and evaluation of pair-wise plots of the ETAs for any correlations. Covariance between ETA terms was estimated in the

model where correlations between ETAs were deemed probable based on these diagnostic plots. Models with shared ETA were also considered.

3. Error models describing residual unexplained variability in the form of additive, proportional or additive and proportional models:

$$y_{ij}=\hat{y}_{ij}*(1+\varepsilon_{ij})+\varepsilon_{2ij}$$

where y_{ij} and $\hat{y}_{ij}$ represent the jth observed and predicted plasma drug concentration for the ith participant and ε is the random residual variability. Each ε (ε_1 and ε_2) is normally distributed with mean 0 and variance σ^2. An allometric function accounting for body weight effect on clearance (CL/F) and volume of distribution (V/F) was included in the model. In addition, the effect of creatinine clearance was added on CL/F since the drug was previously demonstrated to undergo important renal excretion.

Model Evaluation

Consistent with the FDA/EMA Guidance for Industry, evaluation of the models was based on the following.

- Standard model diagnostics and standard statistical criteria of goodness-of-fit criteria such as the log-likelihood difference between alternative models (e.g., a decrease in the objective function value [OFV])
- Successful model convergence
- Examining pertinent graphical representations of goodness-of-fit:
  - Observed data versus population predicted data (DV vs. PRED) and individual predicted data (DV vs. IPRED) with a line of unity and a trend line, on linear and log scales
  - Observed Data versus time after the 1st dose and after the previous dose (DV vs. time and DV vs. TAD) with trend lines of DV and PRED, on linear and log scales
  - Conditional weighted residuals versus predicted data (CWRES vs. PRED) with zero line and a trend line
  - Conditional weighted residuals versus time after the 1st dose and previous dose [CWRES vs. time and CWRES vs. TAD] with zero line and a trend line
  - Quantile-quantile plot of CWRES (QQ plot)
- Estimating shrinkage of the empirical Bayesian estimates (EBEs) of the model parameters was evaluated for diagnostic purpose. The shrinkage magnitude for a structural parameter 0 (i-shrinkage) was calculated as follow:

$$sh_\theta = 1 - \frac{SD(\eta_{EBE,P})}{\omega_\theta}$$

where $SD(\eta_{EBE,P})$ is the standard deviation of the individual EBEs for parameter P, ω_P is the model estimate of the standard deviation associated with parameter P. If no shrinkage in parameter P is present, the ratio between $SD(\eta_{EBE,P})$ and ω_P is unity, and shP becomes zero. Shrinkage reflects the degree of information available in the data to estimate the random effects independently, where a shrinkage of 100% reflects a case where there is no information at all on the random effect and all individual parameters revert back to the population estimate. Covariate effects may be interpreted with caution for PK parameters associated with high shrinkage (e.g., >30%), as the individual random effect estimates are expected to shrink towards zero.

Incorporation of Assay Conversion Factor

All plasma samples were assayed using an LC-MS/MS or an HPLC method. Exploratory analyses were performed to investigate potential differences in concentrations determined using the two different methods, and were used to guide further steps in model development, and whether or not an effect of assay was to be included as part of the base population PK model or the residual error model. As a consequence of the observed differences in concentrations due to use of the two different assay methodologies, an assay conversion factor (CF) was incorporated into the model to scale solriamfetol concentrations from HPLC assay to LC-MS/MS as per the following linear and nonlinear models:

$$\text{Linear } CF: C_{LC\text{-}MS/MS}=(C_{HPLC})\times CF$$

$$\text{Nonlinear } CF: C_{LC\text{-}MS/MS}=(C_{HPLC})^{CF}$$

In addition, different error models were considered for each assay. The CF was tested in the additive and proportional components of the error models. The selection of the final CF model was based on quality-of-fit using standard graphical representations of goodness-of-fit, including the diagnostic plots.

Sources of Variability and Covariate Analysis

The relationships between PK parameters and covariates were explored graphically to identify the covariates likely to affect the PK of solriamfetol. Scatter plots of the relationships between the random effect of PK parameters and continuous variables included LOESS lines, Pearson correlation coefficients, and the corresponding p-value for each relationship. Box plots were used to describe the relationship for categorical covariates. The investigated intrinsic factors included the following.

- Age at baseline (as a continuous covariate in years and/or categorical covariate [i.e., non-elderly (18-64) vs. elderly (≥65 years old)]). Covariate was tested on CL/F, V/F and Ka.
- Gender. Covariate was tested on CL/F and V/F.
- Measures of body size at baseline (i.e., body weight): Included in the base model on CL/F and V/F.
- Ethnic origin/Race. Covariates were tested on CL/F and V/F.
- Markers of renal function at baseline (based on creatinine clearance): Included in the base model on CL/F.
- Markers of liver function at baseline (ALB, ALT and AST). Covariates were tested on CL/F and V/F.

The investigated extrinsic factors included:

- Nominal dose levels of JZP-110. Covariate was tested on CL/F, V/F and Ka.
- Formulation (Over-encapsulated Tablet vs. Tablet vs. drug substance in Capsule). Covariate was tested on CL/F, V/F and Ka.
- Fasted status (i.e., fed vs. fasted). Covariate was tested on Tlag and Ka.
- Disease status. Covariate was tested on CL/F and V/F.
  - Healthy subjects
  - Subjects with narcolepsy
  - Subjects with OSA

In the next step, the most relevant covariates were formally evaluated within the population PK model using a stepwise forward additive approach using a p-value of 0.01 (ΔOFV=6.63, for one degree of freedom [df]) and a backward elimination approach using a p-value of 0.001 (ΔOFV=10.83, for one df).

In addition, a nonparametric bootstrap resampling analysis was performed. The bootstrap technique involves repeatedly drawing random samples from the original data, with replacement. The bootstrap was used to reduce the model by removing covariates for which the 95% prediction interval (PI) included the null value relative to the reference popu-

lation. Statistically significant covariates identified during the covariate analysis were displayed graphically in a forest plot. See, Menon-Andersen D, Yu B, Madabushi R, Bhattaram V, Hao W, Uppoor R S, Mehta M, Lesko L, Temple R, Stockbridge N, Laughren T, Gobburu J V. Essential pharmacokinetic information for drug dosage decisions: a concise visual presentation in the drug label. Clin Pharmacol Ther. 2011 September; 90(3):471-4.

Final Model

The final population PK model was evaluated using visual predictive check (VPC). Based on the estimates of the final model, concentration-time profiles were simulated using 1000 replicates. Observed and simulated data were separated into distinct bins. Within each bin, a 95% confidence interval of the 5th, 50th and 95th prediction intervals was obtained by simulation. The confidence intervals give an indication of the uncertainty of the predictions. The 5th, 50th and 95th percentiles of observed concentrations were compared to the 95% confidence intervals.

The final population PK model was used to simulate rich concentration-time profiles of solriamfetol in adult subjects with renal impairment (mild, moderate, severe, and ESRD) and in pediatric patients following administration of different dosing regimens.

The final population PK model was used to perform simulations in 10000 narcolepsy/OSA patients for each dose level of solriamfetol tablet formulation (37.5, 75, 150, and 300 mg), and exposure parameters (AUCtau, Cmax, Cmin, C14h and t½) were derived.

Descriptive statistics of exposure parameters for each dose level and according to each renal impairment category are presented in Tables 6-10. Boxplots of exposure parameters for each dose level and according to each renal impairment category are presented in FIGS. **3-7**. Simulated concentration-time profiles for each dose level and according to each renal impairment category are presented in Table 8.

TABLE 6

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Normal Renal Function

	Dose (mg)-Solriamfetol			
Parameters	37.5 (n = 10000)	75 (n = 10000)	150 (n = 10000)	300 (n = 10000)
	AUCtau (ng · h/mL)			
Mean (CV %)	1931 (34.4%)	4139 (34.4%)	8874 (34.4%)	19024 (34.4%)
Median	1822	3906	8382	17952
[Min, Max]	[471, 7671]	[1010, 16473]	[2165, 35375]	[4641, 75968]
Geom. Mean (Geom. CV %)	1825 (34.6%)	3912 (34.6%)	8387 (34.6%)	17980 (34.6%)
	Cmax (ng/ml)			
Mean (CV %)	202 (24.5%)	410 (24.6%)	835 (24.8%)	1702 (25.0%)
Median	197	399	811	1654
[Min, Max]	[79.1, 494]	[160, 1004]	[323, 2086]	[656, 4370]
Geom. Mean (Geom. CV %)	196 (24.5%)	398 (24.6%)	810 (24.8%)	1651 (25.0%)
	Cmin (ng/ml)			
Mean (CV %)	19.6 (78.9%)	46.7 (75.0%)	110 (71.5%)	259 (68.4%)
Median	15.8	38.3	92.2	219
[Min, Max]	[0.0290, 194]	[0.104, 432]	[0.362, 961]	[1.21, 2132]
Geom. Mean (Geom. CV %)	14.3 (108%)	35.0 (99.2%)	84.9 (92.1%)	204 (85.9%)
	C14h (ng/mL)			
Mean (CV %)	53.6 (50.3%)	120 (48.5%)	268 (46.9%)	595 (45.5%)
Median [Min, Max]	49.1 [1.21, 296]	111 [3.39, 642]	248 [9.32, 1390]	552 [25.1, 3007]
Geom. Mean (Geom. CV %)	47.1 (57.7%)	106 (54.7%)	240 (52.2%)	536 (50.0%)
	Half-life (h)			
Mean (CV %)	6.35 (30.7%)	6.81 (30.7%)	7.30 (30.7%)	7.82 (30.7%)
Median [Min, Max]	6.08 [1.71, 21.4]	6.52 [1.83, 22.9]	6.99 [1.96, 24.5]	7.50 [2.10, 26.3]
Geom. Mean (Geom. CV %)	6.08 (30.5%)	6.51 (30.4%)	6.98 (30.4%)	7.48 (30.5%)

AUCtau: Area under the concentration-time curve at steady state;
C14h: concentration at 14 h post-dose at steady state;
Cm ax: maximum concentration at steady state;
Cm in: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

TABLE 7

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Mild Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
			AUCtau (ng · h/mL)		
Mean (CV %)	8874 (34.4%)	2624 (34.3%)	5626 (34.2%)	12059 (34.2%)	25853 (34.2%)
Median	8382	2479	5320	11395	24428
[Min, Max]	[2165, 35375]	[721, 9598]	[1548, 20619]	[3321, 44294]	[7124, 95152]
Geom. Mean (Geom. CV %)	8387 (34.6%)	2482 (34.4%)	5321 (34.3%)	11407 (34.3%)	24453 (34.3%)
			Cmax (ng/ml)		
Mean (CV %)	835 (24.8%)	225 (24.8%)	461 (25.1%)	946 (25.3%)	1945 (25.6%)
Median	811	219	448	919	1890
[Min, Max]	[323, 2086]	[82.4, 550]	[167, 1158]	[338, 2444]	[686, 5171]
Geom. Mean (Geom. CV %)	810 (24.8%)	218 (24.8%)	447 (25.1%)	917 (25.3%)	1884 (25.6%)
			Cmin (ng/ml)		
Mean (CV %)	110 (71.5%)	39.8 (64.5%)	91.8 (61.9%)	211 (59.5%)	482 (57.4%)
Median	92.2	34.3	80.1	186	428
[Min, Max]	[0.362, 961]	[0.677, 289]	[2.06, 636]	[6.09, 1396]	[17.5, 3062]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	32.2 (77.9%)	75.7 (73.3%)	177 (69.3%)	409 (65.8%)
			C14h (ng/ml)		
Mean (CV %)	268 (46.9%)	84.9 (43.8%)	187 (42.6%)	411 (41.6%)	902 (40.8%)
Median	248 [9.32, 1390]	79.1 [8.46, 385]	175 [21.3, 830]	384 [52.6, 1791]	845 [128, 3861]
[Min, Max]					
Geom. Mean (Geom. CV %)	240 (52.2%)	77.2 (47.2%)	171 (45.6%)	378 (44.1%)	831 (42.9%)
			Half-life (h)		
Mean (CV %)	7.30 (30.7%)	8.67 (30.8%)	9.29 (30.7%)	9.96 (30.7%)	10.7 (30.7%)
Median	6.99	8.26	8.85	9.48	10.2
[Min, Max]	[1.96, 24.5]	[2.69, 26.1]	[2.88, 28.0]	[3.09, 30.0]	[3.31, 32.2]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	8.29 (30.4%)	8.89 (30.4%)	9.53 (30.4%)	10.2 (30.4%)

AUCtau: Area under the concentration-time curve at steady state;
C14h: concentration at 14 h post-dose at steady state;
Cm ax: maximum concentration at steady state;
Cm in: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

TABLE 8

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Moderate Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
			AUCtau (ng · h/mL)		
Mean (CV %)	8874 (34.4%)	3743 (36.6%)	8024 (36.6%)	17201 (36.5%)	36875 (36.5%)
Median	8382	3518	7539	16157	34617
[Min, Max]	[2165, 35375]	[777, 14484]	[1666, 31285]	[3570, 67577]	[7652, 145970]

TABLE 8-continued

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Moderate Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
Geom. Mean (Geom. CV %)	8387 (34.6%)	3517 (36.4%)	7540 (36.4%)	16164 (36.3%)	34651 (36.3%)
			Cmax (ng/mL)		
Mean (CV %)	835 (24.8%)	266 (26.8%)	550 (27.2%)	1139 (27.6%)	2366 (28.0%)
Median [Min, Max]	811 [323, 20861	255 [87.6, 810]	527 [179, 1712]	1093 [365, 3624]	2267 [748, 7684]
Geom. Mean (Geom. CV %)	810 (24.8%)	257 (26.4%)	531 (26.8%)	1099 (27.2%)	2280 (27.6%)
			Cmin (ng/ml)		
Mean (CV %)	110 (71.5%)	78.3 (57.9%)	177 (56.1%)	397 (54.5%)	888 (53.0%)
Median [Min, Max]	92.2 [0.362, 9611	69.6 [1.00, 434]	158 [2.86, 961]	356 [7.96, 2126]	801 [21.7, 4695]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	66.4 (65.6%)	151 (62.8%)	343 (60.2%)	774 (58.0%)
			C14h (ng/ml)		
Mean (CV %)	268 (46.9%)	135 (42.4%)	293 (41.7%)	638 (41.1%)	1385 (40.5%)
Median [Min, Max]	248 [9.32, 1390]	125 [9.10, 573]	273 [22.4, 1243]	594 [54.3, 26991	1294 [130, 5855]
Geom. Mean (Geom. CV %)	240 (52.2%)	123 (44.1%)	270 (43.1%)	588 (42.3%)	1281 (41.5%)
			Half-life (h)		
Mean (CV %)	7.30 (30.7%)	12.4 (32.6%)	13.2 (32.5%)	14.2 (32.5%)	15.2 (32.5%)
Median [Min, Max]	6.99 [1.96, 24.5]	11.8 [3.14, 40.31	12.6 [3.37, 43.2]	13.5 [3.61, 46.3]	14.5 [3.87, 49.7]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	11.8 (32.4%)	12.6 (32.4%)	13.5 (32.4%)	14.5 (32.4%)

AUCtau: Area under the concentration-time curve at steady state;
C14h: concentration at 14 h post-dose at steady state;
Cm ax: maximum concentration at steady state;
Cm in: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

TABLE 9

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Severe Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
			AUCtau (ng · h/mL)		
Mean (CV %)	8874 (34.4%)	5967 (36.9%)	12790 (36.8%)	27416 (36.8%)	58772 (36.8%)
Median [Min, Max]	8382 [2165, 35375]	5608 [1448, 20711]	12026 [3129, 44391]	25790 [6762, 95179]	55249 [14323, 205161]
Geom. Mean (Geom. CV %)	8387 (34.6%)	5602 (36.6%)	12009 (36.6%)	25744 (36.6%)	55188 (36.5%)
			Cmax (ng/mL)		
Mean (CV %)	835 (24.8%)	353 (29.3%)	738 (29.7%)	1546 (30.1%)	3243 (30.5%)
Median [Min, Max]	811 [323, 2086]	338 [116, 1014]	705 [240, 2150]	1475 [496, 4561]	3089 [1029, 9681]
Geom. Mean (Geom. CV %)	810 (24.8%)	339 (28.8%)	708 (29.2%)	1482 (29.6%)	3105 (30.0%)

TABLE 9-continued

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Severe Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000)	Dose 300 mg (n = 10000)
			Cmin (ng/ml)		
Mean (CV %)	110 (71.5%)	163 (49.6%)	360 (48.6%)	794 (47.6%)	1748 (46.8%)
Median	92.2	149	330	728	1608
[Min, Max]	[0.362, 961]	[15.8, 737]	[37.9, 1606]	[90.0, 3498]	[212, 7613]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	145 (52.5%)	322 (51.0%)	713 (49.7%)	1576 (48.6%)
			C14h (ng/ml)		
Mean (CV %)	268 (46.9%)	231 (39.7%)	498 (39.4%)	1076 (39.0%)	2322 (38.8%)
Median	248	216	468	1010	2178
[Min, Max]	[9.32, 1390]	[45.4, 841]	[101, 1816]	[226, 3919]	[498, 8460]
Geom. Mean (Geom. CV %)	240 (52.2%)	214 (40.1%)	464 (39.7%)	1002 (39.3%)	2164 (38.9%)
			Half-life (h)		
Mean (CV %)	7.30 (30.7%)	19.7 (33.1%)	21.1 (33.0%)	22.6 (33.0%)	24.2 (33.0%)
Median	6.99	18.7	20.0	21.5	23.0
[Min, Max]	[1.96, 24.5]	[5.21, 70.6]	[5.57, 75.7]	[5.96, 81.1]	[6.37, 86.9]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	18.7 (32.9%)	20.0 (32.9%)	21.5 (32.8%)	23.0 (32.8%)

AUCtau: Area under the concentration-time curve at steady state;
C14h: concentration at 14 h post-dose at steady state;
Cm ax: maximum concentration at steady state;
Cm in: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

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TABLE 10

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with ESRD

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	Dose 75 mg (n = 10000)	Dose 150 mg (n = 10000	Dose 300 mg (n = 10000)
			AUCtau (ng · h/mL)		
Mean (CV %)	8874 (34.4%)	25371(42.5%)	54399 (42.6%)	116645 (42.7%)	250132(42.7%)
Median	8382	23288	49948	107070	229500
[Min, Max]	[2165, 35375]	[5989, 136885]	[12737, 292530]	[27087, 625152]	[57605, 1335983]
Geom. Mean (Geom. CV %)	8387 (34.6%)	23394 (41.7%)	50152 (41.8%)	107514 (41.8%)	230486 (41.9%)
			Cmax (ng/ml)		
Mean (CV %)	835 (24.8%)	1153 (39.8%)	2456 (40.0%)	5234 (40.3%)	11162 (40.5%)
Median [Min, Max]	811 [323, 2086]	1065 [290, 5893]	2267 [617, 12563]	4827 [1310, 26789]	10282 [2786, 57133]
Geom. Mean (Geom. CV %)	810 (24.8%)	1074 (38.6%)	2286 (38.9%)	4868 (39.1%)	10373 (39.4%)
			Cmin (ng/ml)		
Mean (CV %)	110 (71.5%)	961 (45.7%)	2075 (45.6%)	4476 (45.4%)	9655 (45.3%)
Median [Min, Max]	92.2 [0.362, 961]	876 [183, 5509]	1891 [398, 11801]	4084 [862, 25275]	8816 [1866, 54124]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	875 (45.6%)	1889 (45.3%)	4079 (45.1%)	8803 (45.0%)

TABLE 10-continued

Simulations to Support Dosing in Sub-Populations-Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with ESRD

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000	300 mg (n = 10000)
		C14h (ng/ml)			
Mean (CV %)	268 (46.9%)	1045 (43.0%)	2243 (43.0%)	4814 (43.0%)	10333 (43.1%)
Median	248	958	2056	4413	9473
[Min, Max]	[9.32, 1390]	[236, 5689]	[505, 12161]	[1079, 25995]	[2304, 55566]
Geom. Mean (Geom. CV %)	240 (52.2%)	962 (42.3%)	2064 (42.2%)	4430 (42.3%)	9509 (42.3%)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	83.6 (38.1%)	89.7 (38.2%)	96.1 (38.3%)	103 (38.4%)
Median	6.99	77.9	83.4	89.6	95.9
[Min, Max]	[1.96, 24.5]	[20.8, 337]	[22.3, 363]	[23.9, 392]	[25.5, 422]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	78.1 (38.1%)	83.7 (38.2%)	89.8 (38.2%)	96.2 (38.3%)

AUCtau: Area under the concentration-time curve at steady state;
C14h: concentration at 14 h post-dose at steady state;
Cm ax: maximum concentration at steady state;
Cm in: concentration at 24 h post-dose at steady state;
CV %: coefficient of variation;
Min: minimum;
Max: maximum;
n: number of subjects.

Ratios were generated to facilitate the comparison across populations of patients with renal impairment in order to optimally match the exposure of the reference dose in adult patients with normal renal function (i.e., 150 mg). Ratios of AUC_{tau}, C_{max}, C_{min}, $C_{1\text{-}4h}$ and $t_{1/2}$ are presented in Table 11.

TABLE 11

Ratio of Mean Steady State PK Parameters of Solriamfetol in Patients with Renal Impairment (at different doses) Relative to Patients with Normal Renal Function (at 150 mg dose)

Sub-Population	Dose (mg)	Ratio Relative to Typical Patient with Normal Renal Function AUC_{tau}	C_{max}	$C_{14\,h}$	C_{min}	$t_{1/2}$
Mild Renal Impairment	300	2.91	2.33	3.37	4.38	1.47
	150	1.36	1.13	1.53	1.92	1.36
	75	0.63	0.55	0.70	0.83	1.27
	37.5	0.30	0.27	0.32	0.36	1.19
Moderate Renal Impairment	300	4.16	2.83	5.17	8.07	2.08
	150	1.94	1.36	2.38	3.61	1.95
	75	0.90	0.66	1.09	1.61	1.81
	37.5	0.42	0.32	0.50	0.71	1.70
Severe Renal Impairment	300	6.62	3.88	8.66	15.89	3.32
	150	3.09	1.85	4.01	7.22	3.10
	75	1.44	0.88	1.86	3.27	2.89
	37.5	0.67	0.42	0.86	1.48	2.70
ESRD	300	28.19	13.37	36.56	87.77	14.11
	150	13.1	6.27	18.0	40.7	13.2
	75	6.13	2.94	8.37	18.9	12.3
	37.5	2.86	1.38	3.90	8.74	11.5

AUC_{tau}: Area under the concentration-time curve at steady state;
C_{max}: maximum concentration at steady state;
$C_{14\,h}$: concentration at 14 h post-dose at steady state;
C_{min}: concentration at 24 h post-dose at steady state;
$t_{1/2}$: elimination half-life.

Based on the inventor's analyses of solriamfetol's pharmacokinetics and safety profile together with population PK simulations, it was discovered that, in patients with mild renal impairment, an equivalent dose used in patients with normal renal function was associated with comparable exposures. A 150 mg dose in patients with mild renal impairment is associated with AUC_{tau} and C_{max} values 36% and 13% higher than those observed in patients with normal renal function for the same dose. Typical $C_{1\text{-}4}$h and C_{min} values in a patient with mild renal impairment are expected to be approximately 1.5- and 2-fold higher than that observed in patients with normal renal function due to the longer tv2. Therefore, no dosage adjustments should be needed in patients with mild renal impairment and this subgroup of renally impaired patients can be safety administered at an initial daily dose equivalent to 75 mg of solriamfetol and escalating to a maximum daily dose equivalent to 150 mg of solriamfetol after at least 3 days, based on solriamfetol's elimination half-life.

In patients with moderate renal impairment, one-half of the dose used in patients with normal renal function was associated with comparable exposures. A 75 mg dose in patients with moderate renal impairment is associated with AUC_{tau} and C_{max} values 10% and 34% lower than those observed in patients with normal renal function at a 150 mg dose. Typical $C_{1\text{-}4h}$ and C_{min} values in a patient with moderate renal impairment is expected to be approximately 9% and 61% higher than that observed in patients with normal renal function due to the longer $t_{1/2}$. Therefore, dosing adjustments are warranted in patients with moderate renal impairment. The appropriate dose escalation regimen for this subgroup of renally impaired patients was determined by the present inventor to be an initial daily dose equivalent to 37.5 mg solriamfetol and escalating to a maximum daily

dose equivalent to 75 mg solriamfetol after at least five days to at least seven days, based on solriamfetol's elimination half-life.

In patients with severe renal impairment, one-quarter of the dose used in patients with normal renal function was associated with comparable exposures. A 75 mg dose in patients with severe renal impairment was associated with AUC_{tau} and C_{max} values 44% higher and 12% lower than those in patients with normal renal function at a 150 mg dose. Typical $C_{14}h$ and C_{min} following a 75 mg dose in patients with severe renal impairment is expected to be approximately 1.9- and 3-fold higher than that in patients with normal renal function. Therefore, it was determined that a 75 mg dose would not be appropriate for patients with severe renal impairment. Therefore, dosing adjustment is warranted in patients with severe renal impairment. A 37.5 mg dose in patients with severe renal impairment was associated with AUC_{tau} and C_{max} values 33% lower and 58% lower than those in patients with normal renal function at a 150 mg dose. Typical $C_{1\text{-}4h}$ and C_{min} values following a 37.5 mg dose in a patient with severe renal impairment are expected to be 14% lower and 48% higher than that in patients with normal renal function. Therefore, dosing adjustments is warranted in patients with severe renal impairment. The appropriate dose escalation regimen for this subgroup of renally impaired patients was determined by the present inventor to be a daily maximum dose equivalent to 37.5 mg of solriamfetol.

Based on the substantial increase in solriamfetol exposure in patients with ESRD, use of solriamfetol in this subpopulation should be avoided.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A method of treating excessive daytime sleepiness in a subject in need thereof, said method comprising:

selecting a subject for not having end stage renal disease;

determining the estimated glomerular filtration rate (eGFR) of the subject, and

(a) providing to the subject having excessive daytime sleepiness and an eGFR of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2:

a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of a dose escalation regimen, and

a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen,

wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1,

wherein the subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC; and

(b) providing to the subject having excessive daytime sleepiness and an eGFR of about 15 mL/min/1.73 m^2 to about 29 mL/min/1.73 m^2:

an oral daily dose equivalent to 37.5 mg APC;

wherein the subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC.

2. The method of claim **1**, wherein the excessive daytime sleepiness is due to narcolepsy.

3. The method of claim **1**, wherein the excessive daytime sleepiness is due to obstructive sleep apnea.

4. The method of claim **1**, wherein the excessive daytime sleepiness is due to shift work disorder.

5. The method of claim **1**, wherein the subject is provided said first oral daily dose or said oral daily dose in the form of about 44.7 mg APC-HCl.

6. The method of claim **1**, wherein the subject is provided said second oral daily dose in the form of about 89.3 mg APC-HCl.

7. The method of claim **1**, wherein said first oral daily dose, said second oral daily dose, and said oral daily dose are each administered upon the subject's awakening.

8. The method of claim **1**, wherein said first oral daily dose, said second oral daily dose, and said oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

9. The method of claim **1**, wherein the subject is a human.

10. The method of claim **1**, wherein the eGFR is determined using the Modification of Diet in Renal Disease equation.

11. The method of claim **1**, wherein n_1 is an integer equal to or greater than 7.

12. A method of treating excessive daytime sleepiness in a subject in need thereof, said method comprising:

selecting a subject for not having end stage renal disease;

determining the estimated glomerular filtration rate (eGFR) of the subject, and

(a) providing to the subject having excessive daytime sleepiness and an eGFR of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2:

a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of a dose escalation regimen, and

a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen,

wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1,

wherein the subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC;

(b) providing to the subject having excessive daytime sleepiness and an eGFR of about 15 mL/min/1.73 m^2 to about 29 mL/min/1.73 m^2:

an oral daily dose equivalent to 37.5 mg APC,

wherein the subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC; and

(c) providing to the subject having excessive daytime sleepiness and an eGFR of about 60 mL/min/1.73 m^2 to about 89 mL/min/1.73 m^2 or about 90 mL/min/1.73 m^2 or greater:

a first oral daily dose equivalent to 37.5 mg APC,

after at least 3 days a second oral daily dose equivalent to 75 mg APC, and

after at least 3 days a third oral daily dose equivalent to 150 mg APC,

wherein the subject is not provided a daily dose exceeding a dose equivalent to 150 mg APC.

13. The method of claim **12**, wherein the excessive daytime sleepiness is due to narcolepsy.

14. The method of claim **12**, wherein the excessive daytime sleepiness is due to obstructive sleep apnea.

15. The method of claim **12**, wherein the excessive daytime sleepiness is due to shift work disorder.

16. The method of claim **12**, wherein the subject is provided said first oral daily dose or said oral daily dose in the form of about 44.7 mg APC-HCl.

17. The method of claim **12**, wherein the subject is provided said second oral daily dose in the form of about 89.3 mg APC-HCl.

18. The method of claim **12**, wherein the subject is provided said third oral daily dose in the form of about 178.5 mg APC-HCl.

19. The method of claim **12**, wherein said first oral daily dose, said second oral daily dose, said third daily dose, and said oral daily dose are each administered upon the subject's awakening.

20. The method of claim **12**, wherein said first oral daily dose, said second oral daily dose, said third daily dose, and said oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

21. The method of claim **12**, wherein the subject is a human.

22. The method of claim **12**, wherein the eGFR is determined using the Modification of Diet in Renal Disease equation.

23. The method of claim **12**, wherein n_1 is an integer equal to or greater than 7.

* * * * *

EXHIBIT C

US011986455B2

(12) **United States Patent**
Zomorodi

(10) **Patent No.: US 11,986,455 B2**
(45) **Date of Patent: *May 21, 2024**

(54) **METHODS OF PROVIDING SOLRIAMFETOL THERAPY TO SUBJECTS WITH IMPAIRED RENAL FUNCTION**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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Assistant Examiner — Michael J Schmitt
(74) *Attorney, Agent, or Firm* — HUESCHEN AND SAGE

(57) **ABSTRACT**

The invention relates to methods for decreasing adverse effects associated with solriamfetol ([R]-2-amino-3-phenylpropylcarbamate) therapy in subjects with impaired renal function. In particular, the invention provides an optimized dose escalation scheme for subjects with moderate renal impairment which results in the subjects having increased tolerance to adverse effects associated with the administration of solriamfetol. The invention also provides adjusted dosing for safe therapeutic use of solriamfetol in subjects having severe renal impairment.

24 Claims, 9 Drawing Sheets

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2023/0310362	A1	10/2023	Zomorodi

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FIG. 1A

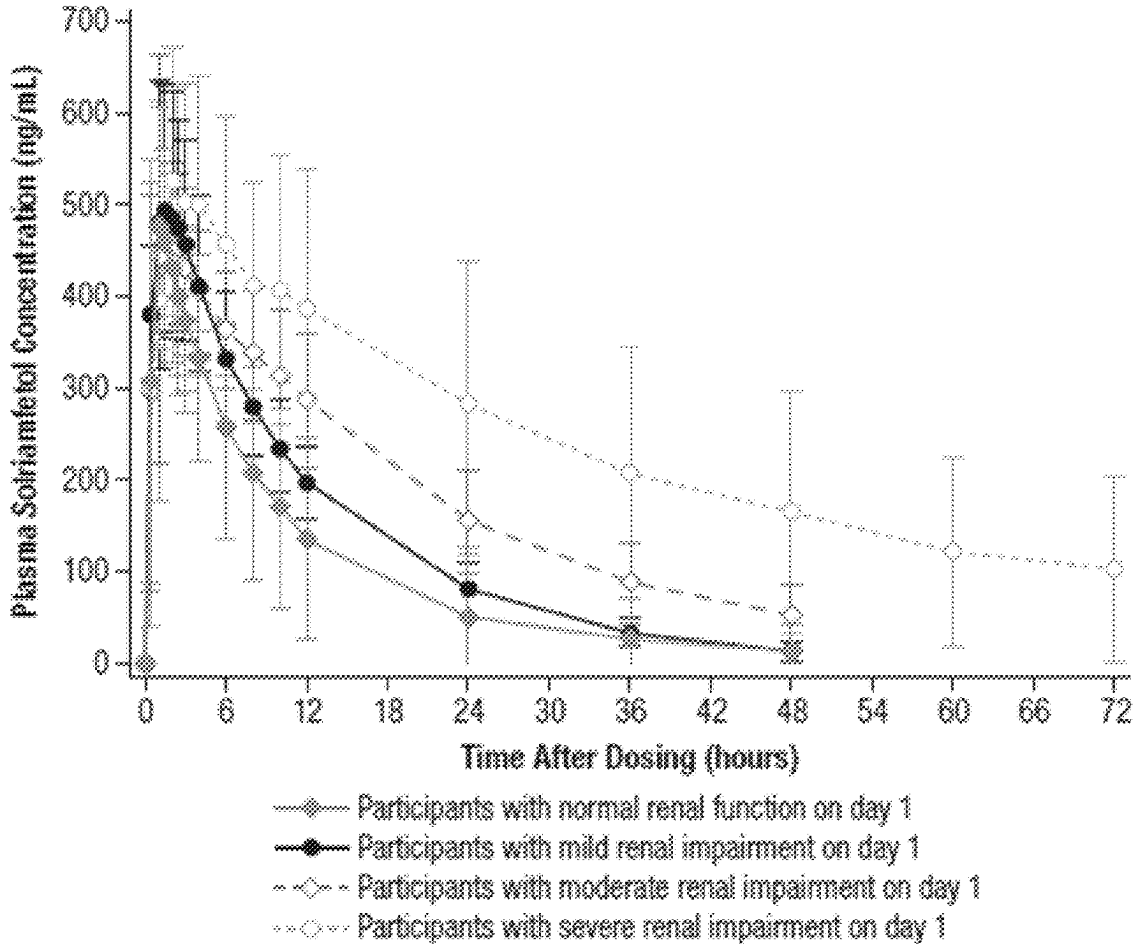

Plasma Sotrlamfetol Concentration (ng/mL)
700
600
500
400
300
200
100
0
0
6
12
18
24
30
36
42
48
54
60
66
72
Time After Dosing (hours)
Participants with normal renal function on day 1
Participants with mild renal impairment on day 1
Participants with moderate renal impairment on day 1
Participants with severe renal impairment on day 1

FIG. 1B

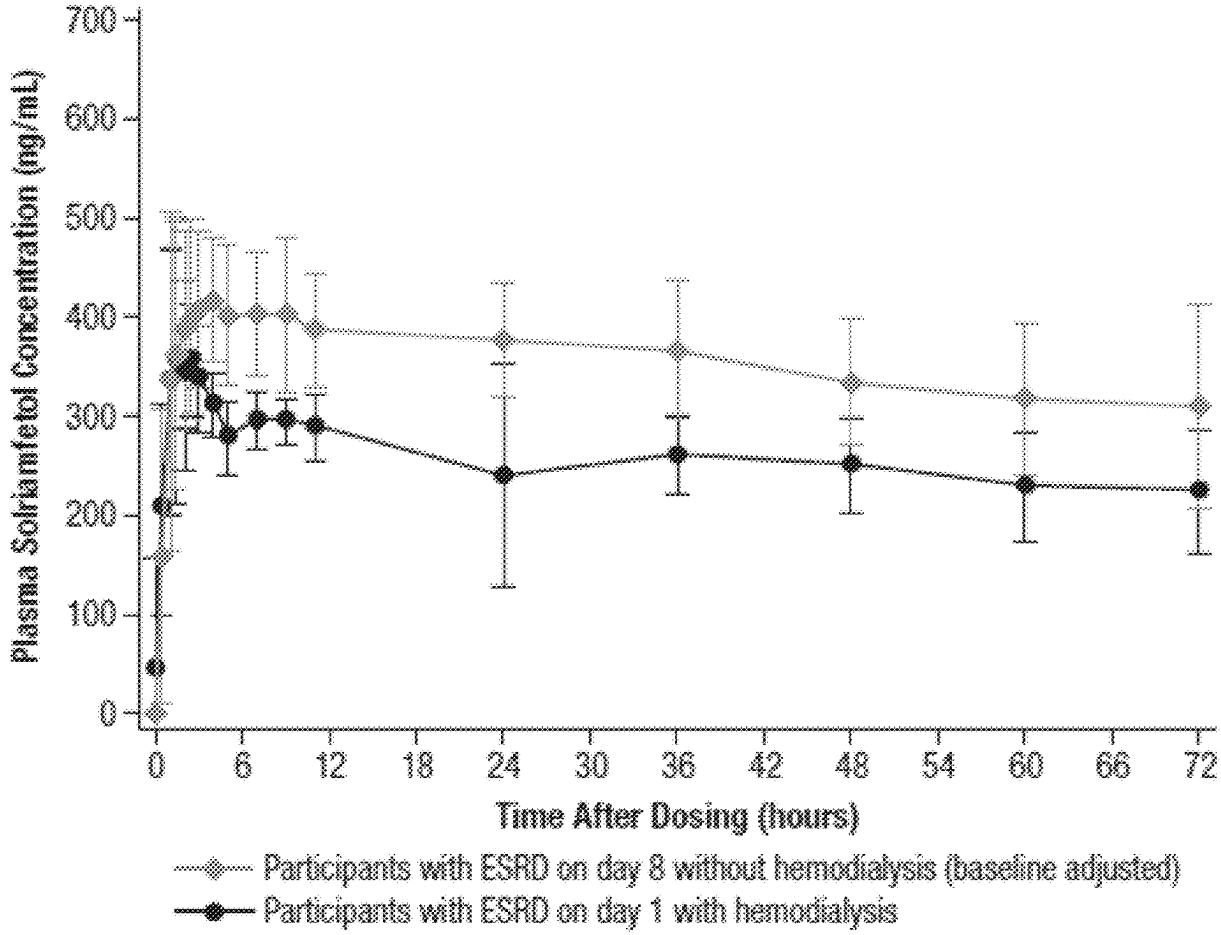
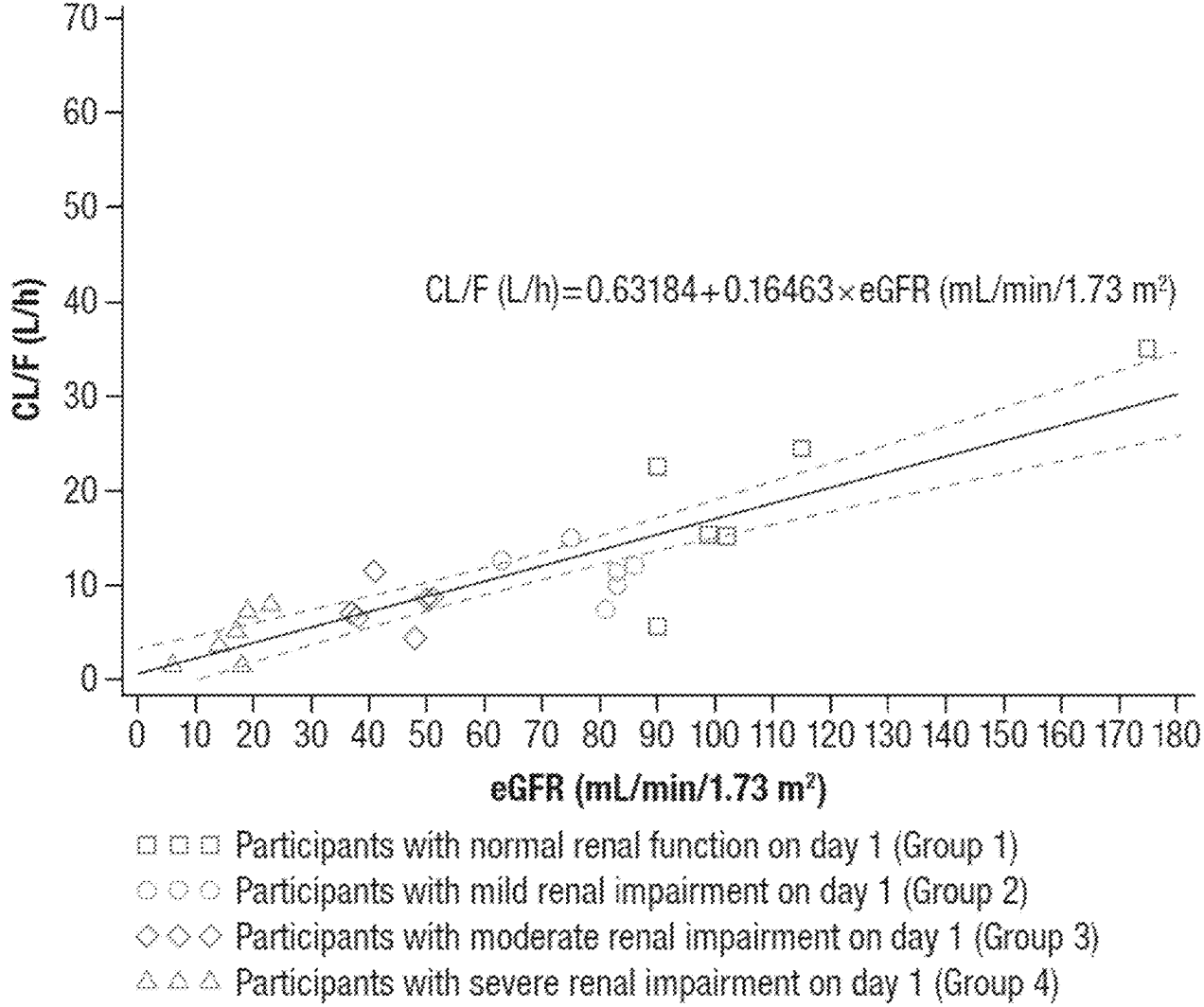

Plasma Soriamfetol Concentration (ng/mL)
700
600
500
400
300
200
100
0
0
6
12
18
24
30
36
42
48
54
60
66
72
Time After Dosing (hours)
Participants with ESRD on day 8 without hemodialysis (baseline adjusted)
Participants with ESRD on day 1 with hemodialysis

FIG. 2


CL/F (L/h)=0.63184+0.16463×eGFR (mL/min/1.73 m²)
CL/F (L/h)
eGFR (mL/min/1.73 m²)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
Participants with normal renal function on day 1 (Group 1)
Participants with mild renal impairment on day 1 (Group 2)
Participants with moderate renal impairment on day 1 (Group 3)
Participants with severe renal impairment on day 1 (Group 4)

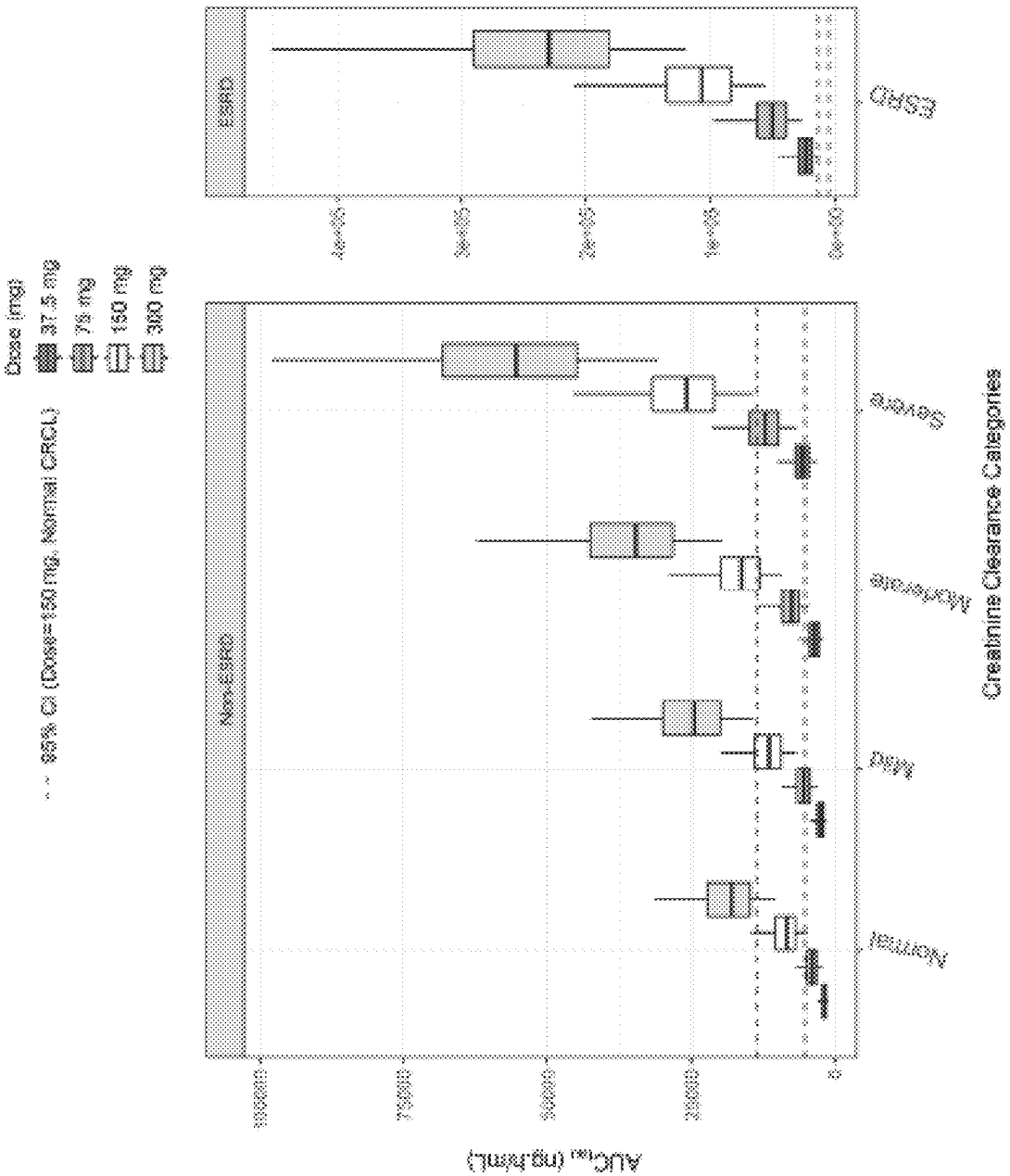

Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)
ESRD
Non-ESRD
Severe
Moderate
Mild
Normal
Creatinine Clearance Categories
AUC∞ (ng.h/mL)

FIG. 3

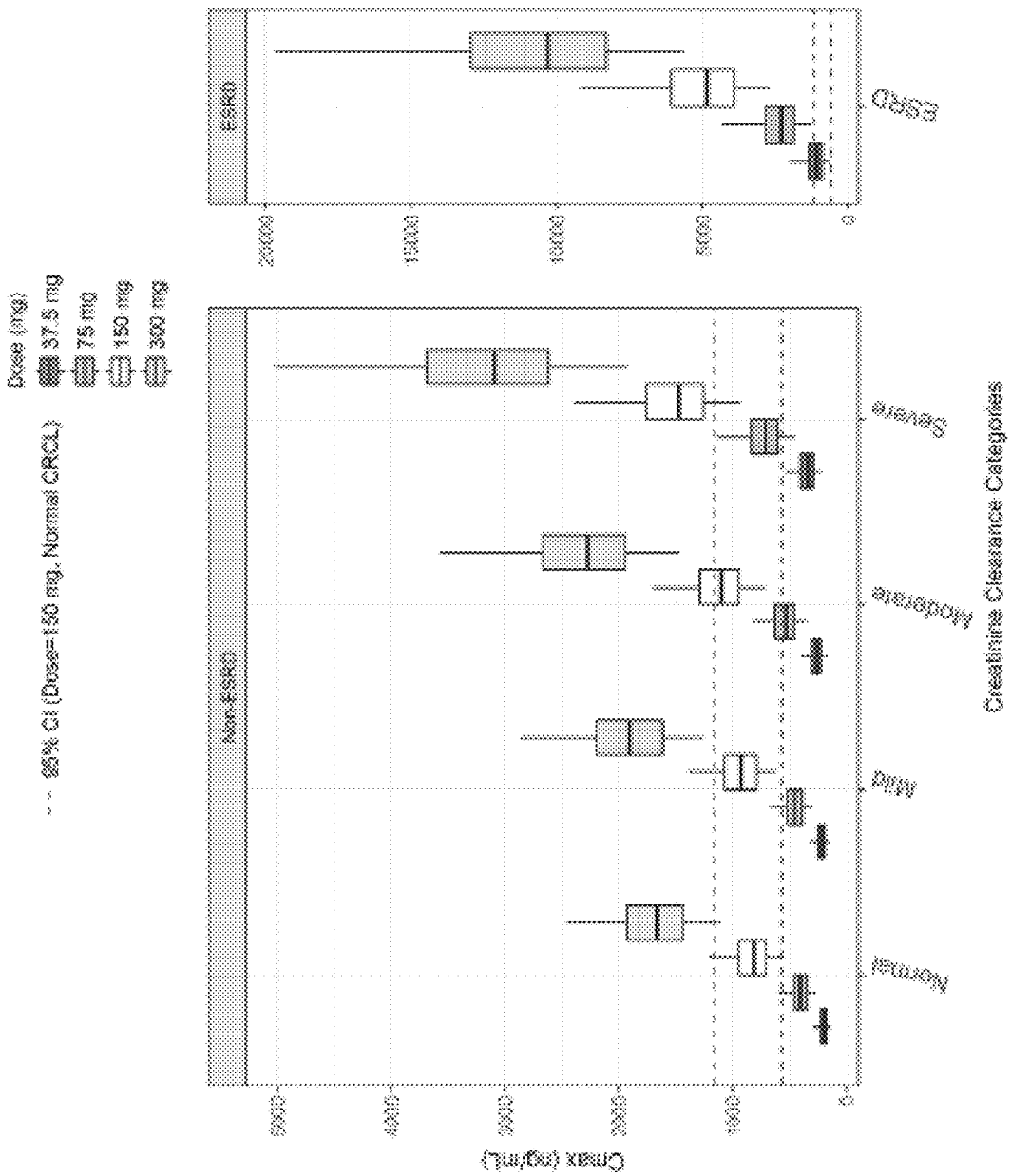

Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)
Cmax (ng/mL)
Creatinine Clearance Categories
Severe
Moderate
Mild
Normal
Non-ESRD
ESRD

FIG. 4

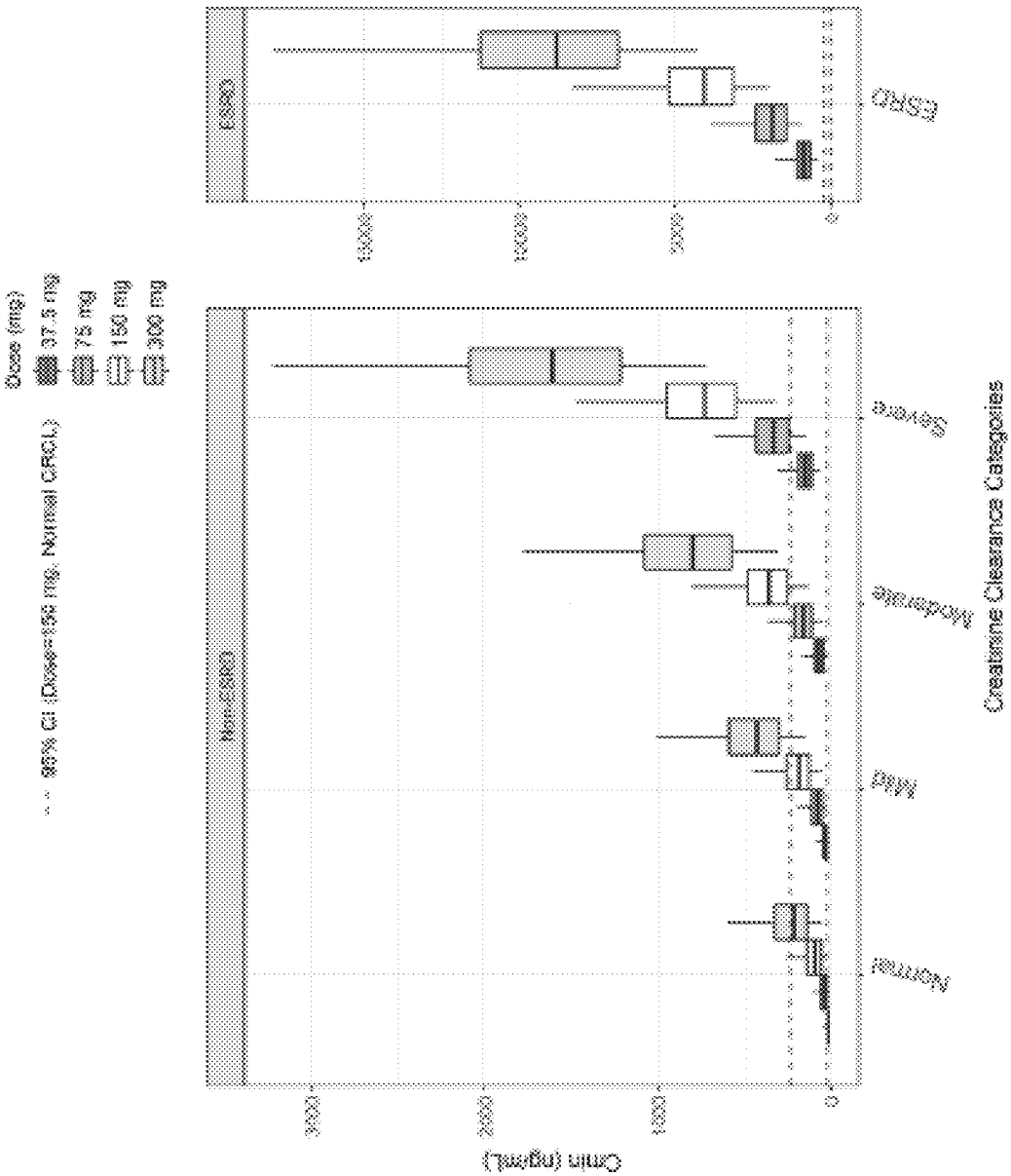

Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)
Cmin (ng/mL)
Creatinine Clearance Categories
Severe
Moderate
Mild
Normal
ESRD
(ESRD)
(Severe)
(Moderate)
(Mild)
(Normal)

FIG. 5

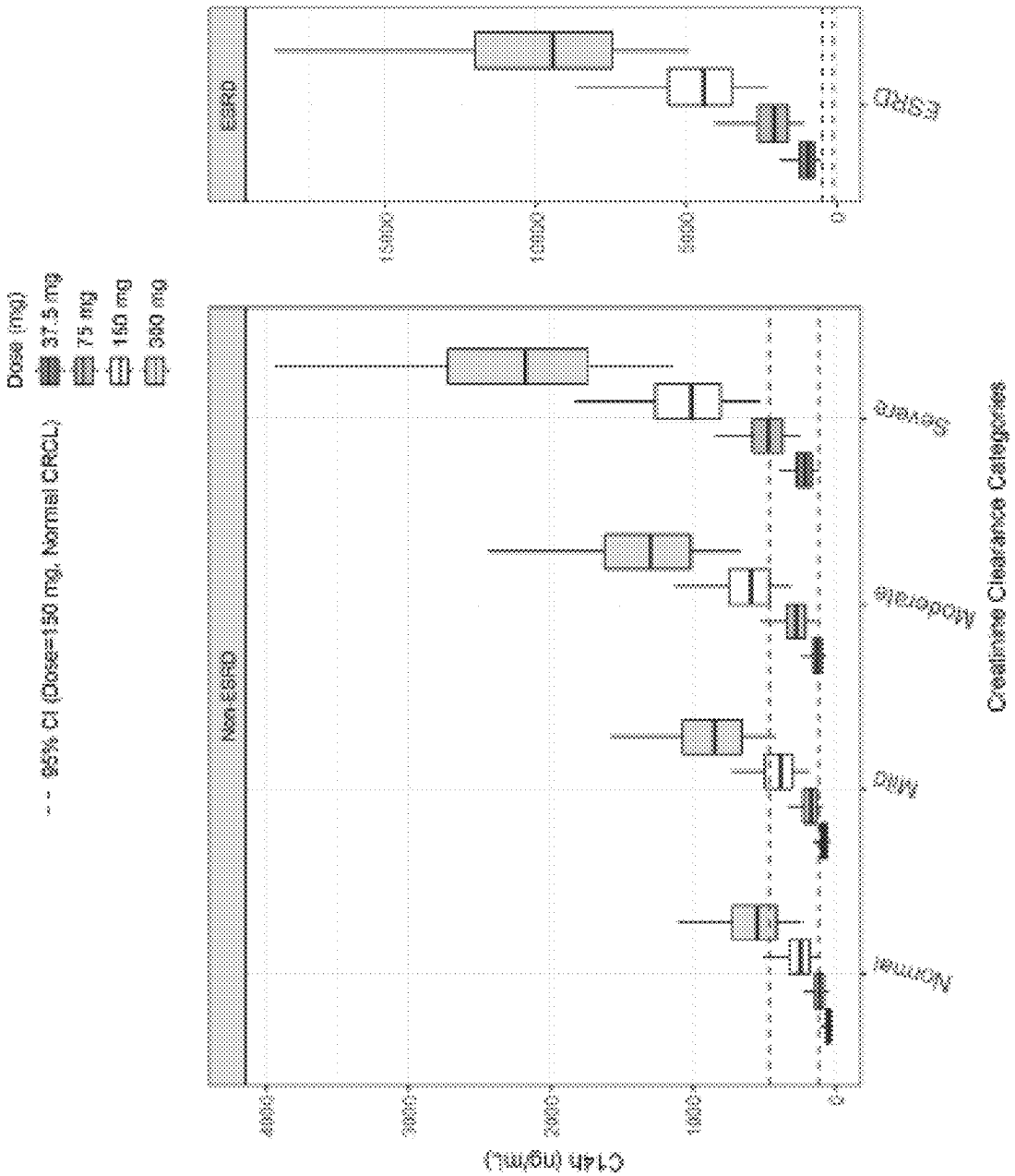

ESRD
Non-ESRD
Severe
Moderate
Mild
Normal
Creatinine Clearance Categories
C14h (ng/mL)
Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)

FIG. 6

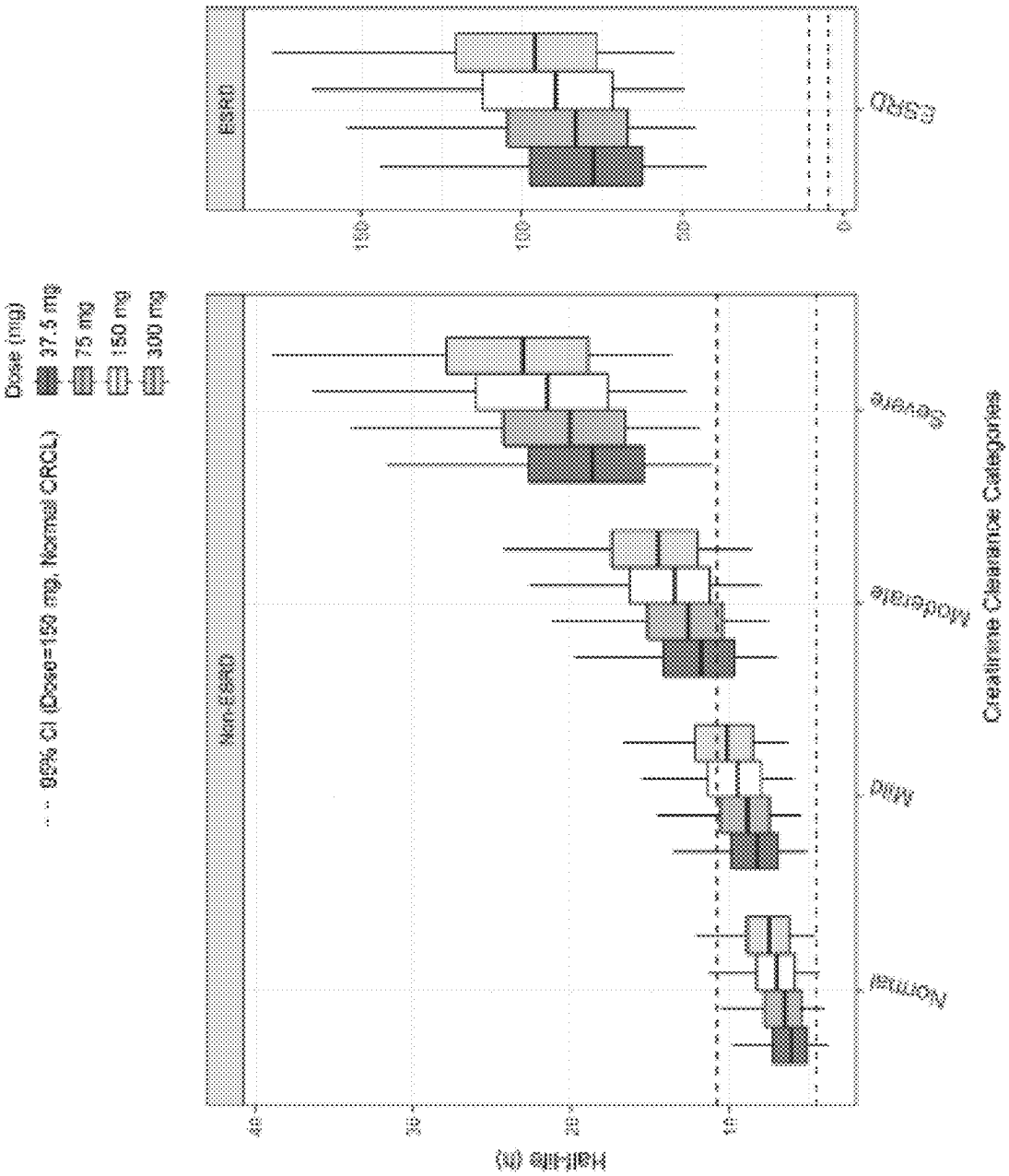

ESRD
Severe
Moderate
Mild
Normal
Creatinine Clearance Categories
Half-life (h)
Dose (mg)
37.5 mg
75 mg
150 mg
300 mg
95% CI (Dose=150 mg, Normal CRCL)

FIG. 7

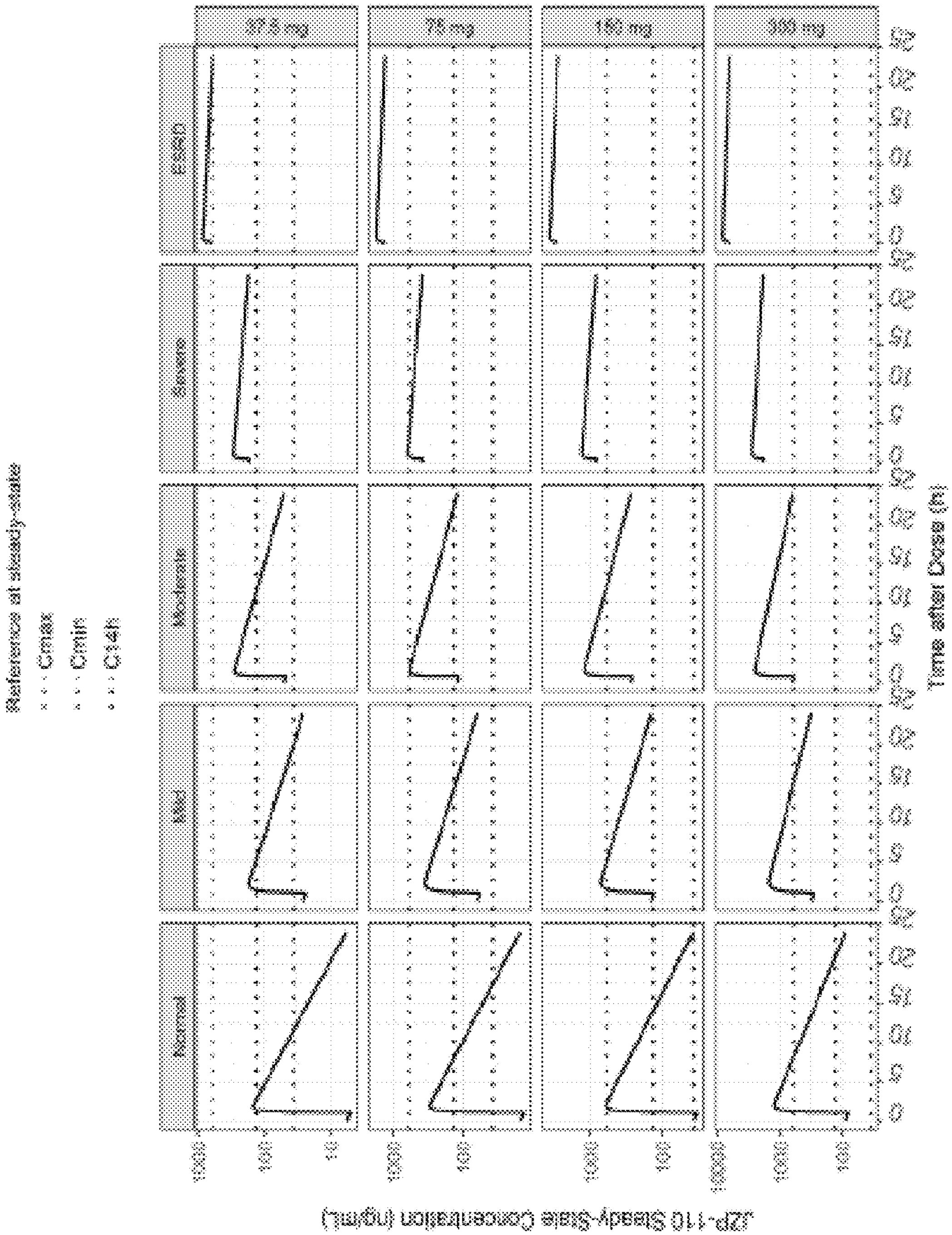

Reference at steady-state
Cmax
Cmin
C24h
37.5 mg
75 mg
150 mg
300 mg
ESRD
Severe
Moderate
Mild
Normal
Time after Dose (h)
JZP-110 Steady-State Concentration (ng/mL)

FIG. 8

METHODS OF PROVIDING SOLRIAMFETOL THERAPY TO SUBJECTS WITH IMPAIRED RENAL FUNCTION

STATEMENT OF PRIORITY

This application is a continuation of and claims priority to U.S. patent application Ser. No. 17/479,121, filed Sep. 20, 2021, which is a continuation of and claims priority to U.S. patent application Ser. No. 17/149,406, filed Jan. 14, 2021, now U.S. Pat. No. 11,160,779, which is a continuation of and claims priority to U.S. patent application Ser. No. 16/824,560, filed Mar. 19, 2020, now U.S. Pat. No. 10,940,133, the entire contents of each of which is incorporated by reference herein in its entirety.

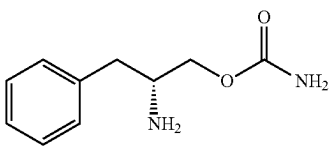
FIELD OF THE INVENTION

The invention relates to methods for decreasing adverse effects associated with solriamfetol ([R]-2-amino-3-phenylpropylcarbamate) therapy in subjects with impaired renal function. In particular, the invention provides an optimized dose escalation scheme for subjects with moderate renal impairment which results in the subjects having increased tolerance to adverse effects associated with the administration of solriamfetol. The invention also provides adjusted dosing for safe therapeutic use of solriamfetol in subjects having severe renal impairment.

BACKGROUND OF THE INVENTION

APC and its phenylalanine analogs have demonstrated application in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, attention deficit/hyperactivity disorder and others. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; 9,359,290; and 9,610,274 and U.S. Publication No. 2015/0018414. The structure of the free base of APC is given below as Formula I.

(I)



Those of skill in the art will appreciate that methods for producing APC (which also has other names) and related compounds can be found in U.S. Pat. Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817.

[R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) is a selective dopamine and norepinephrine reuptake inhibitor. At micromolar concentrations, APC-HCl can selectively bind and inhibit reuptake at dopamine and norepinephrine transporters without promoting monoamine release (See, Carter L, Baladi M, Black J, JZP-110: a dopamine-norepinephrine reuptake inhibitor (DNRI) with robust wake-promoting effects and low abuse potential. Poster presented at: Winter Conference on Brain Research; Jan. 23-28, 2016; Breckenridge, Colorado Poster #Su23, 2016; and Baladi M G, Forster M J, Gatch M B, et al., Characterization of the neurochemical and behavioral

effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. J Pharmacol Exp Ther. 2018; 366:367-376).

As those of skill may recognize, APC-HCl (also referred to as solriamfetol HCl) has been approved by the FDA and EMA as a wake-promoting agent for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea (OSA). Phase 3 trials conducted with APC-HCl on patients having narcolepsy and OSA demonstrated statistically significant reductions in excessive daytime sleepiness measured on the patient-reported Epworth Sleepiness Scale and improvement in objective assessment of wakefulness using the Maintenance of Wakefulness Test. Significantly higher percentages of participants treated with APC-HCl in these trials also reported improvement on the Patient Global Improvement of Change scale relative to placebo at all evaluated time points. See, Johns M W, A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep.* 1991; 14(6):540-545); Thorpy M J, Dauvilliers Y, Shapiro C, et al., A randomized, placebo-controlled, phase 3 study of the safety and efficacy of JZP-110 for the treatment of excessive sleepiness in patients with narcolepsy, *Sleep,* 2017; 40 (suppl): A250; Schweitzer P K, Rosenberg R, Zammit G K, et al., Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial, *Am J Respir Crit Care Med.* 2018; Dec. 6; and Strollo P J, Jr., Hedner J, Collop N, et al., Solriamfetol for the treatment of excessive sleepiness in obstructive sleep apnea: A placebo-controlled randomized-withdrawal study. *Chest.* 2018; Nov. 21.

The most common adverse reactions or effects associated with APC-HCl therapy include headache, nausea, decreased appetite, anxiety, nervousness, panic attack, dry mouth, and diarrhea. Many of these effects can interfere with everyday activities and quality of life. Data from 12-week placebo-controlled clinical trials comparing various doses of solriamfetol support the conclusion that these adverse effects are dose-dependent and that they are exacerbated when APC-HCl is administered at higher doses. Additionally, solriamfetol has been shown to rely on renal excretion of unchanged drug as its primary route of elimination. The fact that the mean renal clearance of APC-HCl is 3 times the glomerular filtration rate suggest that its renal clearance is most likely attributed to a combination of passive diffusion and active renal tubular secretion by multiple cation transporters working in concert, with minimal tubular reabsorption. Therefore, administration of APC-HCl to patients with impaired renal function (which entails reduced passive diffusion and active renal tubular secretion) would be expected to result in higher APC-HCl exposure in this patient population. Prior to the present inventor's discovery however, it was not known what dose, if any, or escalation of APC-HCl would be safe for the renally impaired given the drug's unique pharmacological profile.

SUMMARY OF THE INVENTION

The present invention addresses an unmet medical need by providing methods of administering APC-HCl to renally impaired subjects in a manner that minimizes adverse effects. Of the methods provided is a dose escalation scheme for administering APC-HCl to patients with mild renal impairment, which involves an initial daily dose equivalent to 75 mg APC and waiting until after at least 3 days to reach the maximum daily dose equivalent to 150 mg APC. In another aspect of the invention, the dose escalation scheme of the present invention provides APC-HCl to patients with

moderate renal impairment at an initial daily dose equivalent to 37.5 mg APC and in a manner such that maximum dosage is not reached until after at least five days (in some embodiments of the invention, at least seven days); the method allows for a maximum dosage equivalent to 75 mg APC per day to be administered to a patient so as to reduce the incidence of adverse effects associated with the administration of APC-HCl by tailoring dose escalation to account for tolerance development in the patient. For patients with severe renal impairment (who have further reduced passive diffusion and active renal tubular secretion as compared with moderately impaired patients), the invention provides an alternative dosing regimen involving a daily maximum dose equivalent to 37.5 mg APC. The present inventor, based on analyses of the pharmacokinetics and safety profile of APC-HCl in conjunction with population PK simulations, has additionally discovered that use of APC-HCl should be avoided for patients with end-stage renal disease (with or without hemodialysis).

As such, provided according to embodiments of the present invention are methods of providing APC-HCl to a renally impaired subject in need thereof according to a dose escalation regimen, the method comprising providing to the subject a first oral daily dose equivalent to 37.5 mg APC from day one to day n_1 of the dose escalation regimen; and providing to the subject a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen, wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC, and wherein the renally impaired subject has an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2.

Further provided according to embodiments of the invention are methods of providing APC-HCl to a renally impaired subject with narcolepsy in need thereof, the method comprising providing to the subject an oral daily dose equivalent to 37.5 mg APC, wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent 37.5 mg APC; and wherein the renally impaired subject has an eGFR of about 15 ml/min/1.73 m^2 to about 29 ml/min/1.73 m^2.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of guiding APC therapy in a renally impaired subject with narcolepsy in need thereof, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Further provided according to embodiments of the invention are methods of guiding APC therapy in a renally impaired subject with obstructive sleep apnea in need thereof, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising: administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily; increasing the daily dose to a maximum dose equivalent to 75 mg APC after at least 7 days; wherein the subject has an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl therapy in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising administering to the

subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl in the subject.

Further provided according to embodiments of the invention are methods of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of <15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily after at least 3 days; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease. In some embodiments of the invention, the subject is being treated with the above dosing regimen for excessive daytime sleepiness associated with narcolepsy.

In other embodiments of the invention, methods of reducing toxicity of APC-HCl therapy in a renally impaired subject with obstructive sleep apnea comprise: (a) determining if the subject has mild renal impairment (an estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2), moderate renal impairment (an estimated glomerular filtration rate of 30-59 ml/min/1.73 m^2), severe renal impairment (an estimated glomerular filtration rate of 15-29 ml/min/1.73 m^2), or end stage renal disease (an estimated glomerular filtration rate of <15 ml/min/1.73 m^2); and (b) administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 37.5 mg APC once daily and doubling the dose at intervals of at least 3 days to a maximum dose equivalent to 150 mg APC; or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject APC-HCl if the subject has end stage renal disease.

The present invention is explained in greater detail in the drawings herein and the specification set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A shows the mean (SD) plasma of APC-HCl concentration-time profiles following a single dose equivalent to 75-mg APC for participants with normal renal function and mild-to-severe renal impairment.

FIG. **1**B shows the mean (SD) plasma APC-HCl concentration-time profiles following a single dose equivalent to 75-mg APC for participants with end-stage renal disease with and without hemodialysis.

FIG. **2** shows the apparent oral clearance (CL/F) versus day-1 estimated glomerular filtration rate (eGFR) for Groups 1-4. The broken lines represent the 90% confidence intervals.

FIG. **3** shows results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (narcolepsy/OSA, tablet, fasting conditions) by renal function—AUCtau.

FIG. **4** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—Cmax.

FIG. **5** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—Cmin.

FIG. **6** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—C14h.

FIG. **7** shows the results of simulations to support dosing in sub-populations—comparison of exposure in adult patients (Narcolepsy/OSA, tablet, fasting conditions) by renal function—half-life.

FIG. **8** shows the results of simulations to support dosing in sub-populations—adult patients (Narcolepsy/OSA, tablet, fasting conditions)—individual PK profile (Semi-Log Scale).

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. For example, features illustrated with respect to one embodiment can be incorporated into other embodiments, and features illustrated with respect to a particular embodiment can be deleted from that embodiment. In addition, numerous variations and additions to the embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety for all purposes.

As used herein, "a," "an," or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount.

The term "consists essentially of" (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition. The term "materially altered," as applied to a composition, refers to an increase or decrease in the therapeutic effectiveness of the composition of at least about 20% or more as compared to the effectiveness of a composition consisting of the recited components.

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, prevention or delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Treat" or "treating" or "treatment" refers to any type of action that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art.

"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., Remington's Pharmaceutical Science; 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

The compound [R]-2-amino-3-phenylpropylcarbamate (APC) or solriamfetol is also named (R)-(beta-amino-benzenepropyl) carbamate or O-carbamoyl-(D)-phenylalaninol and has alternatively been called ADX-N05, SKL-N05, SK-N05, YKP10A, and R228060. The hydrochloride salt of the compound is named [R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) or solriamfetol HCl.

A "disorder or condition amenable to treatment" refers to any disorder or condition in which administration of APC to a subject results in the treatment of one or more symptoms of the disorder in the subject. Disorders amenable to treatment with APC include, without limitation, excessive daytime sleepiness, fatigue, drug addiction, sexual dysfunction, depression, fibromyalgia syndrome, attention deficit/hyperactivity disorder, restless legs syndrome, bipolar disorder, cataplexy, obesity, and smoking cessation.

In some embodiments, APC may be used to treat and/or prevent excessive daytime sleepiness (EDS). See U.S. Pat. Nos. 8,440,715; 8,877,806; 9,604,917; and 10,351,517; incorporated by reference herein in their entirety. EDS may be due to, without limitation, a central nervous system (CNS) pathologic abnormality, stroke, narcolepsy, idiopathic CNS hypersomnia, sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder, Alzheimer's disorder, bipolar disorder, cardiac ischemia, misalignments of the body's circadian pacemaker with the environment, or jet lag; or a subject doing shift work or taking sedating drugs.

In some embodiments, APC may be used to treat and/or prevent fatigue. See U.S. Pat. Nos. 8,741,950; 9,464,041; 9,999,609; and 10,507,192; incorporated by reference herein in their entirety. Fatigue may be due to, without limitation, a disease, disorder or condition such as depression, cancer, multiple sclerosis, Parkinson's disease, Alzheimer's disease, chronic fatigue syndrome, fibromyalgia, chronic pain, traumatic brain injury, AIDS, and osteoarthritis. Fatigue may be due to, without limitation, a treatment or medication such as chemotherapy, radiation therapy, bone marrow transplant, and anti-depressant treatment.

In some embodiments, APC may be used to treat drug addiction. See U.S. Pat. No. 8,232,315, incorporated by reference in its entirety. In some embodiments, the addicted drug may be nicotine, opioid, cocaine, amphetamine, methamphetamine, ethanol, heroin, morphine, phencyclidine (PCP), and methylenedioxymethamphetamine (MDMA).

In some embodiments, APC may be used to treat sexual dysfunction. See U.S. Pat. No. 8,552,060, incorporated by reference herein in its entirety. In some embodiments, the treatment may increase interest in sex and/or the ability to have an orgasm. In some embodiments, the sexual dysfunction may be due to treatment with a therapeutic agent, including without limitation, selective serotonin reuptake inhibitors (SSRIs); selective serotonin and norepinephrine reuptake inhibitors (SNRIs); older tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAO-inhibitors), reversible inhibitors of monoamine oxidase (RIMAs), ter-

tiary amine tricyclics and secondary amine tricyclic antidepressants, e.g., therapeutic agents such as fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, 5-MCA-NAT, lithium carbonate, isocarboxazid, phenelzine, tranylcypromine, selegiline, moclobemide, kappa opioid receptor antagonists; selective neurokinin antagonists, corticotropin releasing factor (CRF) antagonists, antagonists of tachykinins, α-adrenoreceptor antagonists, amitriptyline, clomipramine, doxepin, imipramine, venlafaxine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

In some embodiments, APC may be used as an adjunctive therapy to treat depression. See U.S. Pat. No. 8,729,120, incorporated by reference herein in its entirety. In some embodiments, APC is administered to a subject in conjunction with an antidepressant such as, without limitation, fluoxetine, amitriptyline, clomipramine, doxepin, imipramine, trimipramine or a pharmaceutically acceptable salt thereof.

In some embodiments, APC may be used to treat fibromyalgia syndrome. See U.S. Pat. Nos. 8,927,602 and 9,688,620; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to treat attention deficit/hyperactivity disorder (ADHD) or diminish symptoms associated with ADHD. See U.S. Pat. Nos. 8,895,609; 9,663,455; and 10,202,335; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to treat restless legs syndrome. See U.S. Pat. No. 8,623,913, incorporated by reference herein in its entirety.

In some embodiments, APC may be used to treat bipolar disorder. See U.S. Pat. Nos. 9,610,274 and 9,907,777; incorporated by reference herein in their entirety. In some embodiments, APC may be used to diminish manic symptoms in a subject suffering from bipolar disorder.

In some embodiments, APC may be used to treat cataplexy. See U.S. Pat. Nos. 9,359,290; 9,585,863; and 10,259,780; incorporated by reference herein in their entirety. In some embodiments, the cataplexy is secondary to a condition that lowers hypocretin levels in a subject, such as a brain tumor, astrocytoma, glioblastoma, glioma, subependynoma, craniopharyngioma, arterio-venous malformations, ischemic events, multiple sclerosis, head injury, brain surgery, paraneoplastic syndromes, Neimann-Pick type C disease, or encephalitis.

In some embodiments, APC may be used to treat obesity, reduce body weight, reduce or prevent body weight gain, reduce food intake, or treat pathological eating. See U.S. Pat. Nos. 9,226,910; 9,649,291; and 10,105,341; incorporated by reference herein in their entirety.

In some embodiments, APC may be used to promote cessation or reduction in the smoking and/or chewing of tobacco or nicotine-containing products and/or to prevent relapse of the same. See US Publication No. 2015/0018414, incorporated by reference herein in its entirety.

Methods of Treating Excessive Daytime Sleepiness

Provided according to embodiments of the present invention are methods of treating excessive daytime sleepiness in a renally impaired subject in need thereof, comprising administering to the subject an APC salt, such as APC-HCl. In some embodiments, such methods comprise administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject. In particular embodiments, such methods further include increasing the dose to a maximum equivalent of 75 mg APC once daily after at least 7 days. In some embodiments of the invention, the subject has narcolepsy, OSA, or both.

Further provided according to some embodiments of the invention are methods of treating excessive daytime sleepiness in a renally impaired subject in need thereof that comprise administering to the subject an APC salt, such as APC-HCl, at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Further provided according to embodiments of the invention are methods of guiding the treatment of excessive daytime sleepiness in a renally impaired subject in need thereof, comprising:

(a) determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/mm/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

(b) administering to the subject the dose of an APC salt (e.g., APC-HCl) recommended for subjects without renal impairment if the subject has mild renal impairment; or administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject an APC salt if the subject has end stage renal disease.

In some embodiments, the methods further comprise measuring the eGFR in the subject prior to step (a).

Also provided according to other embodiments of the present invention are methods of reducing toxicity of an APC salt (e.g., APC-HCl) in a renally impaired subject, comprising administering to the subject the APC salt at an initial dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of the APC salt. In particular embodiments, such methods further include increasing the dose to a maximum equivalent of 75 mg APC once daily after at least 7 days. "Reducing toxicity," as used herein, refers to reducing the number and/or severity of adverse reactions or effects associated with APC-HCl therapy relative to the number and/or severity of adverse reactions or effects in the absence of the methods of the invention.

Provided according to some embodiments of the present invention are methods of reducing toxicity of an APC salt (e.g., APC-HCl) in a renally impaired subject, such methods comprising administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily, wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby reducing the toxicity of the APC salt in the subject.

Further, provided according to embodiments of the present invention are methods of reducing toxicity of an APC salt in a renally impaired subject, comprising:

(a) determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/mm/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

(b) administering to the subject the dose of an APC salt recommended for subjects without renal impairment if the subject has mild renal impairment; or administering to the subject an APC salt at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg

APC once daily if the subject has moderate renal impairment; or administering to the subject an APC salt at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or not administering to the subject an APC salt if the subject has end stage renal disease. In some embodiments, the methods further comprise measuring the estimated glomerular filtration rate in the subject prior to step (a).

The methods of the invention may be used to treat any disorder or condition amenable to treatment with APC. Disorders amenable to treatment with APC include, without limitation, excessive daytime sleepiness, fatigue, sleep apnea, drug addiction, sexual dysfunction, depression, fibromyalgia syndrome, attention deficit/hyperactivity disorder, restless legs syndrome, bipolar disorder, cataplexy, obesity, as well as induction of smoking cessation.

Excessive Daytime Sleepiness

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift.

In some embodiments of the invention, treating excessive daytime sleepiness in a subject in need thereof may result in the decrease the subject's score on the Epworth Sleepiness Scale (ESS) by 5 or more points, e.g., by 10 or more points, e.g., by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 or more points or any range therein. In some embodiments, the amount of APC salt administered is sufficient to decrease the subject's score on the ESS to a level that is considered normal, e.g., 10 or less. In certain embodiments, at least about 5% of the treated subjects achieve the specified score, e.g., at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

The ESS is a subjective sleepiness test that is well known in the art and routinely used to measure the sleepiness level of a subject. The scale is intended to measure daytime sleepiness through the use of a short questionnaire that asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives. The scores for the eight questions are added together to obtain a single number that estimates the subject's average sleep propensity (ASP). A number in the 0-10 range is considered to be normal while 11-12 indicates mild excessive sleepiness, 13-15 indicates moderate excessive sleepiness, and 16 or higher indicates severe excessive sleepiness. Narcolepsy patients have an average score of about 17. Obstructive sleep apnea (OSA) patients with excessive sleepiness have an average score of about 15.

In some cases, treating excessive daytime sleepiness in a subject in need thereof results in an increase the subject's score on the maintenance of wakefulness test (MWT) by at least 5 minutes, e.g., at least 10 minutes or 15 minutes, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 minutes or more or any range therein. In certain embodiments, at least about 5% of the treated subjects achieve the specified score, e.g., at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more.

The MWT is an objective test used to measure how alert a subject is during the day. The test consists of four sleep trials with two hours in between the trials. The first trial is performed 1.5-3 hours after the subject's normal wake-up time. Sensors are placed on the head, face, and chin to detect when the subject is asleep and awake during the test. The subject sits quietly in bed with his or her back and head supported by a pillow and is asked to sit still and look straight ahead while trying to stay awake as long as possible. Each trial lasts 40 minutes or until the subject is asleep for 90 seconds. Between trials, the subject stays out of bed and occupies himself or herself to remain awake. Falling asleep in an average of less than eight minutes is considered abnormal. About 40-60% of subjects with normal sleep stay awake for the entire 40 minutes of all four trials.

The baseline measurement for determining a change in test results, such as ESS and MWT, may be performed before the subject has been administered APC or at a timepoint during a course of treatment of APC at which a baseline determination is desired. One or more subsequent determinations of test results may be made at any time after administration of one or more doses of APC. For example, determination of a change in test results may be made 1, 2, 3, 4, 5, or 6 days or 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks after the administration of APC has begun or after the baseline determination was made.

The methods of the invention may be effective no matter the cause of the EDS, but in some embodiments of the invention, the EDS is associated with narcolepsy or obstructive sleep apnea (OSA). In other embodiments, the cause of the EDS may be, without limitation, central nervous system (CNS) pathologic abnormalities, stroke, idiopathic CNS hypersomnia; sleep deficiency, other sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder (ADHD), Alzheimer's disorder, major depression, bipolar disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work, or sedating drugs.

The methods of the invention may also be used to increase wakefulness and/or alertness in a subject in need thereof.

Renal Impairment

In embodiments of the present invention, the renal status of the subject may be determined by measuring the "estimated glomerular filtration rate" or "eGFR" of the individual. The eGFR in mL/min/1.73 m^2 is calculated by the Modification of Diet in Renal Disease [MDRD] equation:

$$(\text{eGFR in mL/min})/1.73\ m^2 = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times \text{Age}^{-0.203} \times 0.742\ (\text{if female}) \times 1.212\ (\text{if black}).$$

Further details regarding the calculation of the eGFR may be found in, e.g., Levey A S, Coresh J, Greene T, Marsh J, Stevens L A, Kusek J W, Van Lente F: Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Ann Intern Med. 2009; 150(9):604-12.

Renal impairment status based on Food and Drug Administration (FDA) guidance is as follows.

Normal: eGFR≥90 mL/min/1.73 m^2

Mild: eGFR 60-89 mL/min/1.73 m2 (i.e., ≤60 to <90)

Moderate: eGFR 30-59 mL/min/1.73 m^2 (i.e., ≤30 to <60)

Severe: eGFR 15-29 mL/min/1.73 m^2 (i.e., ≤15 to <30) and not on hemodialysis

End-stage renal disease (ESRD): eGFR<15 mL/min/1.73 m^2 and not on hemodialysis or on hemodialysis

See, Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis and Impact on Dosing and Labeling. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) February 2010. As used herein, a "renally impaired subject" may have mild, moderate, or severe renal impairment, or may have ESRD.

APC Salts

The methods of the present invention may be carried out using compounds, formulations and unit dosage forms provided herein. In some embodiments, the formulations and dosage forms may include pharmaceutically acceptable salts of APC ("APC salt"), which also includes hydrates, solvates, clathrates, inclusion compounds, and complexes thereof.

In some embodiments of the invention, the APC salt is a hydrochloride salt (APC-HCl). However, suitable salts of APC also include, without limitation, acetate, adipate, alginate, aspartate, benzoate, butyrate, citrate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, hydroxynapthoate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, can be employed in the preparation of salts useful as intermediates in obtaining the compound of the invention and their pharmaceutically acceptable acid addition salts. APC salts include those having quaternization of any basic nitrogen-containing group therein.

The discussion herein is, for simplicity, provided without reference to the addition of deuterium atoms, but the APC salts may further include non-ordinary isotopes. Those skilled in the art will appreciate that the APC salt can contain one or more asymmetric centers and thus occur as racemates and racemic mixtures and single optical isomers. In embodiments of the present invention, the APC salt stereoisomer is preferred, but formulations according to embodiments of the invention may include both (R) and (S) isomers in a racemic mixture, or in any ratio of the isomers. In particular embodiments, the (R)-2-amino-3-phenylpropyl carbamate salt stereoisomer is present at a greater concentration than the (S)-2-amino-3-phenylpropyl carbamate salt stereoisomer, and in some embodiments, the formulation includes the 2-amino-3-phenylpropyl carbamate salt as a substantially enantiomerically pure (R)-2-amino-3-phenylpropyl carbamate salt stereoisomer such as having an enantiomeric excess of greater than 80%, 90%, 95%, or 99%. In some embodiments, the (R)-2-amino-3-phenylpropyl carbamate salt is enantiomerically pure, and in some cases is enantiomerically pure (R)-2-amino-3-phenylpropyl carbamate hydrochloride. When the (R)-2-amino-3-phenylpropyl carbamate salt is referenced specifically, it is understood that the dosage (e.g., 37.5 mg or 75 mg) refers to the equivalent weight of the (R) enantiomer only.

The APC salt(s) may be obtained or synthesized by methods known in the art and as described herein. Details of reaction schemes for synthesizing APC have been described in U.S. Pat. Nos. 5,705,640; 5,756,817; 5,955,499; and 6,140,532, all incorporated herein by reference in their entirety.

APC Salt Formulations

Any suitable dosage form comprising the APC salts may be used in the methods of the invention. In some embodiments, the dosage formulation comprises the APC salt (which is pharmaceutically acceptable) and a pharmaceutically acceptable carrier. In some embodiments, the dosage form is an oral dosage form, e.g., a tablet or a capsule, e.g., an immediate release dosage form.

In some embodiments, the dosage form is an immediate release tablet that releases at least 85%, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, or 99%, of the APC salt contained therein within a period of less than 15 minutes after administration of the tablet to a subject. See, for example, U.S. Pat. No. 10,195,151, incorporated herein by reference in its entirety.

Formulations of the APC salt, including immediate release formulations, may be processed into unit dosage forms suitable for oral administration, such as for example, filled capsules, compressed tablets or caplets, or other dosage form suitable for oral administration using conventional techniques Immediate release dosage forms prepared as described may be adapted for oral administration, so as to attain and maintain a therapeutic level of the compound over a preselected interval. In certain embodiments, an immediate release dosage form as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or polygonal. In one such embodiment, the surfaces of the immediate release dosage form may be flat, round, concave, or convex. In some embodiments, the shape may be selected to maximize surface area, e.g., to increase the rate of dissolution of the dosage form.

In particular, when the immediate release formulations are prepared as a tablet, the immediate release tablets may contain a relatively large percentage and absolute amount of the compound and so may be expected to improve patient compliance and convenience by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets as described herein can be administered, by oral ingestion, e.g., closely spaced, in order to provide a therapeutically effective dose of the compound to the subject in a relatively short period of time.

Where desired or necessary, the outer surface of an immediate release dosage form may be coated, e.g., with a color coat or with a moisture barrier layer using materials and methods known in the art.

In some embodiments, the dosage formulation is an immediate release compressed tablet, the tablet comprising: the APC salt thereof in an amount of about 90-98% by weight of the tablet; at least one binder in an amount of about 1-5% by weight of the tablet; and at least one lubricant in an amount of about 0.1-2% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises: the APC salt thereof in an amount of about 91-95% by weight of the tablet; at least one binder in an amount of about 2-3% by weight of the tablet; at least one lubricant in an amount of about 0.1-1% by weight of the tablet; and optionally, a cosmetic film coat in an amount of about 3-4% by weight of the tablet; wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises: the APC salt thereof in an amount of about 93.22% by weight of the tablet; at least one binder (e.g., hydroxypropylcellulose) in an amount of about 2.87% by weight of the tablet; at least one lubricant (e.g., magnesium stearate) in an amount of about 0.52% by weight of the tablet; and optionally, a cosmetic film coat (e.g., Opadry® II yellow) in an amount of about 3-4% by weight of the tablet; wherein the tablet releases at least 85% of the APC salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In some embodiments, the composition is an immediate release oral dosage form of an APC salt, the oral dosage form comprising: the APC salt thereof in an amount of about 90-98% by weight of the oral dosage form; at least one binder in an amount of about 1-5% by weight of the oral dosage form; and at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form; wherein the oral dosage form releases at least 85% of the APC salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject.

In certain embodiments, the tablet does not comprise a disintegrant. The term "disintegrant," as used herein, refers to an agent added to a tablet to promote the breakup of the tablet in an aqueous environment. The tablets of the present invention are advantageous in that they dissolve rather than disintegrate. In the present invention the presence of disintegrant in the formulation may actually slow down release of APC.

In certain embodiments, the APC salt is present in an amount of about 90%, 90.5%, 91%, 91.5%, 92%, 92.5%, 93%, 93.5%, 94%, 94.5%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, or 98% by weight of the tablet or any value or range therein. In certain embodiments, the APC salt thereof is present in an amount of about 90% to about 98%, about 92% to about 98%, about 94% to about 98%, about 96% to about 98%, about 90% to about 92%, about 90% to about 94%, about 90% to about 96%, about 92% to about 94%, about 92% to about 96%, or about 94% to about 96%.

In certain embodiments, the at least one binder is present in an amount of about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the tablet or any value or range therein. In certain embodiments, the at least one binder is present in an amount of about 1% to about 5%, about 2% to about 5%, about 3% to about 5%, about 4% to about 5%, about 1% to about 2%, about 1% to about 3%, about 1% to about 4%, about 2% to about 3%, about 2% to about 4%, or about 3% to about 4%. The tablet may comprise at least one binder, e.g., 1, 2, 3, 4, 5, or more binders.

In certain embodiments, the at least one binder is selected from at least one of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, sodium carboxymethylcellulose, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate or any combination thereof. In some embodiments, the at least one binder is hydroxypropyl cellulose.

In certain embodiments, the at least one lubricant is present in an amount of about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, or 2.0% by weight of the tablet or any value or range therein. In certain embodiments, the at least one lubricant is present in an amount of about 0.1% to about 2.0%, about 0.5% to about 2.0%, about 1.0% to about 2.0%, about 1.5% to about 2.0%, about 0.1% to about 0.5%, about 0.1% to about 1.0%, about 0.1% to about 1.5%, about 0.5% to about 1.0%, about 0.5% to about 1.5%, or about 1.0% to about 1.5%. The tablet may comprise at least one lubricant, e.g., 1, 2, 3, 4, 5, or more lubricants. Where the immediate release formulation is provided as a tableted dosage form, still lower lubricant levels may be achieved with use of a "puffer" system during tableting. Such systems are known in the art, commercially available and apply lubricant directly to the punch and die surfaces rather than throughout the formulation.

In certain embodiments, the at least one lubricant is selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate or any combination thereof. In some embodiments, the at least one lubricant is magnesium stearate. In other embodiments, magnesium stearate may be used in combination with one or more other lubricants or a surfactant, such as sodium lauryl sulfate. In particular, if needed to overcome potential hydrophobic properties of magnesium stearate, sodium lauryl sulfate may also be included when using magnesium stearate (Remington: the Science and Practice of Pharmacy, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000)).

In some embodiments, the at least one binder is hydroxypropyl cellulose. In some embodiments, the at least one lubricant is magnesium stearate. In some embodiments, the at least one binder is hydroxypropyl cellulose and the at least one lubricant is magnesium stearate.

In certain embodiments, the tablet is coated. The coating may be, without limitation, a color overcoat.

The tablet may be any shape that is suitable for immediate release and allows the release of at least 85% of the APC salt contained therein within a period of less than 15 minutes after administration of the tablet to a subject. In some embodiments, the tablet maximizes surface area to volume ratio to promote rapid dissolution. In some embodiments, the tablet is oblong in shape.

The tablet may contain any amount of the APC salt suitable for administration as a unit dosage form. In some embodiments, the tablet contains the equivalent of about 1 mg to about 1000 mg of APC or any range or value therein, e.g., about 100 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

["Immediate release" as used herein, refers to a composition that releases the APC salt substantially completely into the gastrointestinal tract of the user within a period of less than about 15 minutes, usually between about 1 minute and about 15 minutes from ingestion. Such a delivery rate allows the drug to be absorbed by the gastrointestinal tract in a manner that is bioequivalent to an oral solution. Such rapid absorption will typically occur for an immediate release unit dosage form, such as a tablet, caplet or capsule, if the drug included in such dosage form dissolves in the upper portion the gastrointestinal tract.

Release rates can be measured using standard dissolution test methods. For example, the standard conditions may be those described in FDA guidance (e.g., 50 rpm, 37° C., USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel).

Immediate release formulations suitable for oral administration may comprise unit dosage forms, such as tablets, caplets or filled capsules, which can deliver a therapeutically effective dose of the APC salt upon ingestion thereof by the patient of one or more of said dosage forms, each of which

can provide a dosage of, for example, about 37.5 mg to about 75 mg, or 75 mg to about 150 mg of APC. Additionally, the immediate release dosage forms can be shaped or scored to facilitate dose adjustment through tablet splitting. For example, a 75 mg APC tablet or caplet may be scored to facilitate tablet splitting into two 37.5 mg APC doses.

The formulation and structure of an immediate release dosage form as disclosed herein can be adjusted to provide immediate release performance that suits a particular dosing need. In particular, the formulation and structure of the dosage forms as described herein can be adjusted to provide any combination of the immediate release performance characteristics described herein. In particular embodiments, for example, an immediate release dosage form as disclosed herein provides rapid onset of action, releasing more than about 85%, such as, for example, more than about 90% or 95%, of the drug contained therein within a period of time selected from less than 15 minutes, less than 12 minutes, less than 10 minutes, and less than 5 minutes after administration.

Moreover, the rate of drug release from an immediate release dosage form as disclosed herein may be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. In certain such embodiments, the total amount of the APC salt in the dosage formulation may include an equivalent dose of about 10 mg to about 300 mg APC, about 30 mg to about 300 mg APC, about 100 mg to about 300 mg APC, or about 150 mg to about 300 mg APC, about 75 to 150 mg APC, about 37.5 to about 75 mg APC, and about 37.5 to about 150 mg APC. In particular embodiments, the equivalent dose of APC in the dosage formulation is 37.5 mg, and in other particular embodiments, the equivalent dose of APC in the dosage formulation is 75 mg. In some cases, such dosage formulations may be formed (e.g., scoring) to facilitate creating more than one dose from a particular dosage form.

The immediate release formulations provided herein generally include the APC salt and some level of lubricant to facilitate processing of the formulations into a unit dosage form. In some embodiments, therefore, the formulations described herein include a combination of the APC salt and lubricant, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. In other embodiments, the immediate release formulations described herein include a combination of the APC salt, lubricant, and binder, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. Though the immediate release formulations described herein may be formulated using a combination of drug and one or more of a lubricant and binder, in certain embodiments, the compositions described herein may include one or more additional excipients selected from, for example, fillers, compression aids, diluents, disintegrants, colorants, flavorants, buffering agents, coatings, glidants, or other suitable excipients.

The immediate release formulations described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and dry powder blending. Suitable methods for the manufacture of the immediate release formulations and unit dosage forms described herein are provided, for example, in Remington, 20^{th} edition, Chapter 45 (Oral Solid Dosage Forms). It has been found that, even without the aid of binders or non-lubricating excipients, such as compression aids, wet granulation techniques can afford flowable granules with compression characteristics suitable for forming unit dosage forms as described herein. Therefore, in certain embodiments, where a drug content greater than about 85%, 90% or 95% by weight is desired for the immediate release formulation, wet granulation techniques may be used to prepare immediate release formulations as described herein. In such embodiments, as illustrated in the Examples provided herein, conventional organic or aqueous solvents may be used in the wet granulation process. Suitable wet granulation processes can be performed as fluidized bed, high shear, or low shear (wet massing) granulation techniques, as are known in the art.

In addition to one or more the APC salt, lubricant, and binder, where desired, the immediate release formulations described herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. Where a filler or compression aid is used, in certain embodiments, it may be included in the immediate release formulation in an amount ranging from about 1%-15% by weight.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a moisture barrier layer using materials and methods known in the art. For example, where the APC salt delivered by the unit dosage form is highly hygroscopic, providing a moisture barrier layer over the immediate release dosage form as disclosed herein may be desirable. For example, protection of an immediate release dosage form as disclosed herein from water during storage may be provided or enhanced by coating the tablet with a coating of a substantially water soluble or insoluble polymer. Useful water-insoluble or water-resistant coating polymers include ethyl cellulose and polyvinyl acetates. Further water-insoluble or water resistant coating polymers include polyacrylates, polymethacrylates or the like. Suitable water-soluble polymers include polyvinyl alcohol and HPMC. Further suitable water-soluble polymers include PVP, HPC, HPEC, PEG, HEC and the like.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a color overcoat or other aesthetic or functional layer using materials and methods known in the art.

The dosage forms disclosed herein can also be provided as a kit comprising, separately packaged, a container comprising a plurality of immediate release tablets, which tablets can be individually packaged, as in foil envelopes or in a blister pack. The tablets can be packaged in many conformations with or without desiccants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, e.g., sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of APC in vivo for preselected periods of time, to treat a preselected condition.

Daily Dosage and Treatment Regimens

In the methods described herein, the typical daily dose of the APC salt for subjects with normal renal function, equivalent to 75-150 mg of APC, is modified for certain renally impaired subjects. As discussed above, for a subject with an eGFR of 30-59 ml/min/1.73 m^2, i.e., a subject with moderate renal impairment, the APC salt is administered once daily at an initial dose equivalent to 37.5 mg of APC. In some cases, this daily dose may be increased after at least 7 days of the initial dose equivalent to 75 mg of APC. Further, in some embodiments, for a subject with an eGFR of 15-29 ml/min/

1.73 m^2, i.e., a subject with severe renal impairment, the APC salt is administered once daily at a maximum dose equivalent to 37.5 of APC. In some embodiments, such dosages may be used for a subject who has narcolepsy, a subject with OSA, or when reduction of toxicity of the APC salt is indicated. In particular embodiments, the APC salt is APC-HCl.

A dose is "equivalent to" a 37.5 mg or 75 mg of APC, if the weight of the APC base (the "active moiety") in the formulation is 37.5 mg or 75 mg, respectively, regardless of the weight of the APC salt. Thus, the weight of the APC salt may be greater than 37.5 mg or 75 mg, respectively, in the formulation. Where APC is provided in the form of APC-HCl salt, a dose of 37.5 mg APC is equivalent to 44.7 mg (or 44.65 mg) of APC-HCl; a dose of 75 mg APC is equivalent to 89.3 mg of APC-HCl; and a dose of 150 mg APC is equivalent to 178.5 mg of APC-HCl. An "initial dose equivalent" is the daily dose at which the subject starts the treatment regimen, corresponding to the weight of the active moiety (APC), and the initial dose may be increased at some time point, such as in a number of days (e.g., 1, 2, 3, 4, 5, 6, 7, or more days). The "maximum dose equivalent" is the largest dose, corresponding to the weight of the active moiety (APC), that the patient may be administered daily at any time point.

In general, the daily dose is administered once daily. However, in some embodiments, the daily dose may be administered at two or more different time points. Administration of the APC salt can continue for one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve weeks or longer. Alternatively, administration of the APC salt can continue for one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment, the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, the APC salt is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Such agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. In some embodiments, the APC salt is delivered to a subject concurrently with an additional therapeutic agent that is not a monoamine oxidase inhibitor. In still other embodiments, the APC salt is delivered to a subject who has not been treated with a monoamine oxidase inhibitor within the preceding 14 days. In exemplary embodiments of the invention, a subject with obstructive sleep apnea is treated with APC concurrently with adherence to a primary OSA therapy. Examples of primary OSA therapies include, without limitation, positive airway pressure (PAP), continuous positive airway pressure (CPAP), oral appliances, and surgical procedures. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302.

The APC salt can be administered at any time during the day, but in some embodiments, the APC salt is administered to the subject no later than at least 12 hours before the bedtime of the subject. Studies by the present inventors have found that that administration of the APC salt within a few of hours of waking minimizes side effects of the treatment such as insomnia. In some embodiments, the APC is administered shortly after waking, e.g., within about 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, or 3 hours of waking. In exemplary embodiments, the APC is administered at least 9 hours before the bedtime of the subject, e.g., at least 9, 10, 11, 12, 13, 14, 15, or 16 or more hours before bedtime.

Subjects

The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults and geriatric subjects. In some embodiments of the invention, the human subject is an adult.

In particular embodiments, the subject is a human subject that has excessive daytime sleepiness or another disorder amenable to treatment with the APC salt. In other embodiments, the subject used in the methods of the invention is an animal model of excessive daytime sleepiness or another disorder amenable to treatment with APC.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, is suspected of having excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, and/or is anticipated to experience excessive daytime sleepiness or another disorder or condition amenable to treatment with APC, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment. Disorders amenable to treatment with APC include, without limitation, sleep-wake disorder, excessive daytime sleepiness, depression, attention deficit/hyperactivity disorder, drug addiction, bipolar disorder, fibromyalgia, fatigue, obesity, restless legs syndrome, cataplexy, and sexual dysfunction.

Specific embodiments of the invention include, without limitation, the following.

Embodiment 1: A method of providing [R]-2-amino-3-phenylpropylcarbamate hydrochloride (APC-HCl) to a renally impaired subject in need thereof according to a dose escalation regimen, said method comprising

providing to the subject a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of the dose escalation regimen; and

providing to the subject a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen,

wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC, and

wherein the renally impaired subject has an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2.

Embodiment 2: The method of embodiment 1, wherein the subject is provided APC-HCl for the treatment of excessive daytime sleepiness.

Embodiment 3: The method of embodiment 2, wherein the excessive daytime sleepiness is associated with narcolepsy.

Embodiment 4: The method of embodiment 2, wherein the excessive daytime sleepiness is associated with obstructive sleep apnea.

Embodiment 5: The method of embodiment 1, wherein the subject is provided the first oral daily dose in the form of about 44.7 mg APC-HCl.

Embodiment 6: The method of embodiment 1, wherein the subject is provided the second oral daily dose in the form of about 89.3 mg APC-HCl.

Embodiment 7: The method of embodiment 1, wherein the subject is provided a first oral daily dose in the form of about 44.7 mg APC-HCl and a second oral daily dose in the form of about 89.3 mg APC-HCl.

Embodiment 8: The method of embodiment 1, wherein the first oral daily dose and second oral daily dose are each administered upon the subject's awakening.

Embodiment 9: The method of embodiment 1, wherein the first oral daily dose and second oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

Embodiment 10: The method of embodiment 1, wherein the subject is a human.

Embodiment 11: The method of embodiment 1, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

Embodiment 12: The method of embodiment 1, wherein n_1 is an integer equal to or greater than 7.

Embodiment 13: A method of providing APC-HCl to a renally impaired subject with narcolepsy in need thereof, said method comprising:

providing to the subject an oral daily dose equivalent to 37.5 mg APC,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC; and

wherein the renally impaired subject has an eGFR of about 15 ml/min/1.73 m^2 to about 29 ml/min/1.73 m^2.

Embodiment 14: The method of embodiment 13, wherein the oral daily dose is provided to the renally impaired subject in the form of 44.7 mg APC-HCl.

Embodiment 15: The method of embodiment 13, wherein the oral daily dose is administered upon the subject's awakening.

Embodiment 16: The method of embodiment 13, wherein the oral daily dose is administered more than nine hours in advance of the subject's bedtime.

Embodiment 17: The method of embodiment 13, wherein the subject is a human.

Embodiment 18: The method of embodiment 17, wherein the subject is an adult.

Embodiment 19: The method of embodiment 13, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

Embodiment 20: A method of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Embodiment 21: The method of embodiment 20, further comprising increasing the dose to a maximum equivalent to 75 APC once daily after at least 5 days.

Embodiment 22: The method of embodiment 21, wherein the dose is increased to a maximum equivalent to 75 mg APC once daily after at least 7 days.

Embodiment 23: A method of treating excessive daytime sleepiness in a renally impaired subject with narcolepsy in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2; thereby treating excessive daytime sleepiness in the subject.

Embodiment 24: A method of guiding APC therapy in a renally impaired subject with narcolepsy in need thereof, comprising

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of less than 15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily; or

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 25: The method of embodiment 24, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 26: The method of embodiment 24, wherein the dose is increased from a dose equivalent to 75 mg APC to a dose equivalent to 150 mg APC after at least 3 days if the subject has mild renal impairment and the dose is increased from a dose equivalent to 37.5 mg APC to a dose equivalent to 75 mg APC after at least 7 days if the subject has moderate renal impairment.

Embodiment 27: A method of guiding APC therapy in a renally impaired subject with obstructive sleep apnea in need thereof, comprising:

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of less than 15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl according to a regimen recommended for subjects without renal impairment if the subject has mild renal impairment, said regimen comprising an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily;

or administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 28: The method of embodiment 27, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 29: The method of embodiment 27, wherein the regimen comprises doubling the dose of APC-HCl at intervals of at least 3 days if the subject has mild renal impairment and increasing the dose from a dose equivalent to 37.5 mg APC to a dose equivalent to 75 mg APC after at least 7 days if the subject has moderate renal impairment.

Embodiment 30: A method of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily,

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Embodiment 31: The method of embodiment 30, wherein the dose is increased to a maximum equivalent to 75 mg APC once daily after at least 7 days.

Embodiment 32: A method of treating excessive daytime sleepiness in a renally impaired subject with obstructive sleep apnea in need thereof, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily;

wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby treating excessive daytime sleepiness in the subject.

Embodiment 33: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising:

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily;

increasing the daily dose to a maximum dose equivalent to 75 mg APC after at least 7 days;

wherein the subject has an eGFR of 30-59 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl therapy in the subject.

Embodiment 34: The method of embodiment 33, wherein the initial dose is provided in the form of about 44.7 mg APC-HCl and the maximum dose is provided in the form of about 89.3 mg APC-HCl.

Embodiment 35: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APC once daily; wherein the subject has an eGFR of 15-29 ml/min/1.73 m^2, thereby reducing toxicity of APC-HCl in the subject.

Embodiment 36: The method of embodiment 35, wherein the maximum dose is provided in the form of about 44.7 mg APC-HCl.

Embodiment 37: A method of reducing toxicity of APC-HCl therapy in a renally impaired subject, comprising:

a. determining if the subject has mild renal impairment (an eGFR of 60-89 ml/min/1.73 m^2), moderate renal impairment (an eGFR of 30-59 ml/min/1.73 m^2), severe renal impairment (an eGFR of 15-29 ml/min/1.73 m^2), or end stage renal disease (an eGFR of <15 ml/min/1.73 m^2); and

b. administering to the subject APC-HCl at a dose of APC-HCl recommended for subjects without renal impairment if the subject has mild renal impairment, wherein the dose of APC-HCl recommended for subjects without renal impairment comprises an initial dose equivalent to 75 mg APC once daily and a maximum dose equivalent to 150 mg APC once daily after at least 3 days; or

administering to the subject APC-HCl at an initial dose equivalent to 37.5 mg APC once daily and a maximum dose equivalent to 75 mg APC once daily after at least 7 days if the subject has moderate renal impairment; or

administering to the subject APC-HCl at a maximum dose equivalent to 37.5 mg APCl once daily if the subject has severe renal impairment; or

not administering to the subject APC-HCl if the subject has end stage renal disease.

Embodiment 38: The method of embodiment 37, further comprising measuring the eGFR in the subject prior to step a.

Embodiment 39: The method of embodiment 37, wherein the eGFR is calculated by the Modification of Diet in Renal Disease equation.

Embodiment 40: The method of embodiment 37, wherein the subject is a human.

Embodiment 41: The method of embodiment 40, wherein the subject is an adult.

Embodiment 42: The method of embodiment 37, wherein the APC-HCl is administered orally.

Embodiment 43: The method of embodiment 37, wherein the APC-HCl is formulated with a pharmaceutical carrier.

Embodiment 44: The method of embodiment 37, wherein the subject is being treated for excessive daytime sleepiness associated with narcolepsy.

[The present invention is explained in greater detail in the following non-limiting Examples. Each example has a self-contained list of references.

Example 1: Evaluation of the PK of Solriamfetol HCl in Participants with Renal Impairment and Those with ESRD Undergoing Hemodialysis Compared with Healthy Participants with Normal Renal Function

Methods

In healthy subjects with normal renal function, solriamfetol HCl is renally excreted ~90% unchanged within 48 hours of administration. Thus, renal impairment, as well as hemodialysis in individuals with end-stage renal disease (ESRD), could affect the PK of solriamfetol HCl. To ascertain the precise impact of renal impairment and hemodialysis on pharmacokinetics and safety of solriamfetol HCl, a Phase 1, parallel-group, open-label, single-dose study was conducted at 2 U.S. sites. The protocol was approved by the IntegReview Institutional Review Board (Austin, Texas), and the study was conducted in compliance with the protocol, the Guideline for Good Clinical Practice E6; the US Code of Federal Regulations pertaining to conduct and reporting of clinical studies; the Clinical Trials Directive of the European Medicines Agency (Directive 2001/20/EC); and the Declaration of Helsinki. Written informed consent was obtained from each subject before enrollment in the study and before performance of any study-related procedure. See, also, Zomorodi K, Chen D, Lee L, Lasseter K, Marbury T. An Open-Label, Single-Dose, Phase 1 Study of the Pharmacokinetics and Safety of JZP-110 in Subjects With Normal or Impaired Renal Function and With End-Stage Renal Disease Requiring Hemodialysis [abstract]. *Sleep*. 2017; 40 (suppl): A382-383.

Eligible participants were men and non-pregnant, non-lactating women between the ages of 18 and 80 years, with a body mass index (BMI)≤35 kg/m^2. Women of childbearing

potential were required to have used a medically accepted method of birth control for at least 2 months prior to the first dose of study drug, with continued use throughout the study period and for 30 days after study completion. Participants were excluded if they had a clinically significant medical abnormality (other than renal impairment or its underlying causes), or any unstable conditions including neurological or psychiatric disorder, hepatic, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease, or any other abnormality that could interfere with the PK evaluation of the study drug or the participant's completion of the trial.

Eligible participants were assigned to 1 of 5 groups according to renal disease status as measured by the estimated glomerular filtration rate (eGFR) on the day prior to dosing, calculated using the Modification in Diet in Renal Disease equation. Group 1 consisted of healthy participants with normal renal function (eGFR≥90 mL/min/1.73 m^2) and served as the control group. Groups 2, 3, and 4 had mild, moderate, and severe renal impairment based on eGFRs of 60-89, 30-59, and <30 mL/min/1.73 m^2, respectively. Group 5 consisted of participants with ESRD who required ≥3 hemodialysis treatments per week for the preceding 3 months. Every effort was made to ensure that the groups were comparable with respect to age, sex, and body mass index (BMI). Group 1 was enrolled last to facilitate matching the mean age, BMI, and sex distribution of Groups 2-5.

Among participants with impaired renal function, continued use of medications necessary for treatment of renal function and/or coexisting disease was allowed, with the exception of monoamine oxidase inhibitors and medications with known risk for torsade de pointes.

Groups 1-4 received one dose of solriamfetol HCl (89.3 mg; equivalent to 75-mg solriamfetol) on day 1; Group 5 received one dose equivalent to 75-mg dose on day 1 followed by 4-hour hemodialysis (designated Group 5.2), and one dose equivalent to 75-mg solriamfetol on day 8 without hemodialysis (designated Group 5.1). All doses were administered on an empty stomach following an overnight fast except for participants in Group 5, who received a standardized snack on day 7 and breakfast early on day 8 before starting an 8-hour fast. Participants remained fasting for 4 hours after administration, with water allowed except for 1 hour before and after dosing.

In this study, 75 mg solriamfetol was selected as the dose for administration in participants with renal impairment as it was considered sufficiently low and potentially safe for this population. The 75-mg dose was expected to result in plasma concentrations of solriamfetol that were above the assay detection level at time points sufficient to characterize the PK profile.

Serial blood samples of approximately 4 mL were collected within 30 minutes prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-dose in Groups 1-3, with continued sampling at 60 and 72 hours post-dose in Groups 4 and 5. All blood samples were collected into labeled K2EDTA tubes by direct venipuncture or indwelling catheter and kept on ice until the samples were centrifuged within 30 minutes of collection at approximately 2500 rpm (1315×g) at 4° C. for 10 minutes. The plasma was transferred into polypropylene tubes for freezing and storage at −70° C. until analysis.

Urine samples were collected predose and for the time intervals of 0-4, 4-8, 8-12, 12-24, and 24-48 hours in Groups 1-3, with additional collection for the 48-72 hour time interval in Groups 4 and 5. During the hemodialysis period on day 1 for Group 5, dialysate samples and pre- and post-dialyzer paired blood samples were collected at predialysis (2 hours), and at 3, 4, 5, and 6 hours following dosing. Urine and dialysate samples were aliquoted into polypropylene tubes for freezing and storage at −70° C. until analysis. All blood, urine, and dialysate samples were shipped on dry ice to a central bioanalytical laboratory.

Bioanalytical analyses were performed by a central laboratory (KCAS, LLC, Shawnee, Kansas) using validated proprietary methods that included extraction/derivatization and liquid chromatography—tandem mass spectrometry (LC-MS/MS). Measurement of solriamfetol was over the linear range of 8.42 to 4,210 ng/mL in plasma, 0.21 to 84.2 μg/mL in urine, and 1.68 to 842 ng/mL in dialysate. Solriamfetol was removed from dialysate samples with use of the Fresenius Optiflux F180NR dialyzer (Fresenius Medical Care, Waltham, Massachusetts). Assay performance was monitored by spiking blank interference free human plasma with positive controls and internal standards to generate standard curve and quality control samples. After derivatization, samples were chromatographed on a C8 reversed phase analytical HPLC (high-performance liquid chromatography) column, with subsequent monitoring using an API4000 LC-MS/MS unit (Sciex, Framingham, Massachusetts). Quantification was based on setting a calibration graph using the internal standard method. Coefficients of variation (CVs) for quality control samples were 3.2% to 6.0% for the plasma samples, 1.6% to 5.6% for the urine samples, and 3.5% to 7.1% for the dialysate samples.

The following plasma PK parameters were evaluated using non-compartmental analysis in Phoenix® WinNonlin® Version 6.3: C_{max}; time to reach C_{max} following drug administration (t_{max}); $t_{1/2}$; area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_t); AUC from time zero to infinity (AUC_∞); apparent total clearance of the drug from plasma after oral administration (CL/F); and apparent volume of distribution (V_d/F). The PK parameters for solriamfetol in urine included the amount of unchanged drug excreted in urine (A_e) over 48 or 72 hours; the fraction of the dose excreted unchanged in urine (F_e); and renal clearance of the drug (CL_R). For participants on hemodialysis (Group 5), the additional PK parameters included the amount of solriamfetol cleared by the 4-hour hemodialysis (A_{dial}); the fraction of dose removed by the 4-hour hemodialysis (F_{dial}); and hemodialysis clearance (CL_{dial}) calculated as $CL_{dial}=A_{dial}/AUC_{dial}$ where AUC_{dial} is the area under the pre-dialyzer plasma concentration-time curve during the hemodialysis period.

PK parameters were summarized by group using descriptive statistics. To assess differences in PK between each level of renal impairment (Groups 2-5) versus participants with normal renal function (Group 1), a linear effects model was used to compare natural log-transformed PK parameters (C_{max}, AUC_t, and AUC_∞). For Group 5, the participants without dialysis on day 8 (Group 5.1) and the participants who received dialysis on day 1 (Group 5.2) were analyzed and compared separately.

Point estimates and 90% confidence intervals (CIs) for differences on the natural log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. The 90% CIs around the geometric means ratios were presented for each pairwise comparison and expressed as a percentage relative to the geometric means of the reference group (Group 1). The inter-participant CV was estimated. To evaluate effects of dialysis on PK parameters for Group 5, an analysis of variance model was used that included "Day" as a fixed effect and measurements within the participant as a repeated measure. Day 8 was used as the reference for comparison. In addition, nonparametric analysis was conducted for t_{max} as appropriate.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Of the 31 participants who were enrolled and received treatment (6 participants in each of Groups 1 through 4 and

7 participants in Group 5), 30 participants (97%) completed the study. One participant from Group 5 discontinued due to adverse events. Participant demographics (Table 1) show that most participants in Groups 1-4 were white; however, most participants in Group 5 were black. There were at least 2 participants per sex in each group, and mean age for Groups 1, 2, 3, and 4 were comparable with an overlap in the range; the age range in Group 5 was lower than in the other groups. Mean BMI for Groups 1, 2, 3, 4, and 5 were comparable, with an overlap in the range. Furthermore, all participants in Group 1 matched the mean age (±10 years) and BMI (±20%) of participants in Groups 2-5.

TABLE 1

Demographic Characteristics of the Study Population

Variable	Group 1 Normal renal function (n = 6)	Group 2 Mild renal impairment (n = 6)	Group 3 Moderate renal impairment (n = 6)	Group 4 Severe renal impairment (n = 6)	Group 5 End-stage renal disease (n = 7)
Sex, n (%)					
Female	3 (50)	4 (67)	2 (33)	2 (33)	2 (29)
Male	3 (50)	2 (33)	4 (67)	4 (67)	5 (71)
Race, n (%)					
White	5 (83)	5 (83)	4 (67)	5 (83)	1 (14)
Black	1 (17)	1 (17)	2 (33)	1 (17)	6 (86)
Ethnicity, n (%)					
Non- Hispanic or Latino	0	3 (50)	2 (33)	3 (50)	6 (86)
Hispanic or Latino	6 (100)	3 (50)	4 (67)	3 (50)	1 (14)
Age, mean (SD), y	55.8 (3.9)	67.8 (7.4)	70.2 (7.7)	59.7 (15.6)	42.0 (7.6)
Weight, mean (SD), kg	73.1 (6.8)	67.1 (14.2)	76.8 (11.5)	85.5 (16.4)	88.2 (10.5)
BMI, mean (SD), kg/m2	28.1 (2.7)	25.1 (4.1)	28.8 (1.9)	29.3 (3.0)	29.9 (3.0)
eGFR, mean (SD), mL/min/1.73 m2	111.8 (32.3)	78.5 (8.4)	44.2 (6.2)	16.2 (5.8)	7.4 (4.8)

BMI = body mass index

For all study groups, mean PK parameters are summarized in Table 2 and mean plasma solriamfetol concentration-time profiles are shown in FIGS. **1**A and **1**B.

TABLE 2

Solriamfetol Pharmacokinetic Parameters by Level of Renal Function

	Mean ± standard deviation (% coefficient of variation)					
					End-stage renal disease (Group 5)	
	Normal renal function	Renal impairment			Group 5.1	Group 5.2
Variable	Group 1 (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Without hemodialysis[a] (n = 6)	With hemodialysis (n = 7)[b]
C_{max}, ng/mL	499.0 ± 142.4 (28.5)	521.8 ± 118.8 (22.8)	517.3 ± 131.6 (25.4)	552.8 ± 154.4 (27.9)	474.1 ± 79.0 (16.7)	396.4 ± 75.4 (19.0)
t_{max},[c] h	1.3 (0.5, 2.0)	1.5 (0.5, 2.0)	1.5 (1.0, 2.5)	2.0 (0.5, 3.0)	3.3 (1.0, 24.0)	1.5 (1.5, 10.0)
$t_{1/2}$, h	7.6 ± 5.1 (67.7)	9.1 ± 1.6 (18.1)	14.3 ± 4.5 (31.4)	29.6 ± 14.4 (48.7)	100.5 ± 78.8 (78.4)[d]	164.7 ± 81.4 (49.4)[e]
AUC_{τ}, ng · h/mL[f]	4849 ± 3454 (71.2)	6613 ± 1574 (23.8)	9230 ± 2538 (27.5)	17 500 ± 9267 (52.9)	25 580 ± 4544 (17.8)	18 920 ± 3131 (16.5)
AUC_{∞}, ng · h/mL	5273 ± 4104 (77.8)	6836 ± 1730 (25.3)	10 470 ± 3642 (34.8)	23 650 ± 16 776 (70.9)	64 560 ± 35 962 (55.7)[d]	76 770 ± 41 993 (54.7)[e]
CL/F, L/h	19.8 ± 10.1 (50.9)	11.5 ± 2.5 (22.1)	7.8 ± 2.4 (30.5)	4.7 ± 2.8 (59.4)	1.6 ± 1.1 (72.3)[d]	1.5 ± 1.3 (91.0)[e]

TABLE 2-continued

Solriamfetol Pharmacokinetic Parameters by Level of Renal Function

Mean ± standard deviation (% coefficient of variation)

Variable	Normal renal function Group 1 (n = 6)	Renal impairment Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	End-stage renal disease (Group 5) Group 5.1 Without hemodialysis[a] (n = 6)	Group 5.2 With hemodialysis (n = 7)[b]
V_d/F, L	163.9 ± 23.8 (14.5)	147.2 ± 29.1 (19.8)	152.0 ± 32.6 (21.4)	157.2 ± 41.2 (26.2)	153.6 ± 45.6 (29.7)[d]	231.4 ± 28.5 (12.3)[e]

[a]Baseline adjusted to remove the impact of the day 1 dose on the day 8 concentration profile.
[b]Excluding 2 concentration values: 1 participant at predose, and 1 participant at 24 hours.
[c]For t_{max}, median (min, max) is presented.
[d]n = 3.
[e]n = 6.
[f]Over 48 h for normal, mild, and moderate, and over 72 h for severe.

In general, mean C_{max} and t_{max} were not substantially affected by renal impairment across Groups 1-4 (Table 2). However, solriamfetol AUC and $t_{1/2}$ values increased with increasing levels of renal impairment. Solriamfetol mean±SD overall exposure (AUC_∞) increased from 5273±4104 ng·h/mL in participants with normal renal function to 6836 ng·h/mL±1730 in Group 2 (mild impairment), 10,470±3642 in Group 3 (moderate impairment), and 23,650±16,776 in Group 4 (severe impairment) (Table 2) Similarly, solriamfetol mean±SD $t_{1/2}$ was 7.6±5.1 hours in participants with normal renal function and increased with greater levels of renal impairment: 9.1±1.6, 14.3±4.5, and 29.6±14.4 hours in Groups 2, 3, and 4, respectively (Table 2). While CL/F decreased with greater levels of renal impairment, there were no substantial changes in V_d/F (Table 2). A plot of solriamfetol CL/F versus day −1 eGFR for Groups 1-4 is presented in FIG. **2**. This relationship is best described by the equation: solriamfetol CL/F (L/h)= 0.63184+0.16463×eGFR (mL/min/1.73 m^2).

Among participants with ESRD (Group 5), overall exposure (AUC_t) was approximately 5-fold higher for participants without dialysis on day 8 (Group 5.1; 25 580±4544 ng·h/mL) and about 4-fold higher among participants with dialysis on day 1 (Group 5.2; 18 920±3131) relative to Group 1 (4849±3454) (Table 2). Mean $t_{1/2}$ values exceeded 100 hours in both Group 5.1 (100.5 hours) and Group 5.2 (164.7 hours) (Table 2), and compared with Group 1, C_{max} values were slightly lower and t_{max} values differed significantly (P≤0.05 for both).

Ratios of geometric means and their associated 90% CIs for the pairwise comparisons of solriamfetol plasma PK parameters for Groups 2 through 5 versus Group 1 are presented in Table 3.

TABLE 3

Comparisons of Solriamfetol Plasma PK Parameters

PK parameter	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)[a]
			Geometric LS mean			
Cmax, ng/mL	482.3	510.5	503.2	533.0	468.8	389.9
AUCt, ng · h/mLb	4087.3	6469.6	8960.2	15 549	25 253	18 689
AUC∞ ng · h/mL	4363.9	6672.4	10002	19 140	56 319c	65 306d
			Percent ratio (90% confidence interval) of geometric mean relative to Group 1			
Cmax	—	105.9 (80.6, 139.0)	104.3 (78.4, 138.9)	110.5 (81.1, 150.6)	97.2 (76.1, 124.1)	80.9 (63.4, 103.1)
AUCt	—	158.3 (97.5, 256.9)	219.2 (133.7, 359.6)	380.4 (208.4, 694.4)	617.8 (385.3, 990.8)	457.2 (296.6, 704.9)

TABLE 3-continued

Comparisons of Solriamfetol Plasma PK Parameters

PK parameter	Group 1 Normal (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)[a]
AUC∞	—	152.9 (92.9, 251.7)	229.2 (135.6, 387.4)	438.6 (217.3, 885.3)	1290.6 (542.78, 3068.5)	1496.5 (748.7, 2991.2)

Notes:

Parameters were In-transformed prior to analysis. Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the analysis of variance. % mean ratio = 100*(test/reference).

[a]Excluding 2 concentration values: 1 participant at predose, and 1 participant at 24 hours.

bOver 48 hours for Groups 1-3 and over 72 hours for Groups 4 and 5.

cn = 3.

dn = 6.

As shown, small increases were observed in C_{max}, which was approximately 6%, 4%, and 11% higher in Groups 2, 3, and 4, respectively, versus Group 1. However, total solriamfetol exposure (AUC_{∞}) in Groups 2, 3, and 4 was 53%, 129%, and 339% higher, respectively, relative to Group 1. In participants with ESRD, C_{max} was approximately 3% and 19% lower in groups 5.1 (ESRD without hemodialysis) and 5.2 (ESRD with hemodialysis), respectively, versus Group 1, and exposure was approximately 518% and 357% higher in the 2 groups versus Group 1.

Renal clearance (CL_R) and the cumulative amount of solriamfetol excreted in urine decreased as renal impairment increased (Table 4).

TABLE 4

Urinary Excretion of Solriamfetol

PK parameter	Mean ± standard deviation (% coefficient of variation) Group 1 Normal renal function (n = 6)	Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)
$F_{e(0\text{-}48)}$, %	85.8 ± 7.7 (9.0)	80.0 ± 9.0 (11.2)	66.4 + 12.8 (19.2)	57.1 ± 18.6 (32.5)
CL_R, L/h	17.0 ± 7.7 (45.4)	9.3 ± 1.6 (17.1)	5.8 ± 2.0 (34.1)	3.8 ± 2.6 (68.0)

CL_R, renal clearance; $F_{e(0\text{-}48)}$, fraction of the dose excreted unchanged in urine in 48 hours.

In Group 1, the mean±SD percentage of solriamfetol recovered unchanged in urine over 48 hours was 85.8%±7.7% and decreased to 80.0%±9.0%, 66.4%±12.8%, and 57.1%±18.6% in Groups 2, 3, and 4, respectively. Mean solriamfetol renal clearance also decreased with renal impairment, from 17.0±7.7 L/h in the normal renal function group to 9.3±1.6 L/h in Group 2, 5.8±2.0 L/h in Group 3, and 3.8±2.6 L/h in Group 4. Only 1 participant made urine and was able to provide data in Group 5, and the cumulative amount of solriamfetol excreted in urine was lower with hemodialysis, 42.1%, compared with 52.9% without hemodialysis.

Over the 4-hour hemodialysis period on day 1 for participants with ESRD, the mean±SD cumulative fraction of the 75-mg solriamfetol dose removed was 20.6%±1.7% (range 19.2% to 24.1%), and the hemodialysis clearance was 12.4 L/h±1.5 L/h (range 11.3 to 15.9 L/h).

There were no deaths or other serious AEs during this study. A total of 4 participants (13%), 1 each in Groups 2 and 3, and 2 in Group 5 (1 with and 1 without hemodialysis), reported 5 treatment-emergent adverse events (TEAEs; Table 5). This includes single events of nausea, skin abrasion, and headache in 1 participant each, and an increase in alanine aminotransferase (ALT; to 144 IU/L; reference range 8-54 IU/L) and aspartate aminotransferase (AST; to 66 IU/L; reference range 8-40 IU/L) observed 6 days after dosing in 1 participant that led to discontinuation. All TEAEs were considered by the investigator to be mild, and all but the skin abrasion were considered to be related to study drug. All TEAEs resolved, including the increased ALT and AST, which resolved on day 11. No other abnormal laboratory findings were considered clinically meaningful. No clinically significant abnormal findings were observed in vital sign and ECG measurements.

TABLE 5

Number (%) of Participants with Treatment-Emergent Adverse Events (TEAEs)

Adverse event	Normal renal function: Group 1 Normal (n = 6)	Renal impairment: Group 2 Mild (n = 6)	Renal impairment: Group 3 Moderate (n = 6)	Renal impairment: Group 4 Severe (n = 6)	End-stage renal disease (Group 5): Group 5.1 Without hemodialysis (n = 6)	End-stage renal disease (Group 5): Group 5.2 With hemodialysis (n = 7)
Any TEAE	0	1 (17%)	1 (17%)	0	1 (17%)	1 (14%)
Nausea	0	0	0	0	1 (17%)	0
Skin abrasion	0	1 (17%)	0	0	0	0
ALT increased	0	0	0	0	0	1 (14%)

TABLE 5-continued

Number (%) of Participants with Treatment-Emergent Adverse Events (TEAEs)

Adverse event	Normal renal function Group 1 Normal (n = 6)	Renal impairment Group 2 Mild (n = 6)	Group 3 Moderate (n = 6)	Group 4 Severe (n = 6)	End-stage renal disease (Group 5) Group 5.1 Without hemodialysis (n = 6)	Group 5.2 With hemodialysis (n = 7)
AST increased	0	0	0	0	0	1 (14%)
Headache	0	0	1 (17%)	0	0	0

[a]One participant from Group 5 discontinued the study before day 8 due to adverse events of mild elevated ALT and AST.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

This study showed that renal impairment increases overall exposure to solriamfetol, with the magnitude of the increase reflecting the level of impairment. The incremental decreases in CL/F with worsening renal function resulted in corresponding increases in overall solriamfetol exposure that was 53% for mild, 129% for moderate, and 339% for severe impairment relative to normal renal function. Increasing renal impairment was also associated with decreasing cumulative percent of solriamfetol excreted in urine. The mean percentage of solriamfetol dose recovered in urine as unchanged drug over 48 hours was 85.8%, 80.0%, 66.4% and 64.0% (over 72 hours) for subjects with normal renal function and for subjects with mild, moderate, and severe renal impairment, respectively. Additionally, since there were no substantial changes in V_d/F, the decreases in solriamfetol CL/F resulted in increased $t_{1/2}$ by approximately 1.2-, 1.9-, and 3.9-fold in participants with mild, moderate, and severe renal impairment, respectively, compared with participants with normal renal function. In this regard, it should also be noted that while C_{max} values were not substantially affected by renal impairment, the observed increases in $t_{1/2}$ associated with renal impairment are expected to translate to changes in steady-state C_{max} that are not fully accounted for by the single-dose regimen evaluated in this clinical study, due to accumulation. AUC and $t_{1/2}$ values increased with increasing levels of renal impairment. Solriamfetol $AUC_{0\text{-}inf}$ was higher by approximately 53% (1.53-fold), 129% (2.29-fold), and 339% (4.39-fold) compared with subjects with normal renal function.

Consistent with the inability of ESRD participants requiring hemodialysis to eliminate solriamfetol via renal excretion, these participants had increased overall exposure to solriamfetol (≥4-fold), longer $t_{1/2}$ values (≥13-fold), and slightly lower C_{max} values (≤19%), relative to participants with normal renal function. Furthermore, ESRD participants had lower solriamfetol C_{max} and AUC_{∞} values after undergoing a 4-hour hemodialysis session, with 20.6% of the solriamfetol dose removed as unchanged drug. Notably, the solriamfetol hemodialysis clearance of 12.4 L/h estimated from solriamfetol recovered in the dialysate was approximately 30% lower than solriamfetol renal clearance in participants with normal renal function.

Example 2: Simulations of Solriamfetol Exposure in Patients with Renal Impairment

Methods

A population PK model was developed based on data collected in clinical studies. The population PK model provides a unified characterization of solriamfetol and of its sources of variability across studies and sub-populations of subjects. The population PK analysis examined the influence of potential covariates that have not been evaluated in clinical trials, such as potential differences between narcolepsy and OSA patients, as well as healthy subjects and narcolepsy/OSA patients, and investigated other factors such as age, gender, body weight, race/ethnicity, and formulation effects.

The following thorough evaluation of the source data was performed: (1) Visual inspection of individual plasma concentration-time profiles of solriamfetol relative to actual dosing history (e.g., spaghetti plots for rich concentration-time profiles, mean profiles); (2) Evaluation of potential outliers based on preliminary population PK runs (e.g., using a one compartment model without covariate); and (3) Review of demographic data and baseline characteristics for each study.

The dataset included actual time of observation (sampling and dosing) and main demographic characteristics (covariates) such as age, weight, height, body mass index (BMI), gender, race and markers of renal and liver functions. Extrinsic covariates were also included. The following main variables were included in the analysis dataset.

- NMID (unique individual identifier)
- STUDY (study identifier)
- SUBJ (subject ID used in the study)
- DATE (date of the event MM/DD/YYYY)
- TIME (time of the event HH:MM)
- DV (plasma concentration of solriamfetol, ng/mL)
- AMT (actual dose of solriamfetol in mg, calculated based on free base weight)
- EVID (event identification for PK observations only: 0=non-below the limit of quantification [BLQ] PK observation, 1=dose administration, 2=other-type event [BLQ PK records])
- MDV (missing data code: 0=non-missing, 1=missing data or excluded data)
- BLQ (1=BLQ concentration, 0=non-BLQ concentration or dosing event)
- FAST (fasted status during administration: 1=fasted; 0=fed)
- FORM (formulation: 0=drug substance in capsule; 1=tablet; 2=over-encapsulated tablet)
- Daily dose (actual dose of solriamfetol in mg, calculated based on free base weight)
- DS (disease status: 0=healthy subjects, 1=subjects with narcolepsy; 2=subjects with OSA)
- WT (body weight at screening in kg)

Age at baseline (age in years)
Age as a categorical covariate (i.e., non-elderly vs. elderly ≥65 years old)
Race (White, Black, Asian, Native Hawaiian or other Pacific Islander, Hispanic, Oriental, other)
Ethnicity (1=Hispanic or Latino, 0=non-Hispanic or Latino)
Gender (0=female, 1=male)
TAD (time after previous dose in h)
VISIT (visit number)
NTIME (nominal time after the dose in hours)
CRCL at baseline (creatinine clearance in mL/min calculated by Cockcroft-Gault formula) (Cockcroft D W, Gault M H: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41)
eGFR at baseline
Renal impairment status based on Food and Drug Administration (FDA) guidance 10:
Normal: eGFR≥90 mL/min/1.73 m^2
Mild: eGFR 60-89 mL/min/1.73 m^2 (i.e., ≥60 to <90)
Moderate: eGFR 30-59 mL/min/1.73 m^2 (i.e., ≥30 to <60)
Severe: eGFR 15-29 mL/min/1.73 m^2 (i.e., ≥15 to <30) and not on hemodialysis
End-stage renal disease (ESRD): eGFR<15 mL/min/1.73 m^2 and not on hemodialysis or patients on hemodialysis
HT (height in m)
BMI at baseline (body mass index in kg/m2)
BSA at baseline (body surface area, calculated by Dubois and Dubois formula) (DuBois D; DuBois E F: A formula to estimate the approximate surface area if height and weight be known. Arch Int Med 1916 17:863-71)
ALT at baseline (alanine aminotransferase in U/L)
AST at baseline (aspartate aminotransferase in U/L)
ALB at baseline (albumin in g/L)
Bioanalytical method (High performance liquid chromatography [HPLC] or Liquid chromatography-tandem mass spectrometry [LC-MS/MS]).

Base Population PK Model Buildup

In a first step, compartmental PK models without covariates were evaluated to assess the PK of solriamfetol. One and two-compartment models with linear disposition were tested to assess the concentration-time profiles of solriamfetol.

Model Buildup

The population PK model included the following.

1. A structural component describing the relationships between plasma concentration and time using the following equation:

$$Cp_{ij}=C(D_i,t_j,\theta_i)\cdot(1+\varepsilon_{p,ij})+\varepsilon_{a,ij}$$

$$\theta_i=\theta_{i1},\ldots,\theta_{ip})$$

wherein Cp_{ij} is the concentration at the j^{th} collection time t_j for subject i, Di represents dosing history for subject i, θ_i is the vector of p different PK parameters for subject i, and $\varepsilon_{p,ij}$ and $\varepsilon_{a,ij}$ are the proportional and additive random residual error terms, respectively, associated with jth concentration for subject i. ε_p and ε_a are normally distributed with mean 0 and variances σ_p^2 and σ_a^2, respectively.

2. A variance component characterizing between-subject variability (BSV) and, if required, inter-occasion variability (IOV) in model parameters.

$$\theta_{ink}=(\theta_{TV,n}e^{(\eta_{in}+\psi_{ink})})$$

$$(\eta_1,\ldots,\eta_p)=MVN(0,\Omega)$$

$$\psi_{nk}=N(0,\Phi_n)$$

where θ_{ink} is the value of the n^{th} PK parameter of the ith individual on the kth occasion, $\theta_{TV,n}$ is the typical value of the nth PK parameter in the population, η_{in} is the random inter-individual deviation from the typical value $\theta_{TV,n}$ for subject i, and ψ_{ink} is the random inter-occasion subject deviation from the value of the nth parameter for subject i on occasion k. Inter-individual random effects ($\eta_1,\ldots,\eta_m$), also known as ETAs, are multivariate normally distributed with mean 0 and estimated variance ω_n^2 included in the variance-covariance OMEGA (Ω) matrix. Inter-occasion random effects for the nth parameter ψ_{ink} are normally distributed with mean 0 and variance Φ_n, with all $\psi_{n1},\ldots\psi_{nm}$ sharing the same variance, where m is the number of occasions.

The evaluation of the BSV/IOV models included possible addition of BSV terms (ETAs) to the model parameters, evaluation of the most appropriate form of the ETAs, and evaluation of pair-wise plots of the ETAs for any correlations. Covariance between ETA terms was estimated in the model where correlations between ETAs were deemed probable based on these diagnostic plots. Models with shared ETA were also considered.

3. Error models describing residual unexplained variability in the form of additive, proportional or additive and proportional models:

$$y_{ij}=*\hat{y}_{ij}*(1+\varepsilon_{1ij})+\varepsilon_{2ij}$$

where y_j and $\hat{y}_{ij}$ represent the jth observed and predicted plasma drug concentration for the ith participant and ε is the random residual variability. Each ε (ε_1 and ε_2) is normally distributed with mean 0 and variance σ^2. An allometric function accounting for body weight effect on clearance (CL/F) and volume of distribution (V/F) was included in the model. In addition, the effect of creatinine clearance was added on CL/F since the drug was previously demonstrated to undergo important renal excretion.

Model Evaluation

Consistent with the FDA/EMA Guidance for Industry, evaluation of the models was based on the following.

Standard model diagnostics and standard statistical criteria of goodness-of-fit criteria such as the log-likelihood difference between alternative models (e.g., a decrease in the objective function value [OFV])
Successful model convergence
Examining pertinent graphical representations of goodness-of-fit:
Observed data versus population predicted data (DV vs. PRED) and individual predicted data (DV vs. IPRED) with a line of unity and a trend line, on linear and log scales
Observed Data versus time after the 1st dose and after the previous dose (DV vs. time and DV vs. TAD) with trend lines of DV and PRED, on linear and log scales
Conditional weighted residuals versus predicted data (CWRES vs. PRED) with zero line and a trend line
Conditional weighted residuals versus time after the 1st dose and previous dose [CWRES vs. time and CWRES vs. TAD] with zero line and a trend line
Quantile-quantile plot of CWRES (QQ plot)
Estimating shrinkage of the empirical Bayesian estimates (EBEs) of the model parameters was evaluated for

diagnostic purpose. The shrinkage magnitude for a structural parameter 0 (q-shrinkage) was calculated as follow:

$$sh_\theta = 1 - \frac{SD(\eta_{EBE,P})}{\omega_\theta}$$

where $SD_{(\eta EBE,P)}$ is the standard deviation of the individual EBEs for parameter P, ω_P is the model estimate of the standard deviation associated with parameter P. If no shrinkage in parameter P is present, the ratio between $SD_{(\eta EBE,P)}$ and ω_P is unity, and shP becomes zero. Shrinkage reflects the degree of information available in the data to estimate the random effects independently, where a shrinkage of 100% reflects a case where there is no information at all on the random effect and all individual parameters revert back to the population estimate. Covariate effects may be interpreted with caution for PK parameters associated with high shrinkage (e.g., >30%), as the individual random effect estimates are expected to shrink towards zero.

Incorporation of Assay Conversion Factor

All plasma samples were assayed using an LC-MS/MS or an HPLC method. Exploratory analyses were performed to investigate potential differences in concentrations determined using the two different methods, and were used to guide further steps in model development, and whether or not an effect of assay was to be included as part of the base population PK model or the residual error model. As a consequence of the observed differences in concentrations due to use of the two different assay methodologies, an assay conversion factor (CF) was incorporated into the model to scale solriamfetol concentrations from HPLC assay to LC-MS/MS as per the following linear and nonlinear models:

$$C_{LC\text{-}MS/MS}=(C_{HPLC})\times CF \quad \text{Linear CF:}$$

$$C_{LC\text{-}MS/MS}=(C_{HPLC})^{CF} \quad \text{Nonlinear CF:}$$

In addition, different error models were considered for each assay. The CF was tested in the additive and proportional components of the error models. The selection of the final CF model was based on quality-of-fit using standard graphical representations of goodness-of-fit, including the diagnostic plots.

Sources of Variability and Covariate Analysis

The relationships between PK parameters and covariates were explored graphically to identify the covariates likely to affect the PK of solriamfetol. Scatter plots of the relationships between the random effect of PK parameters and continuous variables included LOESS lines, Pearson correlation coefficients, and the corresponding p-value for each relationship. Box plots were used to describe the relationship for categorical covariates. The investigated intrinsic factors included the following.

- Age at baseline (as a continuous covariate in years and/or categorical covariate [i.e., non-elderly (18-64) vs. elderly (?65 years old)]). Covariate was tested on CL/F, V/F and Ka.
- Gender. Covariate was tested on CL/F and V/F.
- Measures of body size at baseline (i.e., body weight): Included in the base model on CL/F and V/F.
- Ethnic origin/Race. Covariates were tested on CL/F and V/F.
- Markers of renal function at baseline (based on creatinine clearance): Included in the base model on CL/F.
- Markers of liver function at baseline (ALB, ALT and AST). Covariates were tested on CL/F and V/F.

The investigated extrinsic factors included:

- Nominal dose levels of JZP-110. Covariate was tested on CL/F, V/F and Ka.
- Formulation (Over-encapsulated Tablet vs. Tablet vs. drug substance in Capsule). Covariate was tested on CL/F, V/F and Ka.
- Fasted status (i.e., fed vs. fasted). Covariate was tested on Tlag and Ka.
- Disease status. Covariate was tested on CL/F and V/F.
  - Healthy subjects
  - Subjects with narcolepsy
  - Subjects with OSA

In the next step, the most relevant covariates were formally evaluated within the population PK model using a stepwise forward additive approach using a p-value of 0.01 (ΔOFV=6.63, for one degree of freedom [df]) and a backward elimination approach using a p-value of 0.001 (ΔOFV=10.83, for one df).

In addition, a nonparametric bootstrap resampling analysis was performed. The bootstrap technique involves repeatedly drawing random samples from the original data, with replacement. The bootstrap was used to reduce the model by removing covariates for which the 95% prediction interval (PI) included the null value relative to the reference population. Statistically significant covariates identified during the covariate analysis were displayed graphically in a forest plot. See, Menon-Andersen D, Yu B, Madabushi R, Bhattaram V, Hao W, Uppoor R S, Mehta M, Lesko L, Temple R, Stockbridge N, Laughren T, Gobburu J V. Essential pharmacokinetic information for drug dosage decisions: a concise visual presentation in the drug label. Clin Pharmacol Ther. 2011 September; 90(3):471-4.

Final Model

The final population PK model was evaluated using visual predictive check (VPC). Based on the estimates of the final model, concentration-time profiles were simulated using 1000 replicates. Observed and simulated data were separated into distinct bins. Within each bin, a 95% confidence interval of the 5th, 50th and 95th prediction intervals was obtained by simulation. The confidence intervals give an indication of the uncertainty of the predictions. The 5th, 50th and 95th percentiles of observed concentrations were compared to the 95% confidence intervals.

The final population PK model was used to simulate rich concentration-time profiles of solriamfetol in adult subjects with renal impairment (mild, moderate, severe, and ESRD) and in pediatric patients following administration of different dosing regimens.

The final population PK model was used to perform simulations in 10000 narcolepsy/OSA patients for each dose level of solriamfetol tablet formulation (37.5, 75, 150, and 300 mg), and exposure parameters (AUCtau, Cmax, Cmin, C14h and t½) were derived.

Descriptive statistics of exposure parameters for each dose level and according to each renal impairment category are presented in Tables 6-10. Boxplots of exposure parameters for each dose level and according to each renal impairment category are presented in FIGS. **3-7**. Simulated concentration-time profiles for each dose level and according to each renal impairment category are presented in Table 8.

TABLE 6

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Normal Renal Function

	Dose (mg) - Solriamfetol			
Parameters	37.5 (n = 10000)	75 (n = 10000)	150 (n = 10000)	300 (n = 10000)
	AUC_{tau} (ng · h/mL)			
Mean (CV %)	1931 (34.4%)	4139 (34.4%)	8874 (34.4%)	19024 (34.4%)
Median	1822	3906	8382	17952
[Min, Max]	[471, 7671]	[1010, 16473]	[2165, 35375]	[4641, 75968]
Geom. Mean (Geom. CV %)	1825 (34.6%)	3912 (34.6%)	8387 (34.6%)	17980 (34.6%)
	C_{max} (ng/mL)			
Mean (CV %)	202 (24.5%)	410 (24.6%)	835 (24.8%)	1702 (25.0%)
Median	197	399	811	1654
[Min, Max]	[79.1, 494]	[160, 1004]	[323, 2086]	[656, 4370]
Geom. Mean (Geom. CV %)	196 (24.5%)	398 (24.6%)	810 (24.8%)	1651 (25.0%)
	C_{min} (ng/mL)			
Mean (CV %)	19.6 (78.9%)	46.7 (75.0%)	110 (71.5%)	259 (68.4%)
Median	15.8	38.3	92.2	219
[Min, Max]	[0.0290, 194]	[0.104, 432]	[0.362, 961]	[1.21, 2132]
Geom. Mean (Geom. CV %)	14.3 (108%)	35.0 (99.2%)	84.9 (92.1%)	204 (85.9%)
	$C_{14\ h}$ (ng/mL)			
Mean (CV %)	53.6 (50.3%)	120 (48.5%)	268 (46.9%)	595 (45.5%)
Median	49.1	111	248	552
[Min, Max]	[1.21, 296]	[3.39, 642]	[9.32, 1390]	[25.1, 3007]
Geom. Mean (Geom. CV %)	47.1 (57.7%)	106 (54.7%)	240 (52.2%)	536 (50.0%)
	Half-life (h)			
Mean (CV %)	6.35 (30.7%)	6.81 (30.7%)	7.30 (30.7%)	7.82 (30.7%)
Median [Min, Max]	6.08 [1.71, 21.4]	6.52 [1.83, 22.9]	6.99 [1.96, 24.5]	7.50 [2.10, 26.3]
Geom. Mean (Geom. CV %)	6.08 (30.5%)	6.51 (30.4%)	6.98 (30.4%)	7.48 (30.5%)

AUC_{tau}: Area under the concentration-time curve at steady state; $C_{14\ h}$: concentration at 14 h post-dose at steady state; C_{max}: maximum concentration at steady state; C_{min}: concentration at 24 h post-dose at steady state; CV %: coefficient of variation; Min: minimum; Max: maximum; n: number of subjects.

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AUC_{tau}: Area under the concentration-time curve at steady state; C_{14h}: concentration at 14 h post-dose at steady state; C_{max}: maximum concentration at steady state; C_{min}: concentration at 24 h post-dose at steady state; CV %: coefficient of variation; Min: minimum; Max: maximum; n: number of subjects.

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TABLE 7

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Mild Renal Impairment

	Reference (Adult, Dose = 150 mg, Normal	Dose			
Parameters	Renal Function)	37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
		AUC_{tau} (ng · h/mL)			
Mean (CV %)	8874 (34.4%)	2624 (34.3%)	5626 (34.2%)	12059 (34.2%)	25853 (34.2%)
Median	8382	2479	5320	11395	24428
[Min, Max]	[2165, 35375]	[721, 9598]	[1548, 20619]	[3321, 44294]	[7124, 95152]
Geom. Mean (Geom. CV %)	8387 (34.6%)	2482 (34.4%)	5321 (34.3%)	11407 (34.3%)	24453 (34.3%)

TABLE 7-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Mild Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
		C_{max} (ng/mL)			
Mean (CV %)	835 (24.8%)	225 (24.8%)	461 (25.1%)	946 (25.3%)	1945 (25.6%)
Median	811	219	448	919	1890
[Min, Max]	[323, 2086]	[82.4, 550]	[167, 1158]	[338, 2444]	[686, 5171]
Geom. Mean (Geom. CV %)	810 (24.8%)	218 (24.8%)	447 (25.1%)	917 (25.3%)	1884 (25.6%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	39.8 (64.5%)	91.8 (61.9%)	211 (59.5%)	482 (57.4%)
Median	92.2	34.3	80.1	186	428
[Min, Max]	[0.362, 961]	[0.677, 289]	[2.06, 636]	[6.09, 1396]	[17.5, 3062]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	32.2 (77.9%)	75.7 (73.3%)	177 (69.3%)	409 (65.8%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	84.9 (43.8%)	187 (42.6%)	411 (41.6%)	902 (40.8%)
Median	248	79.1	175	384	845
[Min, Max]	[9.32, 1390]	[8.46, 385]	[21.3, 830]	[52.6, 1791]	[128, 3861]
Geom. Mean (Geom. CV %)	240 (52.2%)	77.2 (47.2%)	171 (45.6%)	378 (44.1%)	831 (42.9%)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	8.67 (30.8%)	9.29 (30.7%)	9.96 (30.7%)	10.7 (30.7%)
Median	6.99	8.26	8.85	9.48	10.2
[Min, Max]	[1.96, 24.5]	[2.69, 26.1]	[2.88, 28.0]	[3.09, 30.0]	[3.31, 32.2]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	8.29 (30.4%)	8.89 (30.4%)	9.53 (30.4%)	10.2 (30.4%)

AUC_{tau}: Area under the concentration-time curve at steady state; $C_{14\ h}$: concentration at 14 h post-dose at steady state; C_{max}: maximum concentration at steady state; C_{min}: concentration at 24 h post-dose at steady state; CV %: coefficient of variation; Min: minimum; Max: maximum; n: number of subjects.

TABLE 8

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Moderate Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
		AUC_{tau} (ng · h/mL)			
Mean (CV %)	8874 (34.4%)	3743 (36.6%)	8024 (36.6%)	17201 (36.5%)	36875 (36.5%)
Median	8382	3518	7539	16157	34617
[Min, Max]	[2165, 35375]	[777, 14484]	[1666, 31285]	[3570, 67577]	[7652, 145970]
Geom. Mean (Geom. CV %)	8387 (34.6%)	3517 (36.4%)	7540 (36.4%)	16164 (36.3%)	34651 (36.3%)
		C_{max} (ng/mL)			
Mean (CV %)	835 (24.8%)	266 (26.8%)	550 (27.2%)	1139 (27.6%)	2366 (28.0%)
Median	811	255	527	1093	2267
[Min, Max]	[323, 2086]	[87.6, 810]	[179, 1712]	[365, 3624]	[748, 7684]
Geom. Mean (Geom. CV %)	810 (24.8%)	257 (26.4%)	531 (26.8%)	1099 (27.2%)	2280 (27.6%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	78.3 (57.9%)	177 (56.1%)	397 (54.5%)	888 (53.0%)
Median	92.2	69.6	158	356	801

TABLE 8-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Moderate Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
[Min, Max]	[0.362, 961]	[1.00, 434]	[2.86, 961]	[7.96, 2126]	[21.7, 4695]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	66.4 (65.6%)	151 (62.8%)	343 (60.2%)	774 (58.0%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	135 (42.4%)	293 (41.7%)	638 (41.1%)	1385 (40.5%)
Median	248	125	273	594	1294
[Min, Max]	[9.32, 1390]	[9.10, 573]	[22.4, 1243]	[54.3, 2699]	[130, 5855]
Geom. Mean (Geom. CV %)	240 (52.2%)	123 (44.1%)	270 (43.1%)	588 (42.3%)	1281 (41.5%)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	12.4 (32.6%)	13.2 (32.5%)	14.2 (32.5%)	15.2 (32.5%)
Median	6.99	11.8	12.6	13.5	14.5
[Min, Max]	[1.96, 24.5]	[3.14, 40.3]	[3.37, 43.2]	[3.61, 46.3]	[3.87, 49.7]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	11.8 (32.4%)	12.6 (32.4%)	13.5 (32.4%)	14.5 (32.4%)

AUC_{tau}: Area under the concentration-time curve at steady state; $C_{14\ h}$: concentration at 14 h post-dose at steady state; C_{max}: maximum concentration at steady state; C_{min}: concentration at 24 h post-dose at steady state; CV %: coefficient of variation; Min: minimum; Max: maximum; n: number of subjects.

TABLE 9

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Severe Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
		AUC_{tau} (ng · h/mL)			
Mean (CV %)	8874 (34.4%)	5967 (36.9%)	12790 (36.8%)	27416 (36.8%)	58772 (36.8%)
Median	8382	5608	12026	25790	55249
[Min, Max]	[2165, 35375]	[1448, 20711]	[3129, 44391]	[6762, 95179]	[14323, 205161]
Geom. Mean (Geom. CV %)	8387 (34.6%)	5602 (36.6%)	12009 (36.6%)	25744 (36.6%)	55188 (36.5%)
		C_{max} (ng/mL)			
Mean (CV %)	835 (24.8%)	353 (29.3%)	738 (29.7%)	1546 (30.1%)	3243 (30.5%)
Median	811	338	705	1475	3089
[Min, Max]	[323, 2086]	[116, 1014]	[240, 2150]	[496, 4561]	[1029, 9681]
Geom. Mean (Geom. CV %)	810 (24.8%)	339 (28.8%)	708 (29.2%)	1482 (29.6%)	3105 (30.0%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	163 (49.6%)	360 (48.6%)	794 (47.6%)	1748 (46.8%)
Median	92.2	149	330	728	1608
[Min, Max]	[0.362, 961]	[15.8, 737]	[37.9, 1606]	[90.0, 3498]	[212, 7613]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	145 (52.5%)	322 (51.0%)	713 (49.7%)	1576 (48.6%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	231 (39.7%)	498 (39.4%)	1076 (39.0%)	2322 (38.8%)
Median	248	216	468	1010	2178
[Min. Max]	[9.32, 1390]	[45.4, 841]	[101, 1816]	[226, 3919]	[498, 8460]
Geom. Mean (Geom. CV %)	240 (52.2%)	214 (40.1%)	464 (39.7%)	1002 (39.3%)	2164 (38.9%)

TABLE 9-continued

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with Severe Renal Impairment

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	19.7 (33.1%)	21.1 (33.0%)	22.6 (33.0%)	24.2 (33.0%)
Median	6.99	18.7	20.0	21.5	23.0
[Min, Max]	[1.96, 24.5]	[5.21,70.6]	[5.57, 75.7]	[5.96, 81.1]	[6.37, 86.9]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	18.7 (32.9%)	20.0 (32.9%)	21.5 (32.8%)	23.0 (32.8%)

AUC_{tau}: Area under the concentration-time curve at steady state; $C_{14\ h}$: concentration at 14 h post-dose at steady state; C_{max}: maximum concentration at steady state; C_{min}: concentration at 24 h post-dose at steady state; CV %: coefficient of variation; Min: minimum; Max: maximum; n: number of subjects.

TABLE 10

Simulations to Support Dosing in Sub-Populations - Adult Patients (Narcolepsy/OSA, tablet, fasting conditions) with ESRD

Parameters	Reference (Adult, Dose = 150 mg, Normal Renal Function)	Dose 37.5 mg (n = 10000)	75 mg (n = 10000)	150 mg (n = 10000)	300 mg (n = 10000)
		AUC_{tau} (ng · h/mL)			
Mean (CV %)	8874 (34.4%)	25371 (42.5%)	54399 (42.6%)	116645 (42.7%)	250132 (42.7%)
Median	8382	23288	49948	107070	229500
[Min, Max]	[2165, 35375]	[5989, 136885]	[12737, 292530]	[27087, 625152]	[57605, 1335983]
Geom. Mean (Geom. CV %)	8387 (34.6%)	23394 (41.7%)	50152 (41.8%)	107514 (41.8%)	230486 (41.9%)
		C_{max} (ng/mL)			
Mean (CV %)	835 (24.8%)	1153 (39.8%)	2456 (40.0%)	5234 (40.3%)	11162 (40.5%)
Median	811	1065	2267	4827	10282
[Min, Max]	[323, 2086]	[290, 5893]	[617, 12563]	[1310, 26789]	[2786, 57133]
Geom. Mean (Geom. CV %)	810 (24.8%)	1074 (38.6%)	2286 (38.9%)	4868 (39.1%)	10373 (39.4%)
		C_{min} (ng/mL)			
Mean (CV %)	110 (71.5%)	961 (45.7%)	2075 (45.6%)	4476 (45.4%)	9655 (45.3%)
Median	92.2	876	1891	4084	8816
[Min, Max]	[0.362, 961]	[183, 5509]	[398, 11801]	[862, 25275]	[1866, 54124]
Geom. Mean (Geom. CV %)	84.9 (92.1%)	875 (45.6%)	1889 (45.3%)	4079 (45.1%)	8803 (45.0%)
		$C_{14\ h}$ (ng/mL)			
Mean (CV %)	268 (46.9%)	1045 (43.0%)	2243 (43.0%)	4814 (43.0%)	10333 (43.1%)
Median	248	958	2056	4413	9473
[Min, Max]	[9.32, 1390]	[236, 5689]	[505, 12161]	[1079, 25995]	[2304, 55566]
Geom. Mean (Geom. CV %)	240 (52.2%)	962 (42.3%)	2064 (42.2%)	4430 (42.3%)	9509 (42.3%)
		Half-life (h)			
Mean (CV %)	7.30 (30.7%)	83.6 (38.1%)	89.7 (38.2%)	96.1 (38.3%)	103 (38.4%)
Median	6.99	77.9	83.4	89.6	95.9
[Min, Max]	[1.96, 24.5]	[20.8, 337]	[22.3, 363]	[23.9, 392]	[25.5, 422]
Geom. Mean (Geom. CV %)	6.98 (30.4%)	78.1 (38.1%)	83.7 (38.2%)	89.8 (38.2%)	96.2 (38.3%)

AUC_{tau}: Area under the concentration-time curve at steady state; $C_{14\ h}$: concentration at 14 h post-dose at steady state; C_{max}: maximum concentration at steady state; C_{min}: concentration at 24 h post-dose at steady state; CV %: coefficient of variation; Min: minimum; Max: maximum; n: number of subjects.

Ratios were generated to facilitate the comparison across populations of patients with renal impairment in order to optimally match the exposure of the reference dose in adult patients with normal renal function (i.e., 150 mg). Ratios of AUC_{tau}, C_{max}, C_{min}, C_{14h} and $t_{1/2}$ are presented in Table 11.

TABLE 11

Ratio of Mean Steady State PK Parameters of Solriamfetol in Patients with Renal Impairment (at different doses) Relative to Patients with Normal Renal Function (at 150 mg dose)

	Dose	Ratio Relative to Typical Patient with Normal Renal Function				
Sub-Population	(mg)	AUC_{tau}	C_{max}	$C_{14\,h}$	C_{min}	$t_{1/2}$
Mild Renal Impairment	300	2.91	2.33	3.37	4.38	1.47
	150	1.36	1.13	1.53	1.92	1.36
	75	0.63	0.55	0.70	0.83	1.27
	37.5	0.30	0.27	0.32	0.36	1.19
Moderate Renal Impairment	300	4.16	2.83	5.17	8.07	2.08
	150	1.94	1.36	2.38	3.61	1.95
	75	0.90	0.66	1.09	1.61	1.81
	37.5	0.42	0.32	0.50	0.71	1.70
Severe Renal Impairment	300	6.62	3.88	8.66	15.89	3.32
	150	3.09	1.85	4.01	7.22	3.10
	75	1.44	0.88	1.86	3.27	2.89
	37.5	0.67	0.42	0.89	1.48	2.70
ESRD	300	28.19	13.37	36.56	87.77	14.11
	150	13.1	6.27	18.0	40.7	13.2
	75	6.13	2.94	8.37	18.9	12.3
	37.5	2.86	1.38	3.90	8.74	11.5

AUC_{tau}: Area under the concentration-time curve at steady state; C_{max}: maximum concentration at steady state; $C_{14\,h}$: concentration at 14 h post-dose at steady state; C_{min}: concentration at 24 h post-dose at steady state; t 1/2: elimination half-life.

Based on the inventor's analyses of solriamfetol's pharmacokinetics and safety profile together with population PK simulations, it was discovered that, in patients with mild renal impairment, an equivalent dose used in patients with normal renal function was associated with comparable exposures. A 150 mg dose in patients with mild renal impairment is associated with AUC_{tau} and C_{max} values 36% and 13% higher than those observed in patients with normal renal function for the same dose. Typical C_{14h} and C_{min} values in a patient with mild renal impairment are expected to be approximately 1.5- and 2-fold higher than that observed in patients with normal renal function due to the longer $t_{1/2}$. Therefore, no dosage adjustments should be needed in patients with mild renal impairment and this subgroup of renally impaired patients can be safety administered at an initial daily dose equivalent to 75 mg of solriamfetol and escalating to a maximum daily dose equivalent to 150 mg of solriamfetol after at least 3 days, based on solriamfetol's elimination half-life.

In patients with moderate renal impairment, one-half of the dose used in patients with normal renal function was associated with comparable exposures. A 75 mg dose in patients with moderate renal impairment is associated with AUC_{tau} and C_{max} values 10% and 34% lower than those observed in patients with normal renal function at a 150 mg dose. Typical C_{14h} and C_{min} values in a patient with moderate renal impairment is expected to be approximately 9% and 61% higher than that observed in patients with normal renal function due to the longer $t_{1/2}$. Therefore, dosing adjustments are warranted in patients with moderate renal impairment. The appropriate dose escalation regimen for this subgroup of renally impaired patients was determined by the present inventor to be an initial daily dose equivalent to 37.5 mg solriamfetol and escalating to a maximum daily dose equivalent to 75 mg solriamfetol after at least five days to at least seven days, based on solriamfetol's elimination half-life.

In patients with severe renal impairment, one-quarter of the dose used in patients with normal renal function was associated with comparable exposures. A 75 mg dose in patients with severe renal impairment was associated with AUC_{tau} and C_{max} values 44% higher and 12% lower than those in patients with normal renal function at a 150 mg dose. Typical C_{14h} and C_{min} following a 75 mg dose in patients with severe renal impairment is expected to be approximately 1.9- and 3-fold higher than that in patients with normal renal function. Therefore, it was determined that a 75 mg dose would not be appropriate for patients with severe renal impairment. Therefore, dosing adjustment is warranted in patients with severe renal impairment. A 37.5 mg dose in patients with severe renal impairment was associated with AUC_{tau} and C_{max} values 33% lower and 58% lower than those in patients with normal renal function at a 150 mg dose. Typical C_{14h} and C_{min} values following a 37.5 mg dose in a patient with severe renal impairment are expected to be 14% lower and 48% higher than that in patients with normal renal function. Therefore, dosing adjustments is warranted in patients with severe renal impairment. The appropriate dose escalation regimen for this subgroup of renally impaired patients was determined by the present inventor to be a daily maximum dose equivalent to 37.5 mg of solriamfetol.

Based on the substantial increase in solriamfetol exposure in patients with ESRD, use of solriamfetol in this subpopulation should be avoided.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A method of treating excessive daytime sleepiness in a subject in need thereof having moderate or severe renal impairment, said method comprising:

(a) providing to a subject having excessive daytime sleepiness and an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2:

a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of a dose escalation regimen, and

a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen based on efficacy and tolerability,

wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC; and

(b) providing to a subject having excessive daytime sleepiness and an eGFR of about 15 mL/min/1.73 m^2 to about 29 mL/min/1.73 m^2:

an oral daily dose equivalent to 37.5 mg APC,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC.

2. The method of claim **1**, wherein the excessive daytime sleepiness is due to narcolepsy.

3. The method of claim **1**, wherein the excessive daytime sleepiness is due to obstructive sleep apnea.

4. The method of claim **1**, wherein the subject is provided said first oral daily dose or said oral daily dose in the form of about 44.7 mg APC-HCl.

5. The method of claim 1, wherein the subject is provided said second oral daily dose in the form of about 89.3 mg APC-HCl.

6. The method of claim 1, wherein the subject is provided said first oral daily dose in the form of about 44.7 mg APC-HCl and said second oral daily dose in the form of about 89.3 mg APC-HCl.

7. The method of claim 1, wherein said first oral daily dose, said second oral daily dose, and said oral daily dose are each administered upon the subject's awakening.

8. The method of claim 1, wherein said first oral daily dose, said second oral daily dose, and said oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

9. The method of claim 1, wherein the subject is a human.

10. The method of claim 1, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

11. The method of claim 1, wherein n_1 is an integer equal to or greater than 7.

12. A method of treating excessive daytime sleepiness in a subject in need thereof having mild, moderate or severe renal impairment, said method comprising:

(a) providing to a subject having excessive daytime sleepiness and an estimated glomerular filtration rate (eGFR) of about 30 mL/min/1.73 m^2 to about 59 mL/min/1.73 m^2:

a first oral daily dose equivalent to 37.5 mg [R]-2-amino-3-phenylpropylcarbamate (APC) from day one to day n_1 of a dose escalation regimen, and

a second oral daily dose equivalent to 75 mg APC starting on day n_2 of the dose escalation regimen based on efficacy and tolerability,

wherein n_1 is an integer equal to or greater than 5 and n_2 is equal to the sum of n_1+1,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 75 mg APC;

(b) providing to a subject having excessive daytime sleepiness and an eGFR of about 15 mL/min/1.73 m^2 to about 29 mL/min/1.73 m^2:

an oral daily dose equivalent to 37.5 mg APC,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 37.5 mg APC; and

(c) providing to a subject having excessive daytime sleepiness and an eGFR of about 60 mL/min/1.73 m^2 to about 89 mL/min/1.73 m^2:

a first oral daily dose equivalent to 37.5 mg APC,

after at least 3 days a second oral daily dose equivalent to 75 mg APC based on efficacy and tolerability, and

after at least 3 days a third oral daily dose equivalent to 150 mg APC based on efficacy and tolerability,

wherein the renally impaired subject is not provided a daily dose exceeding a dose equivalent to 150 mg APC.

13. The method of claim 12, wherein the excessive daytime sleepiness is due to narcolepsy.

14. The method of claim 12, wherein the excessive daytime sleepiness is due to obstructive sleep apnea.

15. The method of claim 12, wherein the subject is provided said first oral daily dose or said oral daily dose in the form of about 44.7 mg APC-HCl.

16. The method of claim 12, wherein the subject is provided said second oral daily dose in the form of about 89.3 mg APC-HCl.

17. The method of claim 12, wherein the subject is provided said third oral daily dose in the form of about 178.5 mg APC-HCl.

18. The method of claim 12, wherein the subject is provided said first oral daily dose in the form of about 44.7 mg APC-HCl and said second oral daily dose in the form of about 89.3 mg APC-HCl.

19. The method of claim 12, wherein the subject is provided said first oral daily dose in the form of about 44.7 mg APC-HCl, said second oral daily dose in the form of about 89.3 mg APC-HCl, and said third oral daily dose in the form of about 178.5 mg APC-HCl.

20. The method of claim 12, wherein said first oral daily dose, said second oral daily dose, said third daily dose, and said oral daily dose are each administered upon the subject's awakening.

21. The method of claim 12, wherein said first oral daily dose, said second oral daily dose, said third daily dose, and said oral daily dose are each administered more than nine hours in advance of the subject's bedtime.

22. The method of claim 12, wherein the subject is a human.

23. The method of claim 12, wherein the eGFR is determined using the Modification in Diet in Renal Disease equation.

24. The method of claim 12, wherein n_1 is an integer equal to or greater than 7.

* * * * *

EXHIBIT D

US011998639B2

(12) **United States Patent**
Allphin et al.

(10) **Patent No.: US 11,998,639 B2**
(45) **Date of Patent: *Jun. 4, 2024**

(54) **FORMULATIONS OF (R)-2-AMINO-3-PHENYLPROPYL CARBAMATE**

(71) Applicant: **Axsome Malta Ltd.**, Qormi (MT)

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(52) **U.S. Cl.**
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CPC .. A61K 9/2027; A61K 9/2059; A61K 31/165; A61K 9/2068; A61K 9/2054; A61K 31/27
See application file for complete search history.

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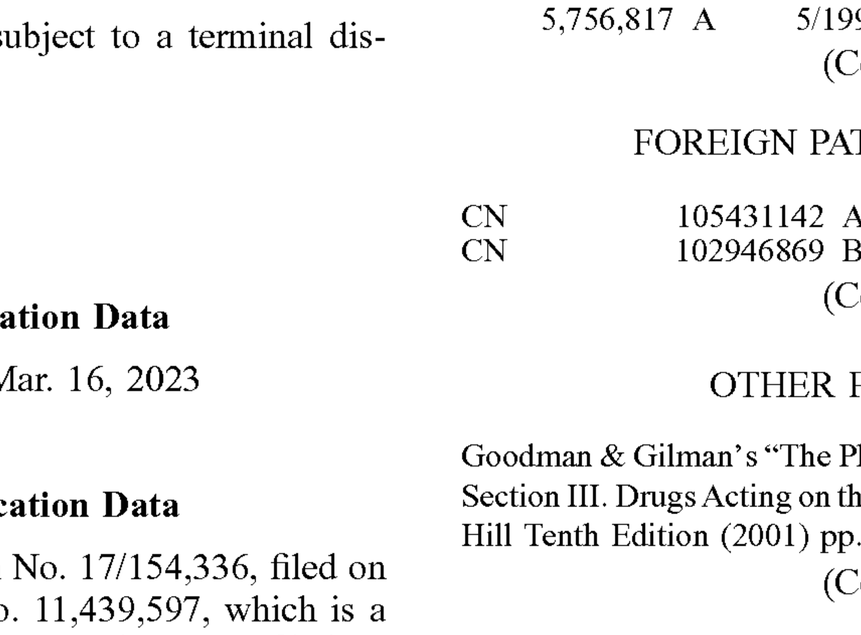
(57) **ABSTRACT**

The present invention relates to immediate release formulations of (R)-2-amino-3-phenylpropyl carbamate and methods of using the same to treat disorders.

19 Claims, 4 Drawing Sheets



SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
4	0%	20%	45%	80%	98%	97%	100%	103%	163.5	182.7	74.5
6	0%	18%	50%	80%	94%	99%			151.4	163.3	*

Related U.S. Application Data

application No. 15/695,913, filed on Sep. 5, 2017, now Pat. No. 10,195,151.

(60) Provisional application No. 62/383,818, filed on Sep. 6, 2016.

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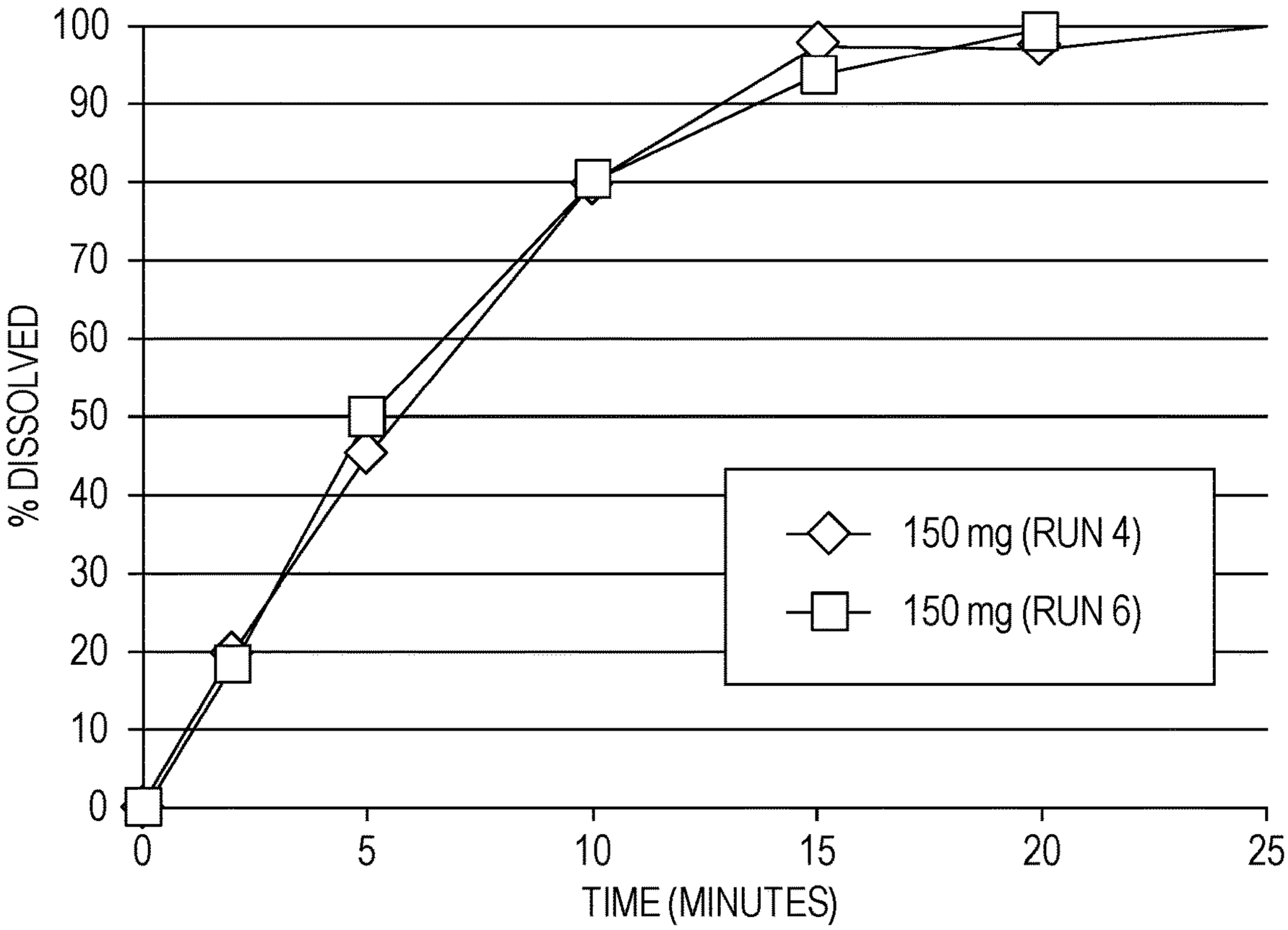
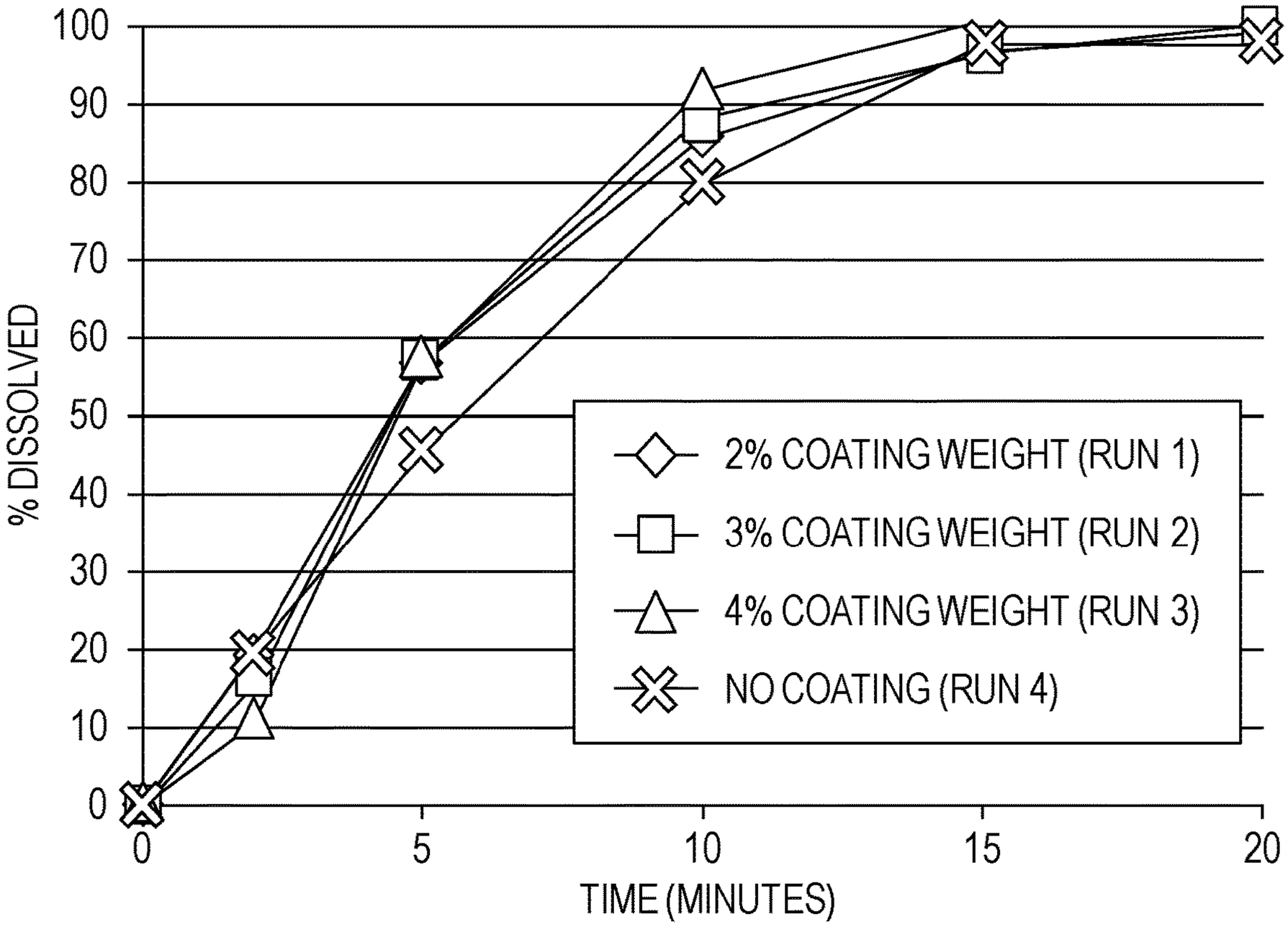


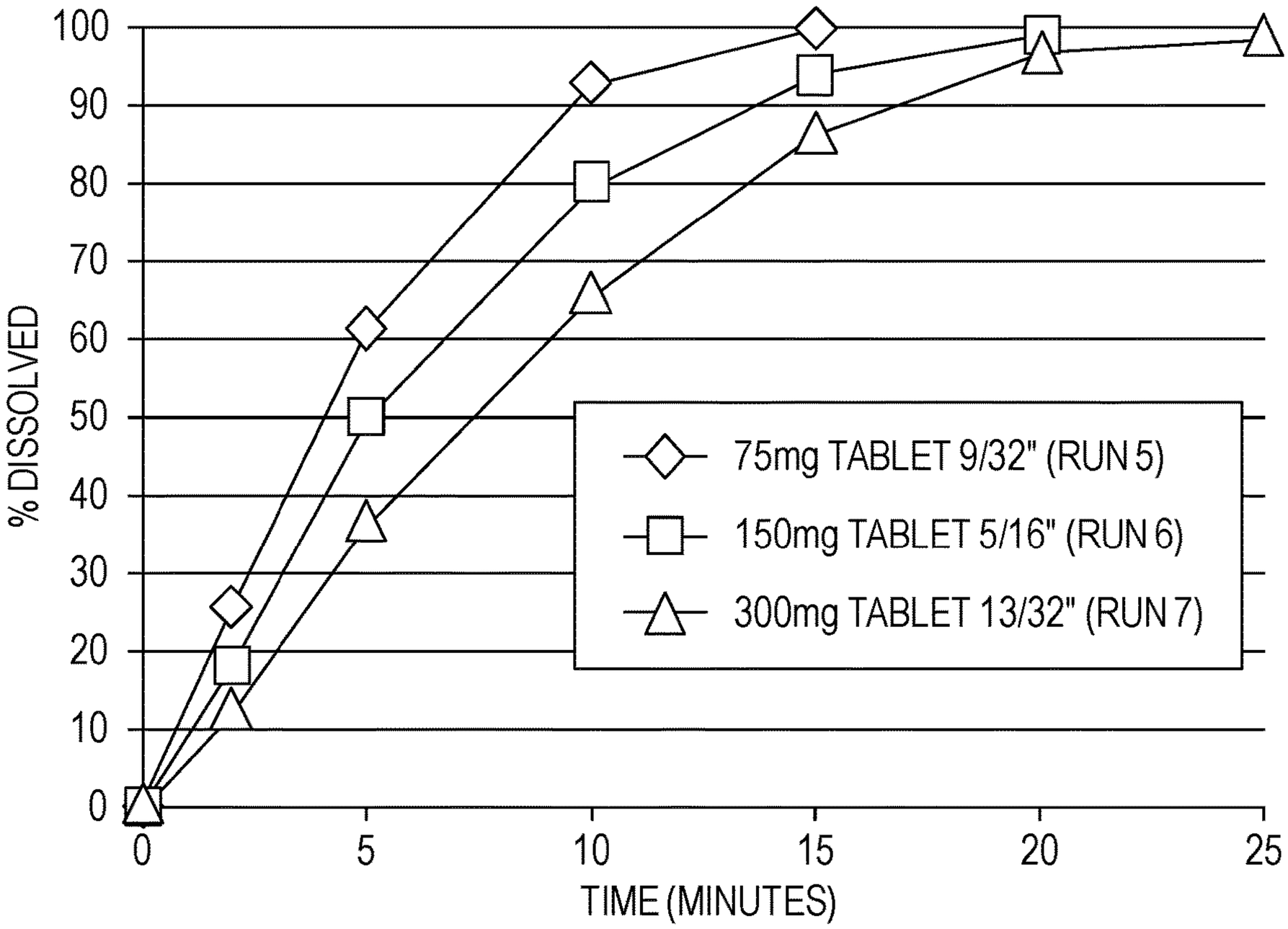
SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
4	0%	20%	45%	80%	98%	97%	100%	103%	163.5	182.7	74.5
6	0%	18%	50%	80%	94%	99%			151.4	163.3	*

FIG. 1



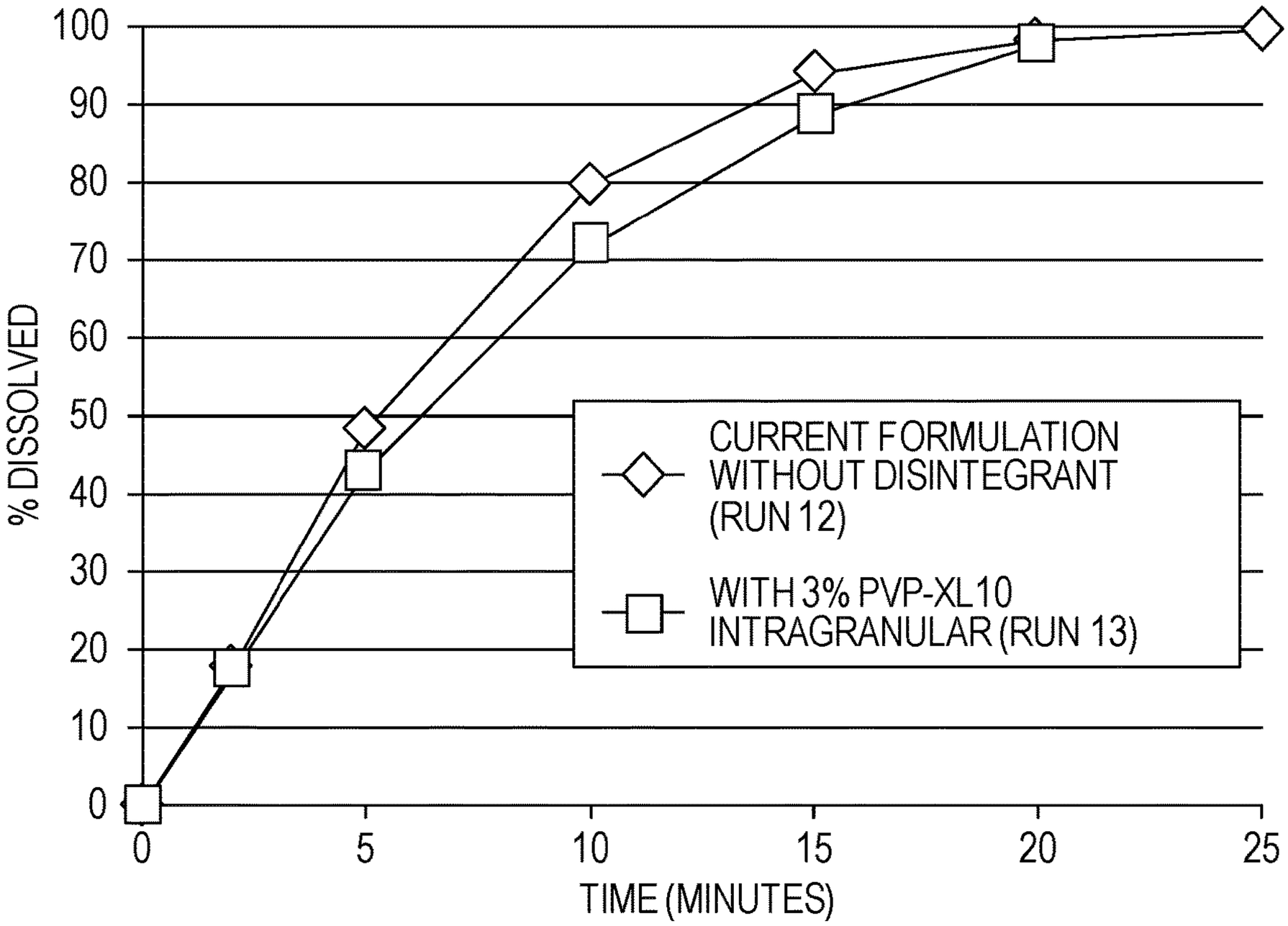
SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
1	0%	20%	57%	85%	97%	99%	98%	100%	148.6	164.4	75.9
2	0%	16%	57%	89%	96%	100%	100%	100%	150.8	166.4	*
3	0%	11%	57%	92%	100%	101%			154.4	172.6	71.5
4	0%	20%	45%	80%	98%	97%	100%	103%	163.5	182.7	52.8

FIG. 2



SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
5	0%	26%	61%	93%	100%				149.2	78.77	48.5
6	0%	18%	50%	80%	94%	99%			151.4	163.3	*
7	0%	13%	37%	66%	86%	96%	99%		153.7	345.7	48.3

FIG. 3



SET	TIME (MINUTES)										
	0	2	5	10	15	20	25	30	STD	TOTAL	F2
12	0%	17%	48%	80%	94%	98%	100%	100%	153.0	162.3	*
13	0%	17%	43%	72%	89%	98%			153.9	166.8	63.3

FIG. 4

FORMULATIONS OF (R)-2-AMINO-3-PHENYLPROPYL CARBAMATE

STATEMENT OF PRIORITY

This application is a continuation of and claims priority to U.S. patent application Ser. No. 17/154,336, filed Jan. 21, 2021, now U.S. Pat. No. 11,439,597, which is a continuation of and claims priority to U.S. patent application Ser. No. 16/689,715, filed Nov. 20, 2019, now abandoned, which is a divisional of and claims priority to U.S. patent application Ser. No. 16/225,890, filed Dec. 19, 2018, now U.S. Pat. No. 10,512,609, which is a divisional of and claims priority to U.S. patent application Ser. No. 15/695,913, filed Sep. 5, 2017, now U.S. Pat. No. 10,195,151, which claims the benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Application No. 62/383,818, filed Sep. 6, 2016, the entire contents of each of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to immediate release formulations of (R)-2-amino-3-phenylpropyl carbamate (APC) and methods of using the same to treat disorders.

BACKGROUND OF THE INVENTION

APC is a phenylalanine analog that has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414. Methods for producing APC (which also has other names) and related compounds can be found in U.S. Pat. Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

The present invention overcomes shortcomings in the art by providing immediate release formulations of APC suitable for treatment of disorders responsive to APC.

SUMMARY OF THE INVENTION

The present invention relates to the development of immediate release formulations of APC. The invention additionally relates to the use of the formulations for the treatment of disorders responsive to APC.

Accordingly, one aspect of the invention relates to an immediate release compressed tablet for oral delivery of APC, the tablet comprising:

APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet;

at least one binder in an amount of about 1-5% by weight of the tablet; and

at least one lubricant in an amount of about 0.1-2% by weight of the tablet;

wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

The invention further relates to an immediate release oral dosage form of APC, the oral dosage form comprising:

APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the oral dosage form;

at least one binder in an amount of about 1-5% by weight of the oral dosage form; and

at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form;

wherein the oral dosage form releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject.

The invention also relates to an immediate release compressed tablet for oral delivery of APC, the tablet comprising APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet; wherein the tablet exhibits substantially identical dissolution rates of the APC or a pharmaceutically acceptable salt thereof at pH 1.2, pH 4.5, and pH 6.8.

The invention further relates to a method of treating a disorder amenable to treatment with APC, e.g., narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject the compressed tablet of the invention.

The present invention is explained in greater detail in the drawings herein and the specification set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution rate of immediate release APC tablets.

FIG. **2** shows the effect of coating on the dissolution rate of immediate release APC tablets.

FIG. **3** shows the effect of tablet size on the dissolution rate of immediate release APC tablets.

FIG. **4** shows the effect of disintegrant on the dissolution rate of immediate release APC tablets.

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. For example, features illustrated with respect to one embodiment can be incorporated into other embodiments, and features illustrated with respect to a particular embodiment can be deleted from that embodiment. In addition, numerous variations and additions to the embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety for all purposes.

As used herein, "a," "an," or "the" can mean one or more than one. For example, "a" cell can mean a single cell or a multiplicity of cells.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount.

The term "consists essentially of" (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition. The term "materially altered," as applied to a composition, refers to an increase or decrease in the therapeutic effectiveness of the composition of at least about 20% or more as compared to the effectiveness of a composition consisting of the recited components.

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Treat" or "treating" or "treatment" refers to any type of action that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art.

A "disorder amenable to treatment with APC" refers to any disorder in which administration of APC to a subject results in the treatment of one or more symptoms of the disorder in the subject. Examples of such disorders include, without limitation, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity.

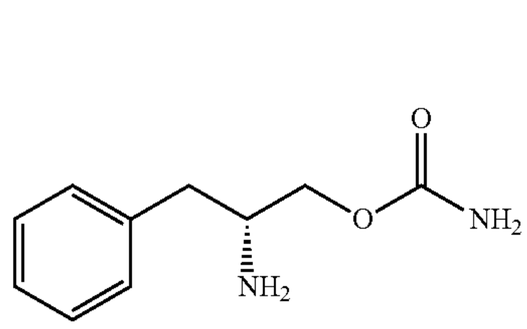
"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., *Remington's Pharmaceutical Science;* 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

The present invention provides formulations and dosage forms for the immediate release of APC or a pharmaceutically acceptable salt thereof. Formulations described herein are suited to the immediate release of high dose drugs that are highly water soluble. In particular embodiments, the immediate release formulations are provided as a unit dosage form, and in certain embodiments, the immediate release formulation is provided as an immediate release tablet.

In certain embodiments, the immediate release APC compositions described herein comprise a therapeutically effective amount of APC or an alternative salt thereof. The structure of the free base of APC is given below as formula I.

(I)



Administration of APC in solid form presents several challenges. Patients treated with APC may have difficulty taking solid medications by mouth because they have disease states that make handling and swallowing difficult. Accordingly, it is desirable to keep the size of the tablet as small as possible while incorporating the largest amount of active ingredient and meeting the desired dissolution profile. In addition, it is desirable to have a formulation that dissolves quickly without high levels of excipients to speed dissolution.

Accordingly, one aspect of the invention relates to an immediate release compressed tablet for oral delivery of APC, the tablet comprising:

APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet;

at least one binder in an amount of about 1-5% by weight of the tablet; and

at least one lubricant in an amount of about 0.1-2% by weight of the tablet;

wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises:

APC or a pharmaceutically acceptable salt thereof in an amount of about 91-95% by weight of the tablet;

at least one binder in an amount of about 2-3% by weight of the tablet;

at least one lubricant in an amount of about 0.1-1% by weight of the tablet; and

optionally, a cosmetic film coat in an amount of about 3-4% by weight of the tablet;

wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In one embodiment, the tablet comprises:

APC or a pharmaceutically acceptable salt thereof in an amount of about 93.22% by weight of the tablet;

at least one binder (e.g., hydroxypropylcellulose) in an amount of about 2.87% by weight of the tablet;

at least one lubricant (e.g., magnesium stearate) in an amount of about 0.52% by weight of the tablet; and

optionally, a cosmetic film coat (e.g., Opadry® II yellow) in an amount of about 3-4% by weight of the tablet;

wherein the tablet releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

The invention further relates to an immediate release oral dosage form of APC, the oral dosage form comprising:

APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the oral dosage form;

at least one binder in an amount of about 1-5% by weight of the oral dosage form; and

at least one lubricant in an amount of about 0.1-2% by weight of the oral dosage form;

wherein the oral dosage form releases at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the oral dosage form to a subject.

The formulations and unit dosage forms provided herein can be utilized to achieve immediate release of APC, as well as pharmaceutically acceptable salts, hydrates, isomers, including tautomers, solvates and complexes of APC.

Suitable salts of APC include, without limitation, acetate, adipate, alginate, aspartate, benzoate, butyrate, citrate, fumarate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, malonate, methane-sulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, hydroxynapthoate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, can be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. In certain embodiments, the salt is the hydrochloride salt.

Compounds of the formulae herein include those having quaternization of any basic nitrogen-containing group therein.

The discussion herein is, for simplicity, provided without reference to stereoisomerism. Those skilled in the art will appreciate that the compounds of the invention can contain one or more asymmetric centers and thus occur as racemates and racemic mixtures and single optical isomers. All such isomeric forms of these compounds are expressly included in the present invention.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

The discussion herein is also provided without reference to polymorphs, hydrates, clathrates, solvates, inclusion compounds, isomers, or other forms of the compound. All such forms of these compounds are expressly included in the present invention.

Further, the compounds of the invention include prodrugs of the compounds that are converted to the active compound in vivo. For example, the compound can be modified to enhance cellular permeability (e.g., by esterification of polar groups) and then converted by cellular enzymes to produce the active agent. Methods of masking charged or reactive moieties as a pro-drug are known by those skilled in the art (see, e.g., P. Korgsgaard-Larsen and H. Bundgaard, A Textbook of Drug Design and Development, Reading U.K., Harwood Academic Publishers, 1991).

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formula, for example, by hydrolysis in blood, see, e.g., T. Higuchi and V. Stella, Prodrugs as Novel delivery Systems, Vol. 14 of the A.C.S. Symposium Series and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated by reference herein. See also U.S. Pat. No. 6,680,299. Exemplary prodrugs include a prodrug that is metabolized in vivo by a subject to an active drug having an activity of the compounds as described herein, wherein the prodrug is an ester of an alcohol or carboxylic acid group, if such a group is present in the compound; an amide of an amine group or carboxylic acid group, if such groups are present in the compound; a urethane of an amine group, if such a group is present in the compound; an acetal or ketal of an alcohol group, if such a group is present in the compound; a N-Mannich base or an imine of an amine group, if such a group is present in the compound; or a Schiff base, oxime, acetal, enol ester, oxazolidine, or thiazolidine of a carbonyl group, if such a group is present in the compound, such as described, for example, in U.S. Pat. Nos. 6,680,324 and 6,680,322.

The term "pharmaceutically acceptable prodrug" (and like terms) as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and/or other animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable risk/benefit ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

In some embodiments, the tablet releases at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of APC or a pharmaceutically

acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject, e.g., less than 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 minutes. In some embodiments, the tablet releases at least 95%, 96%, 97%, 98%, or 99% of APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 30 minutes after administration of the tablet to a subject.

In certain embodiments, the tablet does not comprise a disintegrant. The term "disintegrant," as used herein, refers to an agent added to a tablet to promote the breakup of the tablet in an aqueous environment. The tablets of the present invention are advantageous in that they dissolve rather than disintegrate. In the present invention the presence of disintegrant in the formulation may actually slow down release of APC.

In certain embodiments, APC or a pharmaceutically acceptable salt thereof is present in an amount of about 90%, 90.5%, 91%, 91.5%, 92%, 92.5%, 93%, 93.5%, 94%, 94.5%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, or 98% by weight of the tablet or any value or range therein. In certain embodiments, APC or a pharmaceutically acceptable salt thereof is present in an amount of about 90% to about 98%, about 92% to about 98%, about 94% to about 98%, about 96% to about 98%, about 90% to about 92%, about 90% to about 94%, about 90% to about 96%, about 92% to about 94%, about 92% to about 96%, or about 94% to about 96%.

In certain embodiments, the at least one binder is present in an amount of about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the tablet or any value or range therein. In certain embodiments, the at least one binder is present in an amount of about 1% to about 5%, about 2% to about 5%, about 3% to about 5%, about 4% to about 5%, about 1% to about 2%, about 1% to about 3%, about 1% to about 4%, about 2% to about 3%, about 2% to about 4%, or about 3% to about 4%. The tablet may comprise at least one binder, e.g., 1, 2, 3, 4, 5, or more binders.

In certain embodiments, the at least one binder is selected from at least one of hydroxypropyl cellulose, ethylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, sodium carboxymethylcellulose, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate or any combination thereof. In some embodiments, the at least one binder is hydroxypropyl cellulose.

In certain embodiments, the at least one lubricant is present in an amount of about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, or 2.0% by weight of the tablet or any value or range therein. In certain embodiments, the at least one lubricant is present in an amount of about 0.1% to about 2.0%, about 0.5% to about 2.0%, about 1.0% to about 2.0%, about 1.5% to about 2.0%, about 0.1% to about 0.5%, about 0.1% to about 1.0%, about 0.1% to about 1.5%, about 0.5% to about 1.0%, about 0.5% to about 1.5%, or about 1.0% to about 1.5%. The tablet may comprise at least one lubricant, e.g., 1, 2, 3, 4, 5, or more lubricants. Where the immediate release formulation is provided as a tableted dosage form, still lower lubricant levels may be achieved with use of a "puffer" system during tableting. Such systems are known in the art, commercially available and apply lubricant directly to the punch and die surfaces rather than throughout the formulation.

In certain embodiments, the at least one lubricant is selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate or any combination thereof. In some embodiments, the at least one lubricant is magnesium stearate. In other embodiments, magnesium stearate may be used in combination with one or more other lubricants or a surfactant, such as sodium lauryl sulfate. In particular, if needed to overcome potential hydrophobic properties of magnesium stearate, sodium lauryl sulfate may also be included when using magnesium stearate (Remington: the Science and Practice of Pharmacy, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000)).

In some embodiments, the at least one binder is hydroxypropyl cellulose. In some embodiments, the at least one lubricant is magnesium stearate. In some embodiments, the at least one binder is hydroxypropyl cellulose and the at least one lubricant is magnesium stearate.

In certain embodiments, the tablet is coated. The coating may be, without limitation, a color overcoat.

In some embodiments, the APC or a pharmaceutically acceptable salt thereof is APC hydrochloride.

The tablet may be any shape that is suitable for immediate release and allows the release of at least 85% of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject. In some embodiments, the tablet maximizes surface area to volume ratio to promote rapid dissolution. In some embodiments, the tablet is oblong in shape.

The tablet may contain any amount of APC or a pharmaceutically acceptable salt thereof suitable for administration as a unit dosage form. In some embodiments, the tablet contains about 1 mg to about 1000 mg of the drug or any range or value therein, e.g., about 10 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

APC or a pharmaceutically acceptable salt thereof may be obtained or synthesized by methods known in the art and as described herein. Details of reaction schemes for synthesizing APC have been described in U.S. Pat. Nos. 5,705,640; 5,756,817; 5,955,499; and 6,140,532, all incorporated herein by reference in their entirety.

"Immediate release" as used herein, refers to a composition that releases APC or a pharmaceutically acceptable salt, hydrate, isomer, tautomer, solvate or complex thereof substantially completely into the gastrointestinal tract of the user within a period of less than about 15 minutes, usually between about 1 minute and about 15 minutes from ingestion. Such a delivery rate allows the drug to be absorbed by the gastrointestinal tract in a manner that is bioequivalent to an oral solution. Such rapid absorption will typically occur for an immediate release unit dosage form, such as a tablet, caplet or capsule, if the drug included in such dosage form dissolves in the upper portion the gastrointestinal tract.

Release rates can be measured using standard dissolution test methods. For example, the standard conditions may be those described in FDA guidance (e.g., 50 rpm, 37° C., USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel).

"Dissolution rate," as used herein, refers to the quantity of drug released in vitro from a dosage form per unit time into a release medium.

"Bioavailability," as used herein, refers to the estimated area under the curve, or AUC of the active drug in systemic

circulation after oral administration with a dosage form as disclosed herein when compared with the AUC of the active drug in systemic circulation after intravenous administration of the active drug. The AUC is affected by the extent to which the drug is absorbed in the GI tract.

Products are considered to be "bioequivalent" if the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test product to reference product is within 80% to 125%.

The term "$AUC_{(0-t)}$" means the area under the plasma concentration curve from time 0 to time t.

The term "$AUC_{(0-\infty)}$" or "AUC_{0-inf}" means the area under the plasma concentration time curve from time 0 to infinity.

"C_{max}" refers to the maximum plasma concentration of APC.

"T_{max}" refers to the time to maximum plasma concentration for a given drug.

"$t_{1/2}$" refers to the time to reduce the plasma concentration by 50% during the terminal elimination phase of the drug.

Immediate release formulations suitable for oral administration may comprise unit dosage forms, such as tablets, caplets or filled capsules, which can deliver a therapeutically effective dose of APC upon ingestion thereof by the patient of one or more of said dosage forms, each of which can provide a dosage of, for example, about 1 to about 1000 mg of APC. Additionally, the immediate release dosage forms can be shaped or scored to facilitate dose adjustment through tablet splitting.

The formulation and structure of an immediate release dosage form as disclosed herein can be adjusted to provide immediate release performance that suits a particular dosing need. In particular, the formulation and structure of the dosage forms as described herein can be adjusted to provide any combination of the immediate release performance characteristics described herein. In particular embodiments, for example, an immediate release dosage form as disclosed herein provides rapid onset of action, releasing more than about 85%, such as, for example, more than about 90% or 95%, of the drug contained therein within a period of time selected from less than 15 minutes, less than 12 minutes, less than 10 minutes, and less than 5 minutes after administration.

Moreover, the rate of drug release from an immediate release dosage form as disclosed herein may be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. In one embodiment, the immediate release dosage form may be formulated to deliver as much as 1,000 mg of APC. In particular embodiments, the total amount of drug contained within an immediate release dosage form according to the present description may be between about 10 mg and about 500 mg. For example, in certain such embodiments, the total amount of drug may be selected from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, or 1000 mg or any range or value therein. In certain such embodiments, the total amount of drug may be about 10 mg to about 1000 mg, about 10 mg to about 500 mg, about 10 mg to about 300 mg, about 30 mg to about 1000 mg, about 30 mg to about 500 mg, about 30 mg to about 300 mg, about 100 mg to about 1000 mg, about 10 mg to about 500 mg, about 100 mg to about 300 mg, about 150 mg to about 1000 mg, about 150 mg to about 500 mg, or about 150 mg to about 300 mg.

The immediate release formulations provided herein generally include APC and some level of lubricant to facilitate processing of the formulations into a unit dosage form. In some embodiments, therefore, the formulations described herein include a combination of APC and lubricant, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. In other embodiments, the immediate release formulations described herein include a combination of APC, lubricant, and binder, as described herein, and in certain such embodiments, the immediate release formulations are substantially free of other excipients or adjuvants. Though the immediate release formulations described herein may be formulated using a combination of drug and one or more of a lubricant and binder, in certain embodiments, the compositions described herein may include one or more additional excipients selected from, for example, fillers, compression aids, diluents, disintegrants, colorants, flavorants, buffering agents, coatings, glidants, or other suitable excipients.

The immediate release formulations described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and dry powder blending. Suitable methods for the manufacture of the immediate release formulations and unit dosage forms described herein are provided, for example, in Remington, 20^{th} edition, Chapter 45 (Oral Solid Dosage Forms). It has been found that, even without the aid of binders or non-lubricating excipients, such as compression aids, wet granulation techniques can afford flowable granules with compression characteristics suitable for forming unit dosage forms as described herein. Therefore, in certain embodiments, where a drug content greater than about 85%, 90% or 95% by weight is desired for the immediate release formulation, wet granulation techniques may be used to prepare immediate release formulations as described herein. In such embodiments, as illustrated in the Examples provided herein, conventional organic or aqueous solvents may be used in the wet granulation process. Suitable wet granulation processes can be performed as fluidized bed, high shear, or low shear (wet massing) granulation techniques, as are known in the art.

In addition to one or more of APC, lubricant, and binder, where desired, the immediate release formulations described herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. Where a filler or compression aid is used, in certain embodiments, it may be included in the immediate release formulation in an amount ranging from about 1%-15% by weight.

Immediate release formulations as described herein may be processed into unit dosage forms suitable for oral administration, such as for example, filled capsules, compressed tablets or caplets, or other dosage form suitable for oral administration using conventional techniques. Immediate release dosage forms prepared as described may be adapted for oral administration, so as to attain and maintain a therapeutic level of APC over a preselected interval. In certain embodiments, an immediate release dosage form as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong, cylindrical, or polygonal. In one such embodiment, the surfaces of the immediate release dosage form may be flat, round, concave, or convex. In some embodiments, the shape may be selected to maximize surface area, e.g., to increase the rate of dissolution of the dosage form.

In particular, when the immediate release formulations are prepared as a tablet, the immediate release tablets contain a

relatively large percentage and absolute amount of APC and so are expected to improve patient compliance and convenience, by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets as described herein can be administered, by oral ingestion, e.g., closely spaced, in order to provide a therapeutically effective dose of APC to the subject in a relatively short period of time. For example, dissolution of a 10 mg-1000 mg tablet prepared according to the present description can provide about 80-100% of the APC to the subject in about 10-15 minutes.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a moisture barrier layer using materials and methods known in the art. For example, where the APC delivered by the unit dosage form is highly hygroscopic, providing a moisture barrier layer over the immediate release dosage form as disclosed herein may be desirable. For example, protection of an immediate release dosage form as disclosed herein from water during storage may be provided or enhanced by coating the tablet with a coating of a substantially water soluble or insoluble polymer. Useful water-insoluble or water-resistant coating polymers include ethyl cellulose and polyvinyl acetates. Further water-insoluble or water resistant coating polymers include polyacrylates, polymethacrylates or the like. Suitable water-soluble polymers include polyvinyl alcohol and HPMC. Further suitable water-soluble polymers include PVP, HPC, HPEC, PEG, HEC and the like.

Where desired or necessary, the outer surface of an immediate release dosage form as disclosed herein may be coated with a color overcoat or other aesthetic or functional layer using materials and methods known in the art.

APC is a highly water soluble compound but in a pH dependent manner. The solubility decreases about 20-fold around pH 7 as shown in Table 1. The skilled artisan might expect such a large drop in solubility would result in a change in dissolution as solubility drives the gradient which typically determines dissolution. Surprisingly, APC exhibits a consistent dissolution rate at different pHs above and below the solubility turning point. Further, the lack of a media pH effect has been consistently observed across doses ranging from 37.5 mg to 300 mg.

Thus, one aspect of the invention relates to an immediate release compressed tablet for oral delivery of APC, the tablet comprising APC or a pharmaceutically acceptable salt thereof in an amount of about 90-98% by weight of the tablet; wherein the tablet exhibits substantially identical dissolution rates of the APC or a pharmaceutically acceptable salt thereof at an acidic pH and a neutral pH, e.g., about pH 1.2, pH 4.5, and about pH 6.8. As used herein, the term "substantially identical dissolution rates" is defined as a ratio of the time for a percentage of APC to be released from a dosage form in one condition to the time for the same percentage of APC to be released from a dosage form in another condition in the range of about 1.3 to about 0.7.

In some embodiments, the tablet releases at least 85%, e.g., at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, of the APC or a pharmaceutically acceptable salt thereof contained therein within a period of less than 15 minutes after administration of the tablet to a subject.

In certain embodiments, the tablet comprises, consists essentially of, or consists of the components described above and has one or more of the characteristics described above.

Methods are disclosed herein to treat conditions amenable to treatment by APC, by administering an effective amount of one or more dosage forms as described herein. For example, the present dosage forms can be administered to treat a subject in need of treatment for narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity, or to promoting smoking cessation in a subject in need thereof. See, e.g., U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414; each of which is incorporated by reference in its entirety with respect to the disorder to be treated.

The dosage forms disclosed herein can also be provided as a kit comprising, separately packaged, a container comprising a plurality of immediate release tablets, which tablets can be individually packaged, as in foil envelopes or in a blister pack. The tablets can be packaged in many conformations with or without desiccants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, e.g., sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of APC in vivo for preselected periods of time, to treat a preselected condition.

A daily dose of about 1 to about 2000 mg of APC or a pharmaceutically acceptable salt thereof may be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 10-1000 mg, e.g., about 20-500 mg, in single or divided doses, is administered. In some embodiments, the daily dose may be about 0.01 to about 150 mg/kg body weight, e.g., about 0.2 to about 18 mg/kg body weight.

In one embodiment of the invention, APC is administered to the subject as needed to treat a disorder. The compound can be administered continuously or intermittently. In one embodiment, the compound is administered to the subject more than once a day, e.g., 2, 3, or 4 times per day, or once every 1, 2, 3, 4, 5, 6, or 7 days. In another embodiment, the compound is administered to the subject no more than once a week, e.g., no more than once every two weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or longer. In a further embodiment, the compound is administered using two or more different schedules, e.g., more frequently initially (for example to build up to a certain level, e.g., once a day or more) and then less frequently (e.g., once a week or less). In other embodiments, the compound can be administered by any discontinuous administration regimen. In one example, the compound can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days, or longer. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, APC is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the

same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Further agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302.

The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults and geriatric subjects.

In particular embodiments, the subject is a human subject that has a disorder amenable to treatment with APC. In other embodiments, the subject used in the methods of the invention is an animal model of a disorder amenable to treatment with APC.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing a disorder amenable to treatment with APC, is suspected of having a disorder amenable to treatment with APC, and/or is anticipated to experience a disorder amenable to treatment with APC, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment.

The present invention is explained in greater detail in the following non-limiting Examples.

EXAMPLE 1

Immediate Release Formulation of (R)-2-amino-3-phenylpropyl carbamate hydrochloride

Immediate release tablet formulations of APC were developed with the goal of achieving 85% dissolution in under 15 minutes. Dosage strengths of 75 mg, 150 mg, and 300 mg were targeted. The amount of APC per tablet was maximized to increase the release rate. A formulation of APC with binder and lubricant was found to maximize dissolution.

Tablets were prepared by first dry-blending screened hydroxypropylcellulose (HPC ExF, Ashland, 1.00 g)) and APC (unmilled, 19.00 g) and then wet granulating them in a bullet-type blender while adding 4 g water in 0.5 g increments. Sufficient granules were formed at 3 g, and at 4 g it was slightly over-wetted. The granules were wet sieved, dried partially to remove 0.7 g of moisture, and wet sieved again prior to drying at 60° C. for about 1 hour. Magnesium stearate (0.75% of formulation) was added with blending 24 turns in a plastic container.

The active granulation was compressed with 13/32" standard round tooling, 380 mg, 1 ton force applied by a Carver press to produce the 300 mg strength. The remaining tablets were compressed using 1 ton force and various size tooling.

Tablets were coated with a color overcoat (Aquarius Cool Vanilla BI-1800, Ashland/Aqualon; hydroxypropylmethylcellulose, titanium dioxide, triacetin, polysorbate) using a Caleva air-suspension coater to 2-4% by weight.

Dissolution testing was carried per FDA guidance under standard conditions (50 rpm, 37° C., USP 2 paddles, pH 1.2 and pH 6.8 media, 900 ml, 1 test article per vessel, sinkers for capsules). Samples were taken at 0, 2, 5, 10, 15, 20, 25, and 30 minutes with a tolerance of 2 seconds. After 30 minutes, the stirring speed was increase to 150 rpm for at least 1 minute or until all material had visibly dissolved or dispersed. The speed was then returned to 50 rpm and a sample indicating the total dissolved dose was taken. Samples were diluted 1.00 ml in 8.00 ml DI Water and then analyzed by UV (Shimadzu UV-1200).

The dissolution testing was shown to be reproducible (FIG. **1**). The reference 150 mg tablets (uncoated) were tested on separate days, with different media preparation of the same kind and in different sequence of media recycle.

The color overcoat did not meaningfully retard dissolution (FIG. **2**), although a slight trend was observed at 2 minutes (higher weight caused some delay, lower dissolution). The profile appears to be faster beyond 2 minutes, relative to the reference uncoated tablets. However, this could be an effect of the process (spraying water and drying in air suspension coater) rather than the coating itself. Using the 3% target coating as a reference, all profiles are similar (F2>50) and nearly completely dissolve in 15 minutes.

The three doses achieved by varying tablet size of a common granulation are represented in FIG. **3**. The dissolution slows as the tablet size is increased, reflecting lower values of surface area/volume as expected. All strengths dissolve >85% in 15 minutes, but the highest strength is marginal (86%). An increase in surface area/volume by using an oblong tablet resulted in a statistically significant increase in dissolution rate.

A substantial concern was the effect of media pH. Although APC will be developed as an immediate release product, FDA guidances require comparison of profiles in three media including pH 6.8 (representing intestinal pH). APC is highly soluble in water or acidic media (530 mg/ml) but its solubility is much less at pH 6.8 (26 mg/ml) (see Table 1). Remarkably, the 20-fold drop in solubility does not seem to affect the dissolution behavior, as shown in Table 2. The media used were 0.1 N HCl pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. The dissolution study was carried using 12 tablets per dose, apparatus 1 (basket), 900 ml media volume, 37° C., 100 rpm. The tablets were coated with Opadry white polymer system.

TABLE 1

Solubility of APC in 0.2M phosphate buffers

pH of buffer	pH after equilibration	Solubility (mg/ml)
N/A (water)	4.22	533.74
5.33	4.25	542.49
5.95	4.78	525.46
6.97	6.76	26.60
8.02	7.47	22.53
8.99	7.55	22.38

TABLE 2

Dissolution of APC

Dose	Media	Percent release, time (min) 5	10	15
37.5 mg	pH 1.2	71.9	99.3	99.7
	pH 4.5	76.8	101.8	102.1
	pH 6.8	69.6	100.2	100.7
75 mg	pH 1.2	62.9	98.7	99.4
	pH 4.5	53.9	100.8	102.5
	pH 6.8	57.6	99.4	100.2
150 mg	pH 1.2	46.8	96.9	98.4
	pH 4.5	42.6	97.7	100.4
	pH 6.8	42.4	97.4	100.7
300 mg	pH 1.2	35.0	91.2	99.5
	pH 4.5	30.0	89.1	99.8
	pH 6.8	31.6	89.9	100.2

As mitigation of expected poorer dissolution at pH 6.8 (which was not seen as described above), one dissolution set was performed on tablets made from a formulation containing 3% superdisintegrant (PVP-XL10). The results shown in FIG. **4** confirm that a superdisintegrant will not speed release of the tablet, which dissolves rather than disintegrates. In fact, it may retard dissolution in the later stages, by the slight swelling it may cause.

EXAMPLE 2

Formulation Ranges for Immediate Release Tablet

Materials included binder, drug, optional diluent, and lubricant. Binder was selected from hydroxypropyl cellulose (Klucel ExF PH, Ashland), hydroxypropyl methylcellulose (HPMC E5 premium LV, Dow), povidone (PVP K30, or Kollidon 30, BASF), and Starch 1500 (Colorcon). Lubricants were selected from magnesium stearate (Sigma Aldrich/Riedel-de-Haen), calcium stearate (Strem chemicals), and sodium stearyl fumarate (Spectrum). The optional diluent was mannitol (EMD).

Unless otherwise noted, all experiments were done in the following manner. The binder, drug, and optional diluent were admixed vigorously in a plastic container and then wet massed by hand stirring with addition of water amounting to approximately 13% of the dry mass. The wet granulation was then passed through a 16 mesh screen, dried in a 60° C. oven for no less than 1 h, and then passed through a 16 mesh screen a second time. Based on the dry granulation yield, the formula amount of lubricant was weighed and added to the

cylindrical plastic container, closed, and then gently blended by hand for 24 revolutions at about a 45 degree angle. Granulation and blending involving 5 g or more material was performed in a 2×2 inch (diameter×length) cylindrical polypropylene container, and lesser quantities employed a 1×2 inch container.

The blended granulation was weighed into four 375±2 mg aliquots, each in turn added to 13/32" standard round convex tooling, and compressed with application of 1 metric ton force and about 5 seconds dwell. Two tablets were each characterized for weight, hardness using a Scheuniger 6D hardness tester, and thickness using calipers. The other two tablets were dissolution tested using a USP Type 2 apparatus (paddles), 900 mL of 0.1 N HCl media at 37° C., 50 rpm, and two tablets per vessel. 0.5 mL samples of each vessel were taken at 0, 5, 10, 15, and 30 minutes. After 30 minutes, the stirring speed was increased to 150-200 rpm and maintained until the remainder of the tablets dissolved. The vessels were then sampled again for a total sample, indicating the total amount dissolved as a basis for normalizing. Each sample was then diluted with 8.50 mL DI water and scanned by UV spectrophotometer at 215 nm (Shimadzu UV-1200) using a 1.0 cm quartz flow cell. A calibration curve spanning the range of absorbance achieved was constructed based on a quadratic fit to standards, from which concentrations were derived. Dissolution results were normalized to the total concentration for each vessel at the end of dissolution testing.

To examine the effect of binder level, five individual granulations of 5 g each were made corresponding to binder levels ranging from 0 to 10% by blending binder (HPC ExF 0-0.50 g) and drug (APC 4.5-5.0 g) using the standard procedure. The dried granulations (4.8-5.0 g) were blended with 37 mg lubricant (0.75%) and compressed. The tablet properties and dissolution profile are shown in Table 3. The results show that increasing binder improves hardness but also causes a reduction in dissolution rate.

TABLE 3

Effect of binder (HPC-ExF) level from 0-10%

Set	Gran	Binder	mg Mass	mm Thickness	N Hardness	Dissolution at (minutes): 5	10	15	30
1	A1	0%	374	4.79	59	66%	86%	98%	99%
2	A2	1%	374	4.73	105	68%	95%	102%	101%
3	A3	2%	373	4.70	99	58%	90%	101%	103%
4	A4	5%	375	4.69	150	43%	75%	92%	102%
5	A5	10%	375	4.65	165	32%	57%	77%	98%

To examine the effect of lubricant (magnesium stearate) level, a 15 g granulation was first made according to the standard procedure. This was then subdivided into 2.0 g portions, and each portion was individually blended with varying amount of magnesium stearate. The binder level was 3%. The results are shown in Table 4. The results show that lubricant had little effect on hardness as the level is increase, but caused a substantial reduction in dissolution.

TABLE 4

Effect of lubricant (magnesium stearate) level, binder fixed at 3% HPC

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Lubricant	Mass	Thickness	Hardness	5	10	15	30
6	B1	0.00%	374	4.77	140	78%	97%	101%	101%
7	B2	0.32%	375	4.76	130	71%	93%	101%	99%
8	B3	0.52%	374	4.71	124	63%	87%	99%	100%
9	B4	0.83%	374	4.72	126	57%	83%	96%	100%
10	B5	0.99%	375	4.71	138	50%	77%	93%	101%
11	B6	1.45%	373	4.67	125	41%	69%	85%	99%
12	B7	2.51%	373	4.68	120	33%	53%	68%	99%

To examine the effect of APC level, with lubricant and binder held constant, two 6-gram granulations were first prepared using 3% HPC ExF as binder. One granulation was produced without diluent, thus 97% APC, and the other had mannitol sufficient to reduce the APC loading to 86%. The two granulations were then blended in proportions to make five 2 g granulations ranging from 86% to 97% before blending. The proportions were 2.0/0 g, 0/2.0 g, 1.5/0.5 g, 1.0/1.0 g, and 0.5/1.5 g blending of the high and low granulations, respectively. Each was then blended with 15 mg magnesium stearate (0.75% level). The results are shown in Table 5. The data show that dissolution is not substantially impacted over the tested range of APC.

TABLE 5

Effect of API loading (binder HPC ExF at 3% and lubricant magnesium stearate at 0.75%)

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	API	Mass	Thickness	Hardness	5	10	15	30
14	C2	85.7%	376	4.71	128	50%	79%	93%	96%
17	C5	88.7%	376	4.69	127	47%	80%	94%	99%
16	C4	91.1%	376	4.73	118	50%	85%	98%	103%
15	C3	93.3%	375	4.72	112	49%	81%	95%	100%
13	C1	96.3%	375	4.74	120	51%	85%	101%	103%

To examine the effect of binder type, four binders (HPMC E5, PVP K30, HPC ExF, and Starch 1500), were evaluated at two levels each (2% and 5%) by making individual 5 g granulations. The results are shown in Table 6.

TABLE 6

Effect of binder type and level (2% or 5%), magnesium stearate fixed at 0.75%

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Binder	Mass	Thickness	Hardness	5	10	15	30
18	D1	2% HPMC-E5	375	4.76	92	61%	91%	95%	98%
19	D2	2% PVP-K30	375	4.76	108	66%	95%	98%	101%
20	A3	2% HPC-ExF	375	4.69	128	56%	87%	97%	99%
21	D4	2% Starch 1500	374	4.76	66	41%	68%	82%	97%
22	D5	5% HPMC-E5	376	4.77	127	49%	81%	97%	99%
23	D6	5% PVP-K30	377	4.76	120	62%	94%	99%	99%
4	A4	5% HPC-ExF	375	4.69	150	43%	75%	92%	102%
24	D7	5% Starch 1500	374	4.76	66	29%	51%	64%	90%

To evaluate the effect of lubricant type, a single 15-gram granulation was made with 3% HPC ExF and no diluent. The dried granulation was then subdivided into 5 g aliquots. Each aliquot was then blended with one of three lubricants (magnesium stearate, calcium stearate, or sodium stearyl fumarate—"SSF") using the standard 24 turns. After the initial set of tablets was made, the remaining portion of each granulation was then vigorously shaken for 1 minute to evaluate the consequences of overblending. The standard and overblended results are shown in Table 7. Overblending had no substantial effect on tablet properties, but affected dissolution for all lubricants.

TABLE 7

Effect of lubricant type and overblending

			mg	mm	N	Dissolution at (minutes):			
Set	Gran	Lube & blending	Mass	Thickness	Hardness	5	10	15	30
25	E1	Mg Stearate - standard	374	4.70	103	53%	86%	100%	100%
26	E2	Ca stearate - standard	375	4.70	113	51%	84%	97%	100%
27	E3	SSF - standard	374	4.68	129	57%	87%	99%	99%
28	E1a	Mg stearate - overblend	375	4.70	102	35%	60%	75%	97%
29	E2a	Ca stearate - overblend	374	4.68	91	40%	69%	86%	100%
30	E3a	SSF - overblend	377	4.70	138	44%	72%	89%	98%

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A solid pharmaceutical formulation for oral delivery of (R)-2-amino-3-phenylpropyl carbamate, comprising:

a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of about 90-98% by weight of the formulation;

hydroxypropyl cellulose in an amount of 1-5% by weight of the formulation; and

magnesium stearate in an amount of about 0.1-2% by weight of the formulation;

wherein the formulation releases at least 85% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the formulation to a subject; and

wherein the formulation exhibits substantially identical dissolution rates of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate at pH 1.2, pH 4.5, and pH 6.8; and

wherein the formulation does not comprise a disintegrant.

2. The solid pharmaceutical formulation of claim **1**, wherein the pharmaceutical formulation is a tablet.

3. The solid pharmaceutical formulation of claim **1**, wherein the formulation releases at least 95% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the formulation to a subject.

4. The solid pharmaceutical formulation of claim **1**, further comprising a coating.

5. The solid pharmaceutical formulation of claim **4**, wherein the coating is a color overcoat.

6. The solid pharmaceutical formulation of claim **1**, wherein the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate is (R)-2-amino-3-phenylpropyl carbamate hydrochloride.

7. The solid pharmaceutical formulation of claim **1**, wherein the formulation comprises about 300 mg of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate.

8. The solid pharmaceutical formulation of claim **1**, wherein the formulation comprises about 150 mg of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate.

9. The solid pharmaceutical formulation of claim **1**, wherein the formulation comprises about 75 mg of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate.

10. The solid pharmaceutical formulation of claim **1**, wherein the formulation comprises about 37.5 mg of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate.

11. The solid pharmaceutical formulation of claim **1**, comprising a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of about 90-98% by weight of the formulation and a total weight of between about 30 to about 300 mg.

12. The solid pharmaceutical formulation of claim **1**, comprising hydroxypropyl cellulose in an amount of about 1% to about 3% by weight of the formulation.

13. The solid pharmaceutical formulation of claim **1**, comprising magnesium stearate in an amount of about 0.1% to about 1.0% by weight of the formulation.

14. The solid pharmaceutical formulation of claim **1**, comprising hydroxypropyl cellulose in an amount of about 2% by weight of the formulation.

15. The solid pharmaceutical formulation of claim **1**, comprising magnesium stearate in an amount of about 0.5% by weight of the formulation.

16. A method of treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject solid pharmaceutical formulation for oral delivery of (R)-2-amino-3-phenylpropyl carbamate, the formulation comprising:

a pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate in an amount of about 90-98% by weight of the formulation;

hydroxypropyl cellulose in an amount of 1-5% by weight of the formulation; and

magnesium stearate in an amount of about 0.1-2% by weight of the formulation;

wherein the formulation releases at least 85% of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate contained therein within a period of less than 15 minutes after administration of the formulation to a subject; and

wherein the formulation exhibits substantially identical dissolution rates of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate at pH 1.2, pH 4.5, and pH 6.8; and

wherein the formulation does not comprise a disintegrant.

17. The method claim **16**, wherein the pharmaceutical formulation is a tablet.

18. The method claim **16**, wherein the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate is (R)-2-amino-3-phenylpropyl carbamate hydrochloride.

19. The method of claim **16**, wherein the formulation comprises between about 30 and about 300 mg of the pharmaceutically acceptable salt of (R)-2-amino-3-phenylpropyl carbamate.

* * * * *

EXHIBIT E

US012005036B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 12,005,036 B1**
(45) **Date of Patent: *Jun. 11, 2024**

(54) **METHODS OF ADMINISTERING SOLRIAMFETOL TO LACTATING WOMEN**

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(72) Inventor: **Herriot Tabuteau**, New York, NY (US)

(73) Assignee: **AXSOME MALTA LTD.**, Qormi (MT)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/491,291**

(22) Filed: **Oct. 20, 2023**

Related U.S. Application Data

(63) Continuation-in-part of application No. 18/176,855, filed on Mar. 1, 2023, now Pat. No. 11,793,776, which is a continuation of application No. 18/148,682, filed on Dec. 30, 2022, now Pat. No. 11,771,666.

(51) **Int. Cl.**
A61K 31/165 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/165*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/165
See application file for complete search history.

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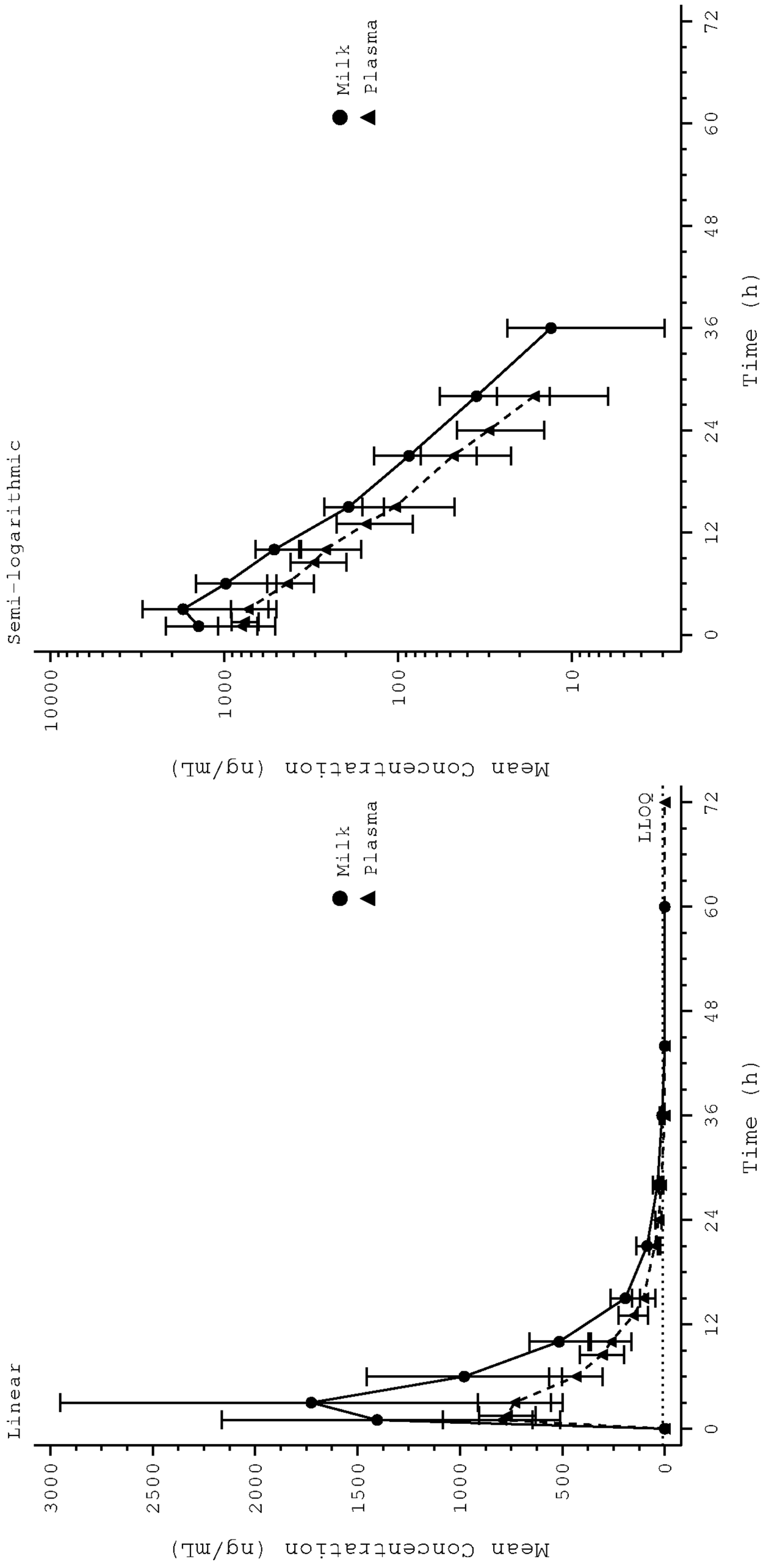
(74) *Attorney, Agent, or Firm* — HUESCHEN AND SAGE

(57) **ABSTRACT**

Provided herein according to some embodiments is a method for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby decreasing potential for adverse events from solriamfetol in an infant.

30 Claims, 2 Drawing Sheets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Time (h)
Milk
Plasma
LLOQ
Linear
Mean Concentration (ng/mL)
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48
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72
Time (h)

FIG. 1

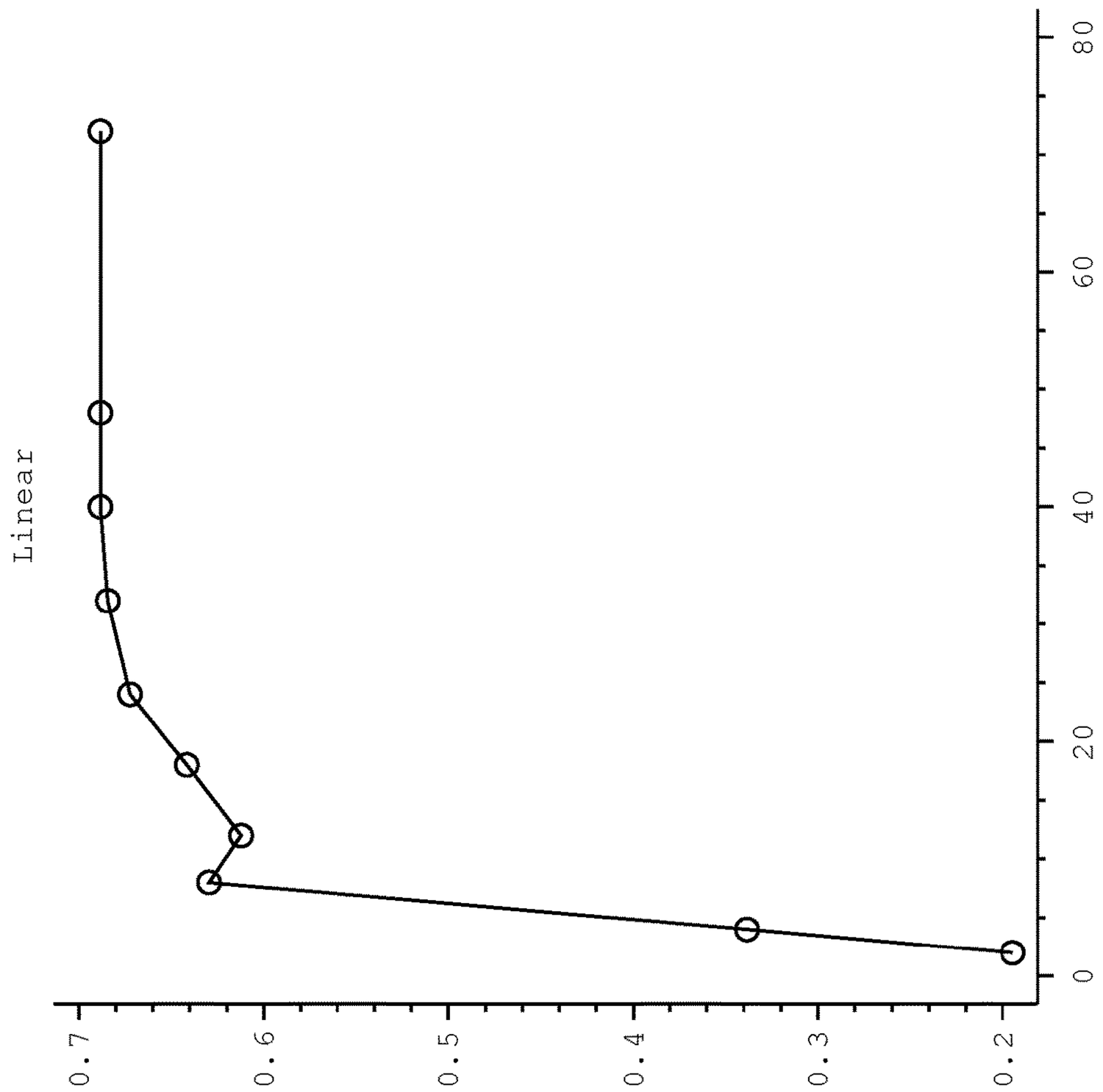


FIG. 2

METHODS OF ADMINISTERING SOLRIAMFETOL TO LACTATING WOMEN

STATEMENT OF PRIORITY

This application is a continuation-in-part of and claims priority to U.S. patent application Ser. No. 18/176,855, filed Mar. 1, 2023, which is a continuation of U.S. patent application Ser. No. 18/148,682, filed Dec. 30, 2022, now U.S. Pat. No. 11,771,666, the entire contents of each of which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to methods of administering solriamfetol to a lactating subject while reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject.

BACKGROUND OF THE INVENTION

Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor that has received marketing approval in the US for improving wakefulness in adult subjects with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA). Solriamfetol has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others.

Pharmacokinetic studies have demonstrated rapid absorption and high oral bioavailability of solriamfetol with dose-proportional exposure (maximum serum concentration and area under the concentration-time curve [AUC]) in animals tested.

The present invention overcomes shortcomings in the art by providing methods of administering solriamfetol to a lactating subject while reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject.

SUMMARY OF THE INVENTION

The present invention relates to the development of methods of reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject. The invention additionally related to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol.

Accordingly, one aspect of the invention relates to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5) hours after administering the solriamfetol to the subject, thereby reducing exposure to solriamfetol in the infant.

Another aspect of the invention relates to a method for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject, thereby decreasing the potential for adverse events from solriamfetol in the infant. In some embodiments, the daily dose of solriamfetol is 150 mg.

An aspect of the invention relates to a method treating a disorder treatable with solriamfetol in a subject producing breast milk for feeding an infant, comprising: administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and reducing exposure to solriamfetol and/or decreasing the potential for adverse events in the infant fed breast milk from the subject comprising feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject. The disorder treatable with solriamfetol can be, without limitation, narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, attention deficit/hyperactivity disorder, cognitive impairment or binge eating disorder.

Another aspect of the invention relates to a method of avoiding exposing an infant of a nursing mother being treated with solriamfetol to peak concentrations of solriamfetol excreted in breast milk, such method comprising not feeding the infant breast milk obtained within at least about 3.5 hours (e.g., at least about 4 or 5 hours) of the mother receiving an oral once-daily dose of solriamfetol, wherein the T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hour.

A further aspect of the invention relates to a method of reducing the exposure to solriamfetol from breast milk, in an infant receiving breast milk from a nursing mother being treated with a once-daily dose of solriamfetol of about 37.5 mg to about 300 mg for a disorder amenable to treatment with solriamfetol, such method comprising feeding the infant breast milk obtained from the mother at least about 5 hours after administering the solriamfetol to the mother, wherein the exposure to solriamfetol in the infant is reduced by at least about 50% compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol.

An additional aspect of the invention relates to a method of treating excessive daytime sleepiness in a lactating mother, with an infant at risk of adverse events from the mother's excessive daytime sleepiness, and who wishes to breastfeed the infant, said method comprising: (a) determining the Epworth Sleepiness Scale (ESS) total score of the mother and if the mother experiences sleep attacks while caring for the infant; (b) providing the mother with an ESS total score of 15 or greater and who experiences sleep attacks while caring for the infant a starting dose of solriamfetol of 37.5 mg once daily if the excessive daytime sleepiness is associated with obstructive sleep apnea, or 75 mg once daily if the excessive daytime sleepiness is associated with narcolepsy, and doubling the dose at intervals of at least 3 days up to 150 mg once daily, wherein the elimination half-life of solriamfetol in plasma in the postpartum or lactating mother is about 5 hours; and (c) feeding the infant breast milk obtained from the mother at least about 3.5 hours (e.g., 4 or 5 hours) after administration of the solriamfetol to the mother, thereby avoiding exposing the infant to the maximum concentrations of solriamfetol in the breast milk, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hours.

In some embodiments, the method provides a daily infant dose of solriamfetol of about 0.3 mg or lower. In some embodiments, the method achieves a relative infant dose of less than about 9% of the subject weight-adjusted dose. In

some embodiments, the method achieves a relative infant dose of less than about 5% of the subject weight-adjusted dose.

In some embodiments, the infant does not experience agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure.

In some embodiments, the subject is from 1 day to 24 months postpartum or from 10 days to 12 months (52 weeks) postpartum.

In some embodiments, the subject is being treated with solriamfetol for narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, attention deficit/hyperactivity disorder, cognitive impairment, or binge eating disorder.

In some embodiments, the subject is a woman between the ages of 18 and 45 years.

In some embodiments, the adverse events are one or more of agitation, insomnia, anorexia, or reduced weight gain.

Methods of treating a disorder amenable to treatment with solriamfetol in a subject who is breastfeeding an infant are provided comprising orally administering solriamfetol at a daily dose of between about 37.5 mg and 300 mg to the subject.

These and other aspects of the invention are set forth in more detail in the description of the invention below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Time course of mean solriamfetol breast milk and plasma concentration-time profiles on linear and semi-logarithmic scales.

FIG. **2**. Mean breast milk cumulative solriamfetol amount-time profiles on linear scale following a single-dose administration of solriamfetol 150 mg tablet.

DETAILED DESCRIPTION

The present invention will now be described in more detail with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. In addition, any references cited herein are incorporated by reference in their entireties.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents, patent publications and other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended

that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

As used in the description of the invention and the appended claims, the singular forms "a," "an," and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

The term "about," as used herein when referring to a measurable value such as an amount of polypeptide, dose, time, temperature, enzymatic activity or other biological activity and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount.

As used herein, the transitional phrase "consisting essentially of" (and grammatical variants) is to be interpreted as encompassing the recited materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. Thus, the term "consisting essentially of" as used herein should not be interpreted as equivalent to "comprising."

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, prevention or delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Pharmaceutically acceptable carrier" (sometimes referred to as a "carrier") refers to a carrier or excipient that is useful in preparing a pharmaceutical or therapeutic composition that is generally safe and non-toxic and includes a carrier that is acceptable for veterinary and/or human pharmaceutical or therapeutic use. The terms "carrier" or "pharmaceutically acceptable carrier" can include, but are not limited to, phosphate buffered saline solution, water, emulsions (such as an oil/water or water/oil emulsion) and/or various types of wetting agents. As used herein, the term "carrier" encompasses, but is not limited to, any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations and as described further herein.

The term "modulate," "modulates," or "modulation" refers to enhancement (e.g., an increase) or inhibition (e.g., a decrease) in the specified level or activity.

The term "enhance" or "increase" refers to an increase in the specified parameter of at least about 1.25-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 8-fold, 10-fold, twelve-fold, or even fifteen-fold and/or can be expressed in the enhancement and/or increase of a specified level and/or activity of at least about 1%, 5%, 10%, 15%, 25%, 35%, 40%, 50%, 60%, 75%, 80%, 90%, 95% or more.

"Inhibit" or "reduce" or grammatical variations thereof as used herein refers to a decrease or diminishment in the

specified level or activity of at least about 1, 5, 10, 15%, 25%, 35%, 40%, 50%, 60%, 75%, 80%, 90%, 95% or more. In particular embodiments, the inhibition or reduction results in little or essentially no detectible activity (at most, an insignificant amount, e.g., less than about 10% or even 5%).

"Treat," "treating" and similar terms as used herein in the context of treating a subject refer to providing medical and/or surgical management of a subject. Treatment may include, but is not limited to, administering an agent or composition (e.g., a pharmaceutical composition) to a subject. Treatment is typically undertaken in an effort to alter the course of a disease (which term is used to indicate any disease, disorder, syndrome, or undesirable condition warranting or potentially warranting therapy) in a manner beneficial to the subject. The effect of treatment may include reversing, alleviating, reducing severity of, delaying the onset of, curing, inhibiting the progression of, and/or reducing the likelihood of occurrence or recurrence of the disease or one or more symptoms or manifestations of the disease. A therapeutic agent may be administered to a subject who has a disease or is at increased risk of developing a disease relative to a member of the general population. In some embodiments a therapeutic agent may be administered to a subject who has had a disease but no longer shows evidence of the disease. The agent may be administered e.g., to reduce the likelihood of recurrence of evident disease. A therapeutic agent may be administered prophylactically, i.e., before development of any symptom or manifestation of a disease. "Prophylactic treatment" refers to providing medical and/or surgical management to a subject who has not developed a disease or does not show evidence of a disease in order, e.g., to reduce the likelihood that the disease will occur, delay the onset of the disease, or to reduce the severity of the disease should it occur. The subject may have been identified as being at risk of developing the disease (e.g., at increased risk relative to the general population or as having a risk factor that increases the likelihood of developing the disease.

Grammatical variations of "administer," "administration," and "administering" to a subject include any route of introducing or delivering to a subject an agent. Administration can be carried out by any suitable route, including oral, topical, intravenous, subcutaneous, transcutaneous, transdermal, intramuscular, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, by inhalation, via an implanted reservoir, parenteral (e.g., subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intraperitoneal, intrahepatic, intralesional, and intracranial injections or infusion techniques), and the like. "Concurrent administration," "administration in combination," "simultaneous administration," or "administered simultaneously" as used herein, means that the compounds are administered at the same point in time, overlapping in time, or one following the other. In the latter case, the two compounds are administered at times sufficiently close that the results observed are indistinguishable from those achieved when the compounds are administered at the same point in time. "Systemic administration" refers to the introducing or delivering to a subject an agent via a route which introduces or delivers the agent to extensive areas of the subject's body (e.g., greater than 50% of the body), for example through entrance into the circulatory or lymph systems. By contrast, "local administration" refers to the introducing or delivery to a subject an agent via a route which introduces or delivers the agent to the area or area immediately adjacent to the point of administration and does not introduce the agent systemically in a therapeutically significant amount. For example, locally administered agents are easily detectable in the local vicinity of the point of administration but are undetectable or detectable at negligible amounts in distal parts of the subject's body. Administration includes self-administration and the administration by another.

"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., Remington's Pharmaceutical Science; 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

"Bioavailability," as used herein, refers to the estimated area under the curve, or AUC of the active drug in systemic circulation after oral administration with a dosage form as disclosed herein when compared with the AUC of the active drug in systemic circulation after intravenous administration of the active drug. The AUC is affected by the extent to which the drug is absorbed in the GI tract.

Products are considered to be "bioequivalent" if the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test product to reference product is within 80% to 125%.

The term "$AUC_{(0-t)}$" means the area under the plasma concentration curve from time 0 to time t.

The term "$AUC_{(0-\infty)}$" or "AUC_{0-inf}" means the area under the plasma concentration time curve from time 0 to infinity.

"C_{max}" refers to the maximum milk or plasma concentration of solriamfetol.

"T_{max}" refers to the time to maximum milk or plasma concentration for a given drug.

"$t_{1/2}$" refers to the time to reduce the milk and plasma concentration by 50% during the terminal elimination phase of the drug.

Milk:plasma ratio means AUC in breast milk divided by AUC in plasma.

"A_{milk}" means the amount excreted in breast milk over 72 hours.

"Vd/F" means the apparent volume of distribution in plasma.

"CL/F" is the apparent oral clearance in plasma.

AUC_{0-t} is the area under the concentration-time curve from time 0 to the time t of the last quantifiable concentration (milk and plasma).

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after

apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift. It is also understood that EDS is medically distinct from fatigue and disorders associated with fatigue.

The present invention is based, in part, on methods of using Sunosi® (referred to herein as solriamfetol (also known as (R)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride, and previously known as JZP-110, ADX-N05, R228060, and YKP10A)) in lactating subjects with a disorder amenable to treatment with solriamfetol while reducing the potential for adverse effects in infants fed the subject's breast milk. Solriamfetol is approved by the FDA for administration at doses equivalent to 37.5 mg. 75 mg, and 150 mg of APC (corresponding to 44.7 mg, 89.3 mg, and 178.5 mg of APC hydrochloride, respectively). Administration of solriamfetol to subjects expressing breast milk presents challenges. In a nonclinical study in rats, solriamfetol was detected in breast milk, with solriamfetol milk concentrations higher than solriamfetol plasma concentrations. It is desirable to reduce or minimize any adverse effects from the daily dose received by an infant fed breast milk from a subject treated with solriamfetol. In addition, it is desirable to identify methods that allow for the safety and tolerability of solriamfetol in nursing subjects.

Accordingly, one aspect of the invention relates to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject, thereby reducing exposure to solriamfetol in the infant.

One aspect of the invention comprises methods for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject, thereby decreasing the potential for adverse events from solriamfetol in the infant. In an embodiment, the adverse event is one or more of agitation, insomnia, anorexia, or reduced weight gain.

Another aspect of the invention relates to a method of avoiding exposing an infant of a nursing mother being treated with solriamfetol to peak concentrations of solriamfetol excreted in breast milk, such method comprising not feeding the infant breast milk obtained within at least about 3.5 hours (e.g., within at least about 4 or 5 hours) of the mother receiving an oral once-daily dose of solriamfetol, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hour. In clinical studies, the range of T_{max} was 1 hour to 3 hours. Thus, waiting at least 3.5 hours after solriamfetol administration ensures avoidance of the T_{max} even for outlier subjects.

A further aspect of the invention relates to a method of reducing the exposure to solriamfetol from breast milk, in an infant receiving breast milk from a nursing mother being treated with a once-daily dose of solriamfetol of about 37.5 mg to about 300 mg for a disorder amenable to treatment with solriamfetol, such method comprising feeding the infant breast milk obtained from the mother at least about 5 hours (e.g., at least 6, 7, 8, 9, or 10 hours) after administering the solriamfetol to the mother, wherein the exposure to solriamfetol in the infant is reduced by at least about 50% (e.g., at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%) compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol. In some embodiments, the resulting relative infant dose is about 2% or lower of the maternal weight-adjusted dose. In some embodiments, the once-daily dose of solriamfetol is 150 mg and the daily amount of solriamfetol passed to the infant through the breast milk is about 0.3 mg or lower. In some embodiments, the once-daily dose of solriamfetol is 75 mg and the daily amount of solriamfetol passed to the infant through the breast milk is about 0.15 mg or lower. In some embodiments, the breast milk is obtained from the mother at least about 10 hours (e.g., about 2 half-lives) after administering the solriamfetol to the mother and the exposure to solriamfetol in the infant is reduced by at least about 75% compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol. In some embodiments, the resulting relative infant dose is about 1% or lower of the maternal weight-adjusted dose.

One aspect of the invention relates to a method for treating a disorder treatable with solriamfetol in a subject producing breast milk for feeding an infant, comprising administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and reducing exposure to solriamfetol and/or decreasing the potential for adverse events in the infant fed breast milk from the subject, comprising feeding the infant breast milk obtained from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject. In one embodiment, the method reduces solriamfetol in the infant and the infant does not experience agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure. In one embodiment, the adverse events are one or more of agitation, insomnia, anorexia, or reduced weight gain.

A "disorder amenable to treatment with solriamfetol" or a "disorder treatable with solriamfetol" refers to any disorder in which administration of solriamfetol to a subject results in the treatment of one or more symptoms of the disorder in the subject. Example disorders amenable to treatment with solriamfetol include narcolepsy, cataplexy, excessive daytime sleepiness, obstructive sleep apnea, shift work disorder, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit hyperactivity disorder (ADHD), cognitive impairment and/or cognitive dysfunction, Parkinson's disease, restless legs syndrome, depression, bipolar disorder, obesity, or binge eating disorder. In some embodiments, the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease. In some embodiments, the disorders amenable to treatment with solriamfetol include narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, cognitive impairment, attention deficit/hyperactivity disorder, or binge eating disorder. In some embodiments, solriamfetol is administered to improve wakefulness. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/

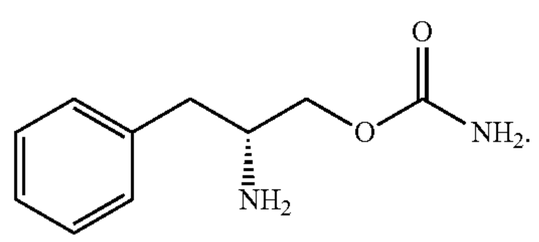
0018414. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift. It is also understood that EDS is medically distinct from fatigue and disorders associated with fatigue.

In some embodiments, the cause of the EDS may be, without limitation, central nervous system (CNS) pathologic abnormalities, stroke, narcolepsy, idiopathic CNS hypersomnia; sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder (ADHD), Alzheimer's disorder, major depression, bipolar disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work disorder, or sedating drugs.

In certain embodiments, solriamfetol structure is given below as formula I:

(I)



Methods for producing solriamfetol and related compounds can be found in U.S. Pat. Nos. 10,829,443, 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

In one embodiment, the methods detailed herein provide an infant fed breast milk from a subject to whom solriamfetol is administered does not experience adverse events, e.g., agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure. Monitoring the infant for agitation, insomnia, anorexia, or reduced weight gain can be performed. For example, monitoring and/or detecting weight loss, reduced weight gain, reduction in number of feedings or lessened intake, reduction in volume of milk ingested can be performed. Monitoring increase in agitation and/or insomnia in the infant, including a reduction of sleeping hours and/or time to fall asleep and stay asleep can also be performed to identify changes in the infant. In some embodiments, the monitoring for changes in the infant is performed at 3 or more hours subsequent to administering of the solriamfetol dose and subsequent to initiation of infant feeding with breast milk from the subject, for example at 3 hours, 4, hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours or more subsequent to administering of the solriamfetol dose. Monitoring for any changes experienced by the infant (e.g., agitation, insomnia, anorexia, or reduced weight gain) can be performed over the time period in which solriamfetol is administered to the subject, which may be over days, weeks, or months, with monitoring over any interval in that time frame, including hourly, daily, weekly, monthly or any time range therein.

In one embodiment, the method provides a daily infant dose of solriamfetol of about 0.4 mg or lower, e.g., about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.335 mg, about 0.33 mg, about 0.32 mg, about 0.21 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, about 0.01 mg, or lower. The daily infant dose means the daily dose that was received by the infant through feeding of breast milk. In some embodiments, the subject is orally administered a once-daily dose of solriamfetol of about 150 mg and the daily infant dose of solriamfetol is reduced to about 0.3 mg or lower due to the waiting period after administration. In some embodiments, the subject is orally administered a once-daily dose of solriamfetol of about 75 mg and the daily infant dose of solriamfetol is reduced to about 0.15 mg or lower due to the waiting period after administration. In some embodiments, the subject is orally administered a once-daily dose of solriamfetol of about 37.5 mg and the daily infant dose of solriamfetol is reduced to about 0.08 mg or lower due to the waiting period after administration.

In one embodiment, the method provides a daily infant dose of solriamfetol of about 0.2 mg/kg (based on a nominal infant weight of 6 kg) or lower, e.g., about 0.19 mg/kg, about 0.18 mg/kg, about 0.17 mg/kg, about 0.16 mg/kg, about 0.15 mg/kg, about 0.14 mg/kg, about 0.13 mg/kg, about 0.12 mg/kg, about 0.11 mg/kg, about 0.10 mg/kg, about 0.09 mg/kg, about 0.08 mg/kg, about 0.07 mg/kg, about 0.06 mg/kg, about 0.05 mg/kg, about 0.04 mg/kg, about 0.03 mg/kg, about 0.02 mg/kg, about 0.01 mg/kg, or lower.

In one embodiment, the method provides a cumulative median infant dose of solriamfetol over 72 hours after a single dose of about 0.7 mg or lower, e.g., about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.355 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, or lower.

In some embodiments, the method provides a cumulative median infant dose of solriamfetol after a single dose of about 75%-80% after 8 hours of the total excreted in 72 hours, e.g., about 75%, 76%, 77%, 78%, 79%, or 80%. In some embodiments, the method provides a cumulative median infant dose of solriamfetol after a single dose of about 95%-100% after 24 hours of the total excreted in 72 hours, e.g., about 95%, 96%, 97%, 98%, 99%, or 100%.

In some embodiments, breast milk for feeding of the infant is expressed or produced from the subject at 2 or more hours, 2.5 or more hours, 3 or more hours, 3.5 or more hours, 4 or more hours, 4.5 or more hours, or 5 or more hours, for example at 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 5.5 hours, 6 hours, 6.5 hours, 7 hours, 7.5 hours, 8 hours, 8.5 hours, 9 hours, 9.5 hours, 10 hours or more, subsequent to administering of the solriamfetol dose to the subject. In some embodiments, the breast milk produced from the subject for infant feeding in the methods detailed herein occurs at about the mean elimination half-life of solriamfetol or later, i.e., at about 5 hours, subsequent to administration of the solriamfetol. In some embodiments, the breast milk produced from the subject for infant feeding in the methods detailed herein occurs at about 2-4 times the median T_{max} of solriamfetol or later, i.e., at about 2 hours, 2.5 hours, 3 hours, 3.5 hours, or 4 hours subsequent to administration of the solriamfetol. In some embodiments, the breastfeeding of the infant is performed at 3 or more hours, 4 or more hours, or 5 or more hours subsequent to administering of the solriamfetol dose to the subject. In some embodiments, the breast milk for feeding the infant is obtained from the subject at 3 or more hours, 4 or more hours, or 5 or more hours subsequent to administering of the solriamfetol dose to the subject.

In some embodiments, the subject refrains from breastfeeding the infant during the waiting period (e.g., the 2 or more hours). In other embodiments, the breast milk produced during the waiting period is expressed and not fed to the infant, e.g., wherein the expressed milk is discarded.

In some embodiments, the method achieves a relative infant dose, the percentage of the weight-adjusted subject dose excreted in breast milk over 24 hours, of less than about 10%, less than about 9.5%, less than about 9%, less than about 8.5%, less than about 8%, less than about 7.5%, less than about 7%, less than about 6.5%, less than about 6%, less than about 5.5%, less than about 5%, less than about 4.9%, less than about 4.8%, less than about 4.7%, less than about 4.6%, less than about 4.5%, less than about 4.4%, less than about 4.3%, less than about 4.2%, less than about 4.1%, less than about 4.0%, less than about 3.9%, less than about 3.8%, less than about 3.7%, less than about 3.6%, less than about 3.5%, less than about 3.4%, less than about 3.3%, less than about 3.2%, less than about 3.1%, less than about 3.0%, less than about 2.9%, less than about 2.8%, less than about 2.7%, less than about 2.6%, less than about 2.5%, less than about 2.4%, less than about 2.3%, less than about 2.2%, less than about 2.1%, less than about 2.0%, less than about 1.9%, less than about 1.8%, less than about 1.7%, less than about 1.6%, less than about 1.5%, less than about 1.4%, less than about 1.3%, less than about 1.2%, less than about 1.1%, less than about 1.0%, of the subject weight-adjusted dose.

In some embodiments, the cumulative median amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.335 mg, about 0.33 mg, about 0.32 mg,

about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, or about 0.01 mg over 72 hours.

In some embodiments, the cumulative median amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, or about 0.01 mg over 24 hours.

In some embodiments, the cumulative median amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, or about 0.01 mg over 8 hours.

A daily dose of about 1 to about 2000 mg of solriamfetol or a pharmaceutically acceptable salt thereof may be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 1-1000 mg, e.g., about 20-500 mg, in single or divided doses, is administered. In some embodiments, the daily dose may be about 0.01 to about 150 mg/kg body weight, e.g., about 0.2 to about 18 mg/kg body weight. In some embodiments, the dose contains about 1 mg to about 1000 mg of the drug or any range or value therein, e.g., about 10 mg to about 500

mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg. For example, in certain such embodiments, the total amount of drug may be selected from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, or any range therein.

In one embodiment of the invention, solriamfetol is administered to the subject as needed to treat a disorder. The compound can be administered continuously or intermittently. In one embodiment, the compound is administered to the subject more than once a day, e.g., 2, 3, or 4 times per day, or once every 1, 2, 3, 4, 5, 6, or 7 days. In another embodiment, the compound is administered to the subject no more than once a week, e.g., no more than once every two weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or longer. In a further embodiment, the compound is administered using two or more different schedules, e.g., more frequently initially (for example to build up to a certain level, e.g., once a day or more) and then less frequently (e.g., once a week or less). In other embodiments, the compound can be administered by any discontinuous administration regimen. In one example, the compound can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days, or longer. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, solriamfetol is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Further agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302. The present invention finds use in research as well as veterinary and medical

applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults, and geriatric subjects. In some embodiments, the subject is postpartum, In some embodiments, the subject is a woman between the ages of 18 and 45 years.

Suitable subjects are generally lactating mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. The human subject can be a lactating individual who is breastfeeding an infant frequently or on a regular basis. In some embodiments, the human subject is a woman. The woman may be between about 18 and 45 years of age. The term "breastfeeding" may also be referred to as chest-feeding, or grammatical variations thereof, refers to delivering breast milk of the individual directly to an infant, extracting breast milk from the individual using a device and subsequently delivering to an infant, extracting breast milk from the individual using a device and storing the breast milk for a period of time and subsequently delivering the stored breast milk to the infant, or a combination thereof.

The subject of the present disclosure can be in lactation, for example, an individual who is lactating (e.g., producing breast milk), nursing or breastfeeding. The subject can be in lactation after pregnancy, i.e., post-partum, or via induced lactation (e.g., with metoclopramide, oral contraceptives, herbal medications, stimulation via pumping, or any combination thereof).

In some embodiments, the subject is between 1 day and 24 months postpartum, between about 1 day and 12 months postpartum, between about 10 days and 12 months (52 weeks) postpartum, or between about 15 weeks to about 37 weeks postpartum. In some embodiments, the subject expresses mature milk, which typically occurs about 10 to about 30 days (e.g., about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days) postpartum, or about 10 to about 20 days postpartum, or about 10 to about 20 days after beginning of milk expression in induced lactation. Infancy starts at birth and ends around the age of 2 years; accordingly, the infant stage being fed breast milk includes the breastfeeding period.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing a disorder amenable to treatment with solriamfetol, is suspected of having a disorder amenable to treatment with solriamfetol, and/or is anticipated to experience a disorder amenable to treatment with solriamfetol, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment.

In some embodiments, the subject is a mother whose disease or disorder is putting her baby at risk of adverse events from the maternal condition (e.g., she falls asleep while caring for the baby), and who wishes to breastfeed. Surveys have shown that at least 60% of women with narcolepsy report difficulties caring for their babies because of their symptoms, and are afraid of being impaired by their disease as it relates to caring for their babies.

Thus, one aspect of the invention relates to a method of treating excessive daytime sleepiness in a lactating mother, with an infant at risk of adverse events from the mother's excessive daytime sleepiness, and who wishes to breastfeed the infant, said method comprising: (a) determining the Epworth Sleepiness Scale (ESS) total score of the mother and if the mother experiences sleep attacks while caring for the infant; (b) providing the mother with an ESS total score of 15 or greater and who experiences sleep attacks while caring for the infant a starting dose of solriamfetol of 37.5 mg once daily if the excessive daytime sleepiness is associated with obstructive sleep apnea, or 75 mg once daily if the excessive daytime sleepiness is associated with narcolepsy, and doubling the dose at intervals of at least 3 days up to 150 mg once daily, wherein the elimination half-life of solriamfetol in plasma in the postpartum or lactating mother is about 5 hours; and (c) feeding the infant breast milk obtained from the mother at least about 3.5 hours (e.g., 4 or 5 hours) after administration of the solriamfetol to the

mother, thereby avoiding exposing the infant to the maximum concentrations of solriamfetol in the breast milk, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hours.

The method selects subjects suitable for treatment based on disease severity, interference with infant care, and desire of the mother to provide the infant the developmental and health benefits of breastfeeding

The ESS is a subjective sleepiness test that is well known in the art and routinely used to measure the sleepiness level of a subject. The scale is intended to measure daytime sleepiness through the use of a short questionnaire that asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives. The scores for the eight questions are added together to obtain a single number that estimates the subject's average sleep propensity (ASP). A number in the 0-10 range is considered to be normal while 11-12 indicates mild excessive sleepiness, 13-15 indicates moderate excessive sleepiness, and 16 or higher indicates severe excessive sleepiness. Narcolepsy patients have an average score of about 17. Obstructive sleep apnea (OSA) patients with excessive sleepiness have an average score of about 15.

A "sleep attack," as used herein, refers to a strong urge to sleep, often followed by a period of sleep in which you cannot control when you fall asleep. These periods can last from a few seconds to a half hour.

In some embodiments, the lactating mother experiences a reduction in the ESS total score of 5 or more, e.g., 6, 7, 8, 9, or 10 or more.

In some embodiments, the lactating mother experiences a reduction in the frequency of sleep attacks while holding, feeding, nursing, or otherwise caring for the infant. The reduction in frequency may be at least about 10$, 20%, 30%, 40%, or 50% relative to an untreated mother. In some embodiments, the lactating mother experiences a reduction in automatic

movements (the movement of parts of the body such as their hands while sleeping) while caring for the infant. The reduction in automatic movements may be at least about 10%, 20%, 30%, 40%, or 50% relative to an untreated mother.

Having described the present invention, the same will be explained in greater detail in the following examples, which are included herein for illustration purposes only, and which are not intended to be limiting to the invention.

EXAMPLES

Example 1. Phase 4 Clinical Trial In Breastfeeding Subjects

A Phase 4, open-label, single-dose study to evaluate the pharmacokinetics (PK) of solriamfetol in the breast milk and plasma of healthy postpartum women following oral administration of a 150 mg solriamfetol tablet.

The study was conducted in 6 healthy adult lactating women who were between 15 and 37 weeks postpartum and were administered a single oral dose of SUNOSI 150 mg. SUNOSI was excreted in breast milk with a milk to plasma AUC ratio of approximately 2:1. The median T_{max} for SUNOSI in breast milk was approximately 1.1 hours, and the mean elimination half-life in breast milk was approximately 5.0 hours. The average amount that would be passed to the infant was estimated to be 0.59 mg over 24 hours, which is about 4.0% of the maternal dose on a weight-adjusted basis. The data from the lactation study indicate that SUNOSI is transferred to breastmilk in nursing mothers, with the relative infant dose (RID) is approximately 4% of the maternal weight-adjusted dosage. Data to assess the effects of SUNOSI on a breastfed infant or on milk production is not provided. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition. Breastfed infants should be monitored for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Solriamfetol had a short systemic elimination half-life of 5.0 to 7.6 hours, and with once daily dosing the estimated accumulation ratio of 1.06 was marginally higher than 1, indicating essentially no accumulation with repeated dosing. Therefore, a single therapeutic dose of solriamfetol was administered in this study. Since the objective of this study was to evaluate solriamfetol PK in breast milk and plasma, as well as to estimate the daily drug dose received by the infant from breast milk, the highest approved therapeutic dose of 150 mg solriamfetol was administered.

The subjects were between 10 days and 52 weeks postpartum. The lower time limit of 10 days postpartum represented a time after which mature milk was developed (US FDA 2019). The upper time limit of 52 weeks postpartum was chosen based on a prospective study that showed that fat, total solids, and "energy" (kcal/dL) were all statistically increased in breast milk collected 12 to 18 months postpartum (N=25) compared with breast milk collected 1 to 12 months postpartum (N=35) (Czosnykowska Lukacka 2018). Also, there was a paucity of data regarding breast milk nutrient composition at >12 months postpartum (Wu 2018). The study included frequent maternal milk sample collections during a 72-hour period postdose to enable detection of the potential presence of solriamfetol in breast milk. Plasma concentrations of solriamfetol were also evaluated during the same time period to assess solriamfetol's potential accumulation in breast milk relative to the plasma.

Subjects were instructed to refrain from breastfeeding their infants for 72 hours postdose. Based on the drug's short half-life, this period (10×half-life) was expected to be of sufficient duration for complete elimination of solriamfetol from both the systemic circulation and breast milk.

Pharmacokinetic Results

All subjects in the PK Population were included in the PK analysis. Pharmacokinetic Population was defined as all subjects who received study drug and provided postdose breast milk or plasma PK data for at least one collection interval or time point. Subject **1003**, **1004**, and **1007** had multiple protocol deviations documented with regards to the timing of food consumption, however, these deviations are not likely to impact solriamfetol PK and these subjects were included in the descriptive statistics or PK parameter analysis. Furthermore, the PK of solriamfetol in fed versus fasted subjects satisfied the criteria for bioequivalence, indicating that solriamfetol can be taken regardless of food intake.

The mean plasma and breast milk solriamfetol concentration time profiles are shown in FIG. **1**. FIG. **1** shows the time course of mean plasma and breast milk solriamfetol concentrations on Day 1 following a single-dose administration of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. After reaching maximum solriamfetol concentrations approximately 1.00 to 3.00 hours after oral administration, plasma and breast milk exposures followed a parallel monoexponential decline.

Solriamfetol concentrations in breast milk were approximately 2-fold higher than plasma concentrations

The mean breast milk cumulative solriamfetol amount-time profiles are shown in FIG. **2**. FIG. **2** shows the mean breast milk cumulative solriamfetol amount-time profiles following a single-dose administration of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. Arithmetic mean±SD amount excreted in breast milk over 72 hours was 0.6880±0.4672 mg. However, near complete excretion was observed within 24 hours of dosing.

No subjects had Rsq adjusted values <0.700, or % AUC_{ex}>20%, therefore Lambda_z and AUC0-inf related parameters were all considered reliable and included in descriptive statistics.

Table 1 summarizes the plasma and breast milk PK parameters for solriamfetol following single-dose administration.

Solriamfetol exposure was approximately 2-fold higher, on average, in breast milk than plasma with geometric mean C_{max} of 1861 vs 892.5 ng/ml, AUC_{0-t} of 12770 vs 6236 h*ng/ml, and AUC_{0-inf} of 12940 vs 6340 h*ng/mL, respectively. The geometric mean milk:plasma ratio was 2.047.

Plasma solriamfetol t_{max} (from 0.98 to 3.02 hours, median 1.25 hours) was similar to breast milk (from 1.00 to 3.00 hours, median 1.12 hours).

The geometric mean solriamfetol $t_{1/2}$ appear similar between plasma (4.751 hours) and breast milk (4.869 hours). Furthermore, the geometric mean plasma solriamfetol CL/F was 23.66 L/h and V_z/F was 162.2 L. Geometric mean A_{milk} was 0.5651 mg, with a daily and relative infant dose of 0.5856 mg and 4.030%, respectively.

TABLE 1

Summary of Pharmacokinetic Parameters for Solriamfetol in Plasma and Breast Milk (Pharmacokinetic Population)

	Arithmetic Mean (CV %) [Geometric Mean]	
Pharmacokinetic Parameters	Plasma (N = 6)	Breast Milk (N = 6)
AUC_{0-inf} (h*ng/mL)	6543 (27.7) [6340]	13850 (41.0) [12940]
AUC_{0-t} (h*ng/mL)	6439 (27.9) [6236]	13700 (41.4) [12770]
C_{max} (ng/mL)	905.2 (18.0) [892.5]	2068 (48.7) [1861]
t_{max} (h)[a]	1.25 (0.98, 3.02)	1.12 (1.00, 3.00)
Lambda_z (1/h)	0.1478 (19.1) [0.1459]	0.1446 (18.8) [1424]
$t_{1/2}$ (h)	4.804 (15.2) [4.751]	4.954 (21.4) [4.869]
CL/F (L/h)	24.40 (26.8) [23.66]	NC
V_z/F (L)	168.9 (31.9) [162.2]	NC
Milk:Plasma Ratio	NC	2.136 (35.8) [2.047]
A_{milk} (mg)	NC	0.6880 (67.9) [0.5651]
Daily Infant Dose (mg)	NC	0.6927 (63.5) [0.5856]
Relative Infant Dose (%)	NC	4.602 (60.6) [4.030]

NC = not calculated.
Note:
CV % was based on the arithmetic mean.
[a]Median (min, max).

Pharmacokinetic Conclusion

Solriamfetol t_{max} for both plasma and breast milk were similar and ranged between 1 to 3 hours. After reaching maximum solriamfetol concentrations, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol breast milk exposure (C_{max} and AUC_s) was 2-fold higher than plasma. Furthermore, the geometric mean milk:plasma ratio was 2.047. The solriamfetol $t_{1/2}$ appeared similar in plasma and breast milk at approximately 5 hours. This study was exclusively in post-partum women, a very different population than the ones for the studies reported in the Pharmacokinetics section of the current Sunosi® label which were healthy male and female patients who were not postpartum. The Sunosi® label reports oral bioavailability of solriamfetol is approximately 95% with peak plasma concentration of solriamfetol occurs at a median T_{max} of 2 hours (range 1.25 to 3.0 hours) post-dose under fasted conditions healthy male and female patients who were not postpartum. Indeed, while the median T_{max} reported for healthy male and female patients who were not postpartum is reported in the label as 2 hours, the T_{max} in the present lactation study is 1 hour. Similarly, the apparent mean elimination plasma half-life is 7.1 hours for healthy male and female patients who were not postpartum on the Sunosi® label compared to 4.8 hours in plasma and 4.95 hours in breast milk in the present lactation study.

CL/F and were determined for plasma solriamfetol only. Arithmetic mean of CL/F was 24.40 L/h and was 168.9 L. A_{milk}, daily infant dose, and relative infant dose were determined for breast milk solriamfetol only. Arithmetic mean of was 0.6880 mg, daily infant dose was 0.6927 mg, and relative infant dose was 4.602% Safety Results

Adverse Events: The overall summary of Treatment Emergent Adverse Events (TEAEs) is summarized in Table 2. A total of 3 (50%) subjects had at least 1 AE; of 2 (33.3%) subjects had TEAEs related to the study drug and 1 (16.7%) subject had TEAE unrelated to the study drug. The mild TEAEs were reported in 2 (33.3%) subjects and moderate TEAEs were reported in 1 (16.7%) subject. No SAEs were reported in the study. None of the subjects discontinued due to TEAEs.

TABLE 2

Overall Summary of Treatment Emergent Adverse Events (Safety Population)

Category	Solriamfetol 150 mg (N = 6) n (%)
Subjects with at least 1 AE	3 (50.0)
Subjects with an	
AE considered related to study drug	2 (33.3)
AE considered unrelated to study drug	1 (16.7)
Subjects with[a]	
SAE	0
SAE considered related to study drug	0
SAE considered unrelated to study drug	0
Subjects who discontinued due to	
AE	0
AE considered related to study drug	0
AE considered unrelated to study drug	0
Subjects with[a]	
Mild AE	2 (33.3)
Moderate AE	1 (16.7)
Severe AE	0
Life-threatening AE	0
Fatal AE	0

AE = adverse event;
N = number of subjects exposed;
SAE = serious adverse event.
Note:
Percentages are based on N
[a]Subjects reporting an adverse event in more than one category were counted only once for the category.

Out of 3 subjects reporting TEAEs, 1 subject had dizziness and headache (SOC: Nervous system disorder), 1 subject had agitation (SOC: Psychiatric disorder), and 1 subject had an event of headache (SOC: Nervous system

disorder) (Table 3). A total of 4 TEAEs were reported where 3 TEAEs (dizziness, headache, and agitation) were mild and 1 TEAE (headache) was moderate in intensity. All the 3 mild TEAEs were related to the study drug and the moderate TEAE was unrelated to the study drug. All the TEAEs were resolved.

TABLE 3

Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Safety Population)

System Organ Class (SOC) Preferred Term (PT)	Solriamfetol 150 mg (N = 6) n (%)
Nervous system disorders	2 (33.3)
Dizziness	1 (16.7)
Headache	2 (33.3)

TABLE 3-continued

Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Safety Population)

System Organ Class (SOC) Preferred Term (PT)	Solriamfetol 150 mg (N = 6) n (%)
Psychiatric disorders	1 (16.7)
Agitation	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

A subject with multiple adverse events within a primary system organ class was counted only once.

A subject with multiple occurrences of an AE was counted only once in the AE category

System organ classes are presented in alphabetical order; preferred terms are presented within system organ class in alphabetical order

Adverse events were coded using the MedDRA coding dictionary, MedDRA180 Mixed

Vital Signs: There were no major changes in vital sign parameters from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4. The summary of clinically notable vital signs at any post-baseline visit are summarized in Table 4.

TABLE 4

Summary of Clinically Notable Vital Signs at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
Systolic blood pressure (mmHg)	Blood pressure change by >20% from the study baseline value/recordings	1 (16.7)
Diastolic blood pressure (mmHg)	Average diastolic blood pressure ≥95 mmHg or ≤60 mmHg	2 (33.3)
Pulse rate (beats/min)	Pulse change by >20% from the study baseline value/recordings	2 (33.3)
Body temperature (C)	Change in body temperature > 1.8% from the subjects baseline temperature recordings	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

Baseline was defined as the last non-missing measurement taken prior to dosing. All post-baseline assessments, including unscheduled, were considered for this summary.

There were no major changes in ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. No abnormal clinically significant ECG findings were reported.

The summary of clinically notable ECG findings at any post-baseline visit are summarized in Table 5.

TABLE 5

Summary of Clinically Notable Electrocardiograms at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
ECG mean heart rate (bpm)	Ventricular rate ≥ 100 beats/min or ≤60 beats/min	2 (33.3)
PR interval, single beat (msec)	PR interval ≥ 200 msec or ≤120 msec	2 (33.3)

TABLE 5-continued

Summary of Clinically Notable Electrocardiograms at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
QRS duration, single beat (msec)	QRS duration ≥ 100 msec or ≤80 msec	4 (66.7)
QT interval, single beat (msec)	QT interval ≥ 440 msec or ≤350 msec	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

Baseline was defined as the last non-missing measurement taken prior to dosing. All post-baseline assessments, including unscheduled, were considered for this summary.

None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

Safety Conclusions

Overall, 6 subjects were enrolled in the safety analysis and treated with the single oral dose of Solriamfetol which was safe and well tolerated.

Out of 6 subject **3** (50%) subjects had at least 1 AE. Out of 3 subjects reporting TEAEs: 1 subject had dizziness and headache (SOC: Nervous system disorder) both of mild intensity and were related to study drug; 1 subject had agitation (SOC: Psychiatric disorder) of mild intensity and was related to study drug; 1 subject had an event of headache (SOC: Nervous system disorder) of moderate intensity and was not related to study drug. No SAEs, deaths, or other significant AEs were reported in the study. None of the subjects discontinued due to TEAEs. None of the subjects had abnormal, clinically significant laboratory findings. There were no major changes in vital sign from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4 and ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

DISCUSSION

The instant study was a Phase 4, open-label, single-dose study to evaluate the PK of solriamfetol in the breast milk and plasma of healthy postpartum women following oral administration of a 150 mg solriamfetol tablet. A total of 6 subjects were enrolled and were included in both PK and safety analysis. All the 6 subjects had completed the study. There were no premature discontinuations reported in the study.

The primary objective (PK) of this study was to assess the PK of solriamfetol in plasma and breast milk after single oral dose of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. Solriamfetol exposure was approximately 2-fold higher, on average, in breast milk than plasma with geometric mean C_{max} of 1861 vs 892.5 ng/mL, AUC_{0-t} of 12770 vs 6236 h*ng/ml, and AUC_{0-inf} of 12940 vs 6340 h*ng/ml, respectively. The geometric mean milk:plasma ratio was 2.047. Plasma solriamfetol t_{max} (from 0.98 to 3.02 h, median 1.25 h) was similar to breast milk (from 1.00 to 3.00 hours, median 1.12 hours). The geometric mean solriamfetol $t_{1/2}$ appeared similar between plasma (4.751 hours) and breast milk (4.869 hours). Furthermore, the geometric mean plasma solriamfetol CL/F was 23.66 L/h and V_z/F was 162.2 L. Geometric mean A_{milk} was 0.5651 mg, with a daily and relative infant dose of 0.5856 mg and 4.030%, respectively.

The secondary objective of study was to assess the safety and tolerability of the solriamfetol in healthy postpartum women. Overall, the study drug was safe and well tolerated. No SAEs, deaths, or other significant AEs were reported in the study. None of the subjects discontinued due to TEAEs. Out of 6 subjects, 3 subjects reported adverse events. All AE (dizziness, headache, and agitation) were of mild intensity except 1 AE (headache) was of moderate intensity.

None of the subjects had abnormal or clinically significant laboratory findings. There were no major changes in vital sign from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4 and ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

CONCLUSION

Solriamfetol T_{max} for both plasma and breast milk were similar and ranged between 1 to 3 hours. After reaching maximum solriamfetol concentrations, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol breast milk exposure (C_{max}, AUC_s) was 2-fold higher than plasma. Furthermore, the geometric mean milk:plasma ratio was 2.047. Solriamfetol $t_{1/2}$ appeared similar in plasma and breast milk at approximately 5 hours. Solriamfetol was safe and well tolerated.

Further analysis of the data indicate that the daily infant dose is 0.112 mg/kg (based on nominal infant weight of 6 kg) and the relative infant dose (RID) is approximately 5.5% of the maternal weight-adjusted dosage. Data are insufficient to determine effects of solriamfetol on a breastfed infant or its effects on milk production.

The cumulative median amount excreted in breast milk was 0.67 mg over 72 hours, which is about 5.5% of the maternal dose on a weight-adjusted basis. Of the total amount of solriamfetol excreted in breast milk over 72 hours, approximately 78% and 98% were excreted by 8 and 24 hours, respectively, with an apparent mean elimination half-life in breast milk of about 5 hours.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for solriamfetol and any potential adverse effects on the breastfed infant from solriamfetol or from the underlying maternal condition.

Infants exposed to solriamfetol should be monitored for signs of agitation, insomnia, and reduced weight gain.

METHODOLOGY

On Day −1, eligible subjects underwent the baseline procedures. On Day 1, 2 hours after a light breakfast, subjects were to receive a single dose of solriamfetol 150 mg with 240 mL of water. Subjects had to fast for approximately 4 hours after the first dose; water was allowed except for 1 hour before and 1 hour after dosing with the study drug.

Pharmacokinetic analysis of breast milk obtained from both breasts (by pumping) was evaluated prior to dose administration and at intervals up to 72 hours postdose. Blood samples were also collected for plasma solriamfetol quantitation and PK analysis predose and at timepoints up to 72 hours postdose. Solriamfetol breast milk and plasma concentrations were measured using validated bioanalytical methods. Safety was assessed throughout the study by 12-lead ECG, vital sign measurements, the Columbia-Suicide Severity Rating Scale (C-SSRS), and the incidence of adverse events (AE).

The study drug was yellow, film-coated tablets that contained the excipients hydroxypropyl cellulose and magnesium stearate and a polymer film coat (Opadry®).

The total overall study duration (first subject screened to safety follow-up of last subject) was approximately 11 months.

Vital signs (blood pressure, pulse rate, temperature, and respiratory rate) were measured with the subject in a seated or supine position and resting for at least 5 minutes prior to taking the measurement. The dominant arm was used for blood pressure and pulse rate measurements. On Day 1, vital signs were collected at predose, and at approximately 2 (blood pressure and pulse) and 4 hours (blood pressure and pulse) postdose.

12-lead ECG was taken with the subject in a supine position and resting for at least 10 minutes prior to taking the measurement. On Day 1, ECGs were collected predose and at approximately 2 hours postdose.

Subjects must fast for at least 8 hours before chemistry and hematology blood draws. All clinical laboratory tests were performed at Screening only (rescreening is permitted).

Screening/Baseline C-SSRS version at Screening, and since Last Visit version on Day −1 and Day 2 (or at ET).

Breast milk collection occurred at −2 to 0 (prior to dose), 0-2, 2-4, 4-8, 8-12, 12-18, 24-32, 32-40, 40-48 and 48-72 hours postdose on Days 1-4.

Blood samples for plasma PK evaluation were collected at the following time points: Predose, 1, 1.5, 3, 6, 8.5, 10, 13, 15, 21, 24, 28, 36, 44, and 72 hours following dosing on Day 1. General study methodology is outlined in Table 6.

TABLE 6

Screening	Check-in (Baseline)	Study drug dosing	Check-out	Safety Follow-up	Lactation Follow-up
	PK sampling				
Days −21 to −2	Day −1	Day 1	Day 4	Days 9-11	Days 39-41

Standardized meals include meals as needed on Day −1, a light breakfast approximately 2.5 hours before dosing on Day 1 (to be completed approximately 2 hours before dosing) followed by lunch approximately 4 hours after dosing, dinner approximately 8 hours after dosing, and a snack approximately 11 hours after dosing, and standardized meals thereafter.

Record was from 30 days prior to screening through the Safety Follow Up telephone call 5 to 7 days after check-out from the study facility (at Day 4 or ET).

Adverse events were monitored throughout the study by safety assessments, observations, and subject reporting, including the Safety FU telephone call 5-7 days (i.e., Days 9-11) after check-out from the study facility on Day 4, or ET.

Breast milk collection: Solriamfetol concentration in breast milk and plasma was evaluated based on samples collected prior to and postdose on Days 1 to 4. Breast milk was collected from both breasts, using electronic breast pumps, during the following intervals: From −2 to 0 at predose and at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, 24 to 32, 32 to 40, 40 to 48, and 48 to 72 hours postdose on Day 1. The midpoint of each breast milk collection interval was used as the time variable.

Breast milk was collected as often as needed during the assigned intervals; however, at the end of each interval, breast milk was pumped from both breasts and collected. At the end of each collection interval, all milk expressed from both breasts during that interval was pooled. The milk was thoroughly mixed by gently inverting the collection vessel 10 times to ensure homogeneity in milk composition. The weight and volume of the collected milk during each interval was also recorded.

Serial blood samples (4 mL) were collected and dispensed into labeled K2EDTA tubes. The actual time of blood collection for all samples was recorded on the eCRF. Solriamfetol concentration in breast milk and plasma were determined using a validated bioanalytical method (LC-MS/MS) at Origin Bioanalytical Laboratory. The analytical range (lower limit of quantitation [LLOQ] to upper limit of quantitation) for plasma solriamfetol was 8.42 to 4210.00 ng/mL, and breast milk solriamfetol was 10.0 to 8000 ng/mL.

Pharmacokinetic parameters were derived with Phoenix® WinNonlin® Version 8.3 (Certara, Inc., Princeton, New Jersey, USA) and/or SAS® Version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Criteria for Subjects: Each subject who met the following criteria were enrolled in the study: Healthy adult female 18 to 50 years of age, inclusive, at the time of consent; At least 50 kg body weight and body mass index (BMI) within 18 to 35 kg/m^2 inclusive; Postpartum between 10 days and 52 weeks, inclusive, after delivery of a normal, healthy infant by the time of dosing, and actively lactating from both breasts; If breastfeeding, agreed to withhold breastfeeding their infant(s) from approximately 2 hours before dosing to approximately 72-hours after dosing and resumed breastfeeding after completion of study Day 4 procedures or would have made a decision to wean their infants before enrollment in the study; Agreed not to use nicotine-containing products including tobacco (cigarettes, cigars, chewing tobacco, snuff), e-cigarettes, and nicotine lozenge/gum/patch within 3 days prior to check-in on Day −1, and for the duration of the study; Had used a medically acceptable method of contraception for at least the 2 months prior to dosing on Day 1, and consented to use a medically acceptable method of contraception throughout the entire study period and for 30 days after the study was completed; Agreed to comply with study-specified diet while in the study; Able to understand and comply with study requirements; Ensured that their breastfed infant(s) was able to feed from a bottle before study participation begins; Agreed to ensure nutrition was available for their infant(s) through stored breast milk, or alternative nutritional sources as necessary, for the duration of the study; Participants who:

Were fully vaccinated for at least 14 days after the last (or only) dose of the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2 [COVID-19]) vaccine; or Elected not to be vaccinated prior to the study, with Participant who chooses not to be fully vaccinated prior to the start of the study did not receive any dose of the COVID-19 vaccine and remained on the study.

Clinical laboratory tests including hematology, serum chemistry, urinalysis, and thyroid panel, were collected at Screening only.

A complete physical examination included, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight were also measured and recorded. At Screening and Baseline/Randomization visits, BMI was calculated by the site in order to verify eligibility.

Vital signs included oral temperature, pulse rate, respiratory rate, and BP. Clinically significant abnormal vital signs results reported during Screening/Randomization were recorded as medical history and those reported after study drug were recorded as AEs.

Blood pressure and pulse measurements were assessed with the subject in a seated or supine position and resting for at least 5 minutes prior to taking the measurement. The dominant arm was used for blood pressure and pulse rate measurements. On Day 1, vital signs were collected at predose, and at approximately 2 (blood pressure and pulse) and 4 hours (blood pressure and pulse) postdose.

The 12-lead ECGs were collected at Screening, Day −1 until Day 4. Single 12-lead ECG was obtained using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT, and corrected QT interval (QTc) intervals. Any abnormal safety assessments including ECG readings considered clinically significant in the medical and scientific judgment of the investigator were reported as an AE. The investigator had to review the ECG and document it in the source documents. Clinically significant abnormal ECG results reported during Screening were recorded as medical history and those reported after study drug were recorded as AEs.

All laboratory tests were to be performed in accordance with Laboratory Manual. The tests detailed in Table 7 were performed by the central laboratory. Additional tests might be performed at any time during the study as determined necessary by the investigator or required by local regulations.

All laboratory tests with abnormal values considered clinically significant during the study or within 14 days after the last dose of study drug (and considered by the investigator to be related to study drug) were repeated until the values return to normal or Baseline or were no longer considered clinically significant by the investigator or medical monitor. If clinically significant values did not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology were to be identified.

TABLE 7

Safety Laboratory Test	
Hematology:	Serum Chemistry:
Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential (absolute count and percent)	Albumin (ALB)
	Alkaline phosphatase (ALK-P)
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
Urinalysis:	Blood urea nitrogen (BUN)
Appearance	Calcium (Ca)
Bilirubin	Carbon dioxide (CO2)

TABLE 7-continued

Safety Laboratory Test	
Color	Chloride (Cl)
Glucose	Creatinine
Ketones	Creatine kinase
Nitrite	Glucose
Occult blood	Phosphorus
pH	Potassium (K)
Protein	Sodium (Na)
Specific gravity	Total bilirubin
Urobilinogen	Direct bilirubin
Leukocyte esterase	Total cholesterol
Drug Screening:	Total protein
Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opiates, phencyclidine)	Triglycerides
	Uric acid
	Pregnancy*:
Breath alcohol test	Serum at Screening
	Urine at Baseline (Day −1)

ALB = albumin;
ALK-P = alkaline phosphatase;
ALT = alanine aminotransferase;
AST = aspartate aminotransferase;
BUN = blood urea nitrogen;
Ca = calcium;
CBC = complete blood count;
CO2—carbon dioxide;
Cl = chlorine;
K = potassium;
Na = sodium;
WBC = white blood cell count.
*Pregnancy screening required for all subjects in the study.

STATISTICAL/ANALYTICAL

Unless otherwise specified, continuous data was summarized using descriptive statistics comprising of the number of subjects exposed (N) and with data to be summarized (n), mean, standard deviation (SD), median, minimum (min), maximum (max), geometric mean (Geo-mean), coefficient of variation (CV %), and geometric coefficient of variation (CV %). Categorical variables were presented using counts and percentages. Analyses and summary outputs were generated using SAS® Version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

The PK Population consisted of all subjects who received study drug and provided postdose breast milk or plasma PK data for at least one collection interval or time point. This population was used for evaluable PK concentration data and PK parameter summaries and listings. The Safety Population consisted of all subjects who received the dose of study drug. This population was used for demographic and baseline characteristics and for safety data summaries and listings.

Pharmacokinetic concentrations and parameters were summarized using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (CV %), median, min, max, Geometric mean (Geo-mean) and the geometric coefficient of variation (Geo-CV %). For the PK parameter t_{max}, only n, median, minimum, and maximum was presented.

Subjects with partial data were evaluated on a case-by-case basis to determine if sufficient data was available for reliable calculation of PK parameters. In case of an incomplete milk collection (partial/spilt sample with inaccurate information of the total milk volume of the by-interval samples), the by-interval recovery was listed but not included in the summary, and cumulative recovery was only reported through the most recent prior complete milk collection. By-interval data during which a subject was unable

to lactate (produce any milk), was treated as an amount of zero (for the affected interval) in the summation of cumulative recovery calculation.

Plasma and milk concentrations were summarized using descriptive statistics. Concentrations that were below the lower limit of quantitation (BLQ) were treated as follows for the computation of descriptive statistics:

The summary statistics at a time with one or more BLQ values were calculated by assigning ½ LLOQ to all values less than LLOQ. If the calculated arithmetic (and geometric) mean value was BLQ, then SD and CV % were presented as "ND.", and the mean was presented as "BLQ. However, since a high proportion of BLQ values may have affected the SD; if more than 50% of values were imputed, then no mean was calculated for that time point and again a value of BLQ was presented only for the mean value. Within the summary statistics, any minimum, or median values that were calculated to be BLQ were presented as BLQ within the summary presentation.

Concentrations collected outside of the protocol allowed sampling windows were included in descriptive statistics, unless the PK scientist observed that the deviation was substantial enough to impact descriptive statistics. In this case, the excluded concentrations were identified in the CSR.

For plotting arithmetic mean concentration profiles: The arithmetic mean value at a time with one or more BLQ values were calculated by assigning ½ LLOQ to all values BLQ. If the calculated mean value was BLQ, then that time point was plotted as zero in the mean pharmacokinetic profiles. However, since a high proportion of BLQ values may have affected the SD; if more than 50% of values were imputed, then no mean was calculated for that time point and again a value of zero plotted. A line with a label of LLOQ in the concentration axis was overlaid to show the level of LLOQ.

Safety analyses were based on the Safety Population. The secondary endpoints for evaluating subject safety and tolerance were the incidence of reported AEs and the laboratory test results for all subjects.

Adverse events: Adverse events recorded in the electronic case report forms (eCRFs) were coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as any event with onset date on or after the first dose of study drug or any ongoing event that worsened in severity after the date of the first dose of study drug or any event that was present at baseline but was subsequently considered drug-related by the investigator through the end of the study. The incidence of TEAEs were presented by severity, relationship to study drug, start and end date, seriousness, and outcome. The investigator assessed the severity and relatedness of each AE to study drug. Columbia-Suicide Severity Rating Scale (C-SSRS) data were summarized at scheduled visits and were listed. Other safety analyses were performed as appropriate.

12 Lead ECG: The number and percentage of subjects who had the following postbaseline clinically notable ECG interval abnormality was summarized: Ventricular rate ≥100 beats/min or ≤60 beats/min; PR interval ≥200 msec or ≤120 msec; QRS duration ≥100 msec or ≤80 msec; QT interval ≥440 msec or ≤350 msec; QTc Bazett and QTc Fredericia ≥470 msec or ≤330 msec; RR interval ≥1200 msec or ≤600 msec; and QTc Bazette and QTc Fredericia increase from study Baseline Value >30 msec.

Vital Signs: The following clinically notable vital sign abnormalities were presented: Average systolic blood pressure ≥150 mmHg or ≤80 mmHg; Average diastolic blood pressure ≥95 mmHg or ≤60 mmHg; Average heart rate ≥120 bpm or ≤50 bpm; Respiratory rate <10 breaths/min or >24 breaths/min; Body temperature >37.9° C. or <35.5° C.; Systolic and diastolic blood pressure change by >20% from the study baseline value/recordings; Pulse change by >20% from the study baseline value/recordings; Change in body weight by ≥7% from subject's baseline value (weight loss/weight gain); and Change in body temperature >1.8% from the subject's baseline temperature recordings.

Physical Examination: Physical examination data for each subject was presented in a listing. A clinically significant adverse change (i.e., worsening) of a physical examination finding after screening was recorded as an AE.

Disposition of Subjects. A total of 6 subjects were enrolled and treated in the study. All 6 subjects had completed the study. There were no premature discontinuations reported in the study. All 6 subjects received the study drug (safety population) and provided post-dose breast milk or plasma PK data for at least one collection interval or time point (PK population). All 6 subjects were females and belonged to not Hispanic or Latino ethnicity. The mean (SD) of age, weight, height, and BMI of the overall population was 28.7 (5.54) years, 79.15 (12.162) kg, 168.62 (6.013) cm, and 27.90 (4.513) kg/m^2, respectively.

TABLE 8

Demographics and Baseline Characteristics (Safety Population)

Characteristic	Solriamfetol 150 mg (N = 6)
Age (years)	
n	6
Mean (SD)	28.7 (5.54)
Median	29.5
Min, Max	21, 35
Gender, n (%)	
Female	6 (100%)
Missing	0
Race, n (%)	
White	3 (50.0)
Black or African American	3 (50.0)
Missing	0
Ethnicity, n (%)	
Not Hispanic or Latino	6 (100%)
Missing	0
Height (cm)	
n	6
Mean (SD)	168.62 (6.013)
Median	170.00
Min, Max	160.0, 177.5
Weight (kg)	
n	6
Mean (SD)	79.15 (12.162)
Median	77.90
Min, Max	64.1, 99.1
BMI (kg/m^2)	
n	6
Mean (SD)	27.90 (4.513)
Median	27.95
Min, Max	22.4, 34.3

BMI = body mass index;
N = number of subjects exposed
Note:
Percentages are based on N.

Prior and Concomitant Medication: Two subjects had taken medications during the study for AEs. One subject received acetaminophen and other received ibuprofen.

Medical and Surgical History: A total of 5 of 6 subjects had the medical and surgical history. Of these subjects, 1 subject had the medical history of appendectomy, C-section, and tubal ligation. One subject had asthma and C-section. One subject had cholelithiasis, pancreatitis, and gall bladder removal. One subject had umbilical hernia repair, heartburn, and C-section, and 1 subject had natural childbirth and hip pain during to natural childbirth.

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The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A method of avoiding exposing an infant of a nursing human mother being treated with solriamfetol to peak concentrations of solriamfetol excreted in breast milk, the method comprising not feeding the infant breast milk obtained within at least about 3.5 hours of the mother receiving an oral once-daily dose of about 150 mg solriamfetol, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hour, wherein a daily infant dose of solriamfetol is reduced to about 0.3 mg or lower.

2. The method of claim **1**, wherein the infant is not fed breast milk obtained within at least about 5 hours of the mother receiving an oral once-daily dose of solriamfetol.

3. The method of claim **1**, wherein the infant does not experience agitation due to exposure to the solriamfetol.

4. The method of claim **1**, wherein the infant does not experience insomnia due to exposure to the solriamfetol.

5. The method of claim **1**, wherein the infant does not experience anorexia and/or reduced weight gain due to exposure to the solriamfetol.

6. The method of claim **1**, wherein the solriamfetol is excreted in the breast milk with a milk to plasma AUC ratio of approximately 2:1.

7. The method of claim **1**, wherein the elimination half-life of the solriamfetol excreted in the breast milk is approximately 5 hours.

8. The method of claim **1**, wherein breast milk produced by the nursing mother during the at least about 3.5 hours of the mother receiving an oral once-daily dose of solriamfetol is expressed and discarded.

9. The method of claim **1**, wherein the mother is being treated with solriamfetol for excessive daytime sleepiness, narcolepsy, obstructive sleep apnea, shift work disorder, attention deficit hyperactivity disorder, Parkinson's disease, binge eating disorder, or cognitive impairment.

10. The method of claim **9**, wherein the excessive daytime sleepiness is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

11. The method of claim **9**, wherein the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

12. The method of claim **1**, wherein the mother is being treated with solriamfetol to improve wakefulness.

13. The method of claim **1**, wherein the lactating mother is from about 1 day to about 24 months postpartum.

14. The method of claim **1**, wherein the lactating mother is from about 10 days to about 52 weeks postpartum.

15. The method of claim **1**, wherein the lactating mother is between the ages of 18 and 45 years.

16. A method of avoiding exposing an infant of a nursing human mother being treated with solriamfetol to peak concentrations of solriamfetol excreted in breast milk, the method comprising not feeding the infant breast milk obtained within at least about 3.5 hours of the mother receiving an oral once-daily dose of about 75 mg solriamfetol, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hour, wherein a daily infant dose of solriamfetol is reduced to about 0.15 mg or lower.

17. The method of claim **16**, wherein the infant is not fed breast milk obtained within at least about 5 hours of the mother receiving an oral once-daily dose of solriamfetol.

18. The method of claim **16**, wherein the infant does not experience agitation due to exposure to the solriamfetol.

19. The method of claim **16**, wherein the infant does not experience insomnia due to exposure to the solriamfetol.

20. The method of claim **16**, wherein the infant does not experience anorexia and/or reduced weight gain due to exposure to the solriamfetol.

21. The method of claim **16**, wherein the solriamfetol is excreted in the breast milk with a milk to plasma AUC ratio of approximately 2:1.

22. The method of claim **16**, wherein the elimination half-life of the solriamfetol excreted in the breast milk is approximately 5 hours.

23. The method of claim **16**, wherein breast milk produced by the nursing mother during the at least about 3.5 hours of the mother receiving an oral once-daily dose of solriamfetol is expressed and discarded.

24. The method of claim **16**, wherein the mother is being treated with solriamfetol for excessive daytime sleepiness, narcolepsy, obstructive sleep apnea, shift work disorder, attention deficit hyperactivity disorder, Parkinson's disease, binge eating disorder, or cognitive impairment.

25. The method of claim **24**, wherein the excessive daytime sleepiness is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

26. The method of claim **24**, wherein the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

27. The method of claim **1**, wherein the mother is being treated with solriamfetol to improve wakefulness.

28. The method of claim **1**, wherein the lactating mother is from about 1 day to about 24 months postpartum.

29. The method of claim **1**, wherein the lactating mother is from about 10 days to about 52 weeks postpartum.

30. The method of claim **1**, wherein the lactating mother is between the ages of 18 and 45 years.

* * * * *

EXHIBIT F

United States of America

To Promote the Progress of Science and Useful Arts

The Director

of the United States Patent and Trademark Office has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this United States

Patent

grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America, and if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States of America, products made by that process, for the term set forth in 35 U.S.C. 154(a)(2) or (c)(1), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b). See the Maintenance Fee Notice on the inside of the cover.

Katherine Kelly Vidal

Director of the United States Patent and Trademark Office

Maintenance Fee Notice

If the application for this patent was filed on or after December 12, 1980, maintenance fees are due three years and six months, seven years and six months, and eleven years and six months after the date of this grant, or within a grace period of six months thereafter upon payment of a surcharge as provided by law. The amount, number and timing of the maintenance fees required may be changed by law or regulation. Unless payment of the applicable maintenance fee is received in the United States Patent and Trademark Office on or before the date the fee is due or within a grace period of six months thereafter, the patent will expire as of the end of such grace period.

Patent Term Notice

If the application for this patent was filed on or after June 8, 1995, the term of this patent begins on the date on which this patent issues and ends twenty years from the filing date of the application or, if the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121, 365(c), or 386(c), twenty years from the filing date of the earliest such application ("the twenty-year term"), subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b), and any extension as provided by 35 U.S.C. 154(b) or 156 or any disclaimer under 35 U.S.C. 253.

If this application was filed prior to June 8, 1995, the term of this patent begins on the date on which this patent issues and ends on the later of seventeen years from the date of the grant of this patent or the twenty-year term set forth above for patents resulting from applications filed on or after June 8, 1995, subject to the payment of maintenance fees as provided by 35 U.S.C. 41(b) and any extension as provided by 35 U.S.C. 156 or any disclaimer under 35 U.S.C. 253.

US012036194B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 12,036,194 B1**
(45) **Date of Patent: *Jul. 16, 2024**

(54) **METHODS OF ADMINISTERING SOLRIAMFETOL TO LACTATING WOMEN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/491,301**

(22) Filed: **Oct. 20, 2023**

Related U.S. Application Data

(63) Continuation-in-part of application No. 18/176,855, filed on Mar. 1, 2023, now Pat. No. 11,793,776, which is a continuation of application No. 18/148,682, filed on Dec. 30, 2022, now Pat. No. 11,771,666.

(51) **Int. Cl.**
A61K 31/165 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/165*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/165
See application file for complete search history.

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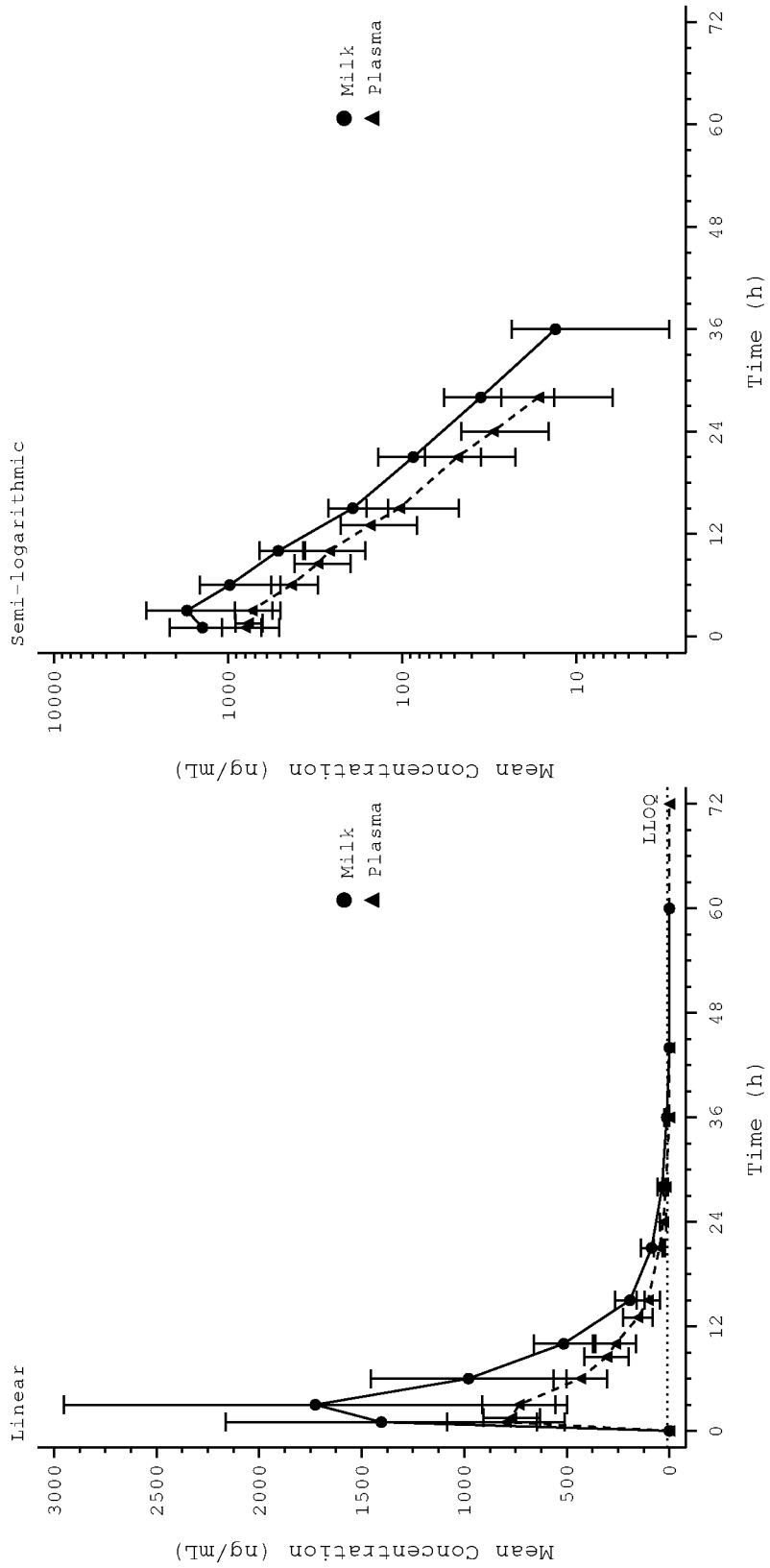
(74) *Attorney, Agent, or Firm* — HUESCHEN AND SAGE

(57) **ABSTRACT**

Provided herein according to some embodiments is a method for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby decreasing potential for adverse events from solriamfetol in an infant.

28 Claims, 2 Drawing Sheets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Plasma
10000
1000
100
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Mean Concentration (ng/mL)
0
12
24
36
48
60
72
Time (h)
Linear
Milk
Plasma
LLOQ
3000
2500
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500
0
Mean Concentration (ng/mL)
0
12
24
36
48
60
72
Time (h)

FIG. 1

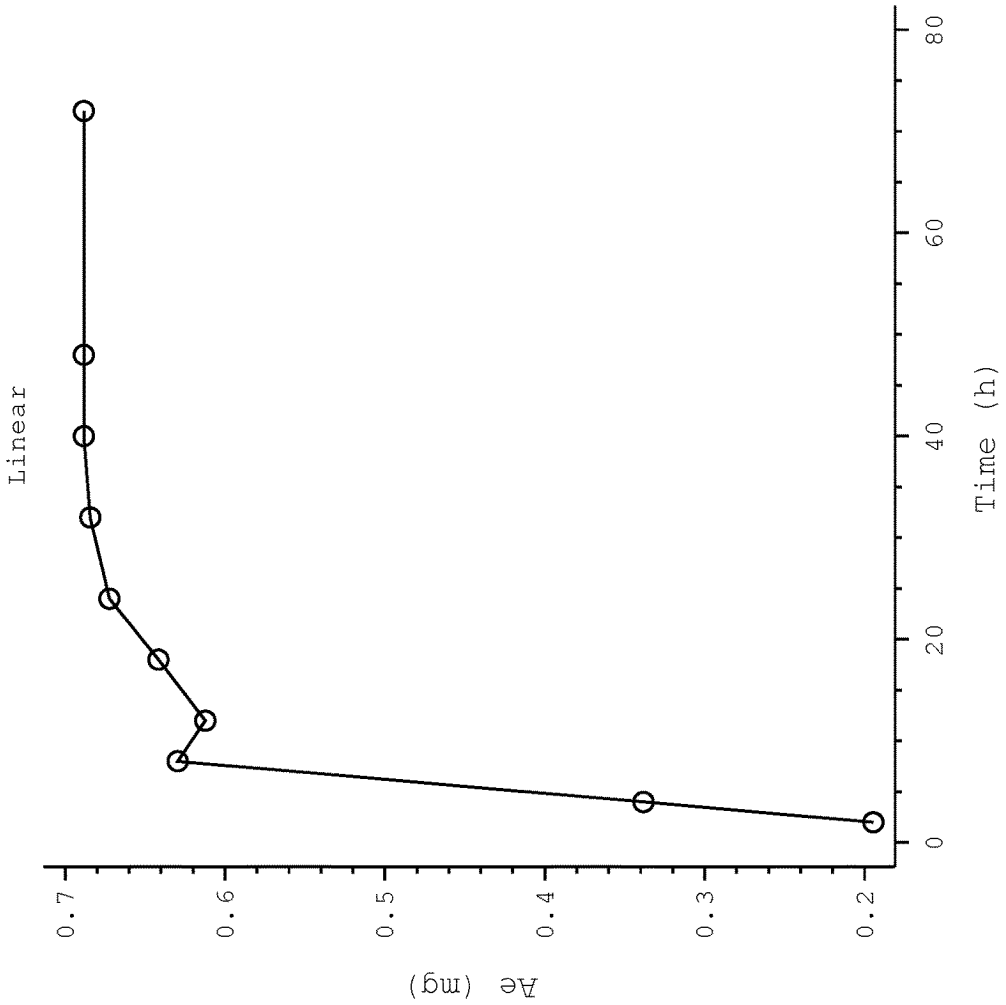


FIG. 2

METHODS OF ADMINISTERING SOLRIAMFETOL TO LACTATING WOMEN

STATEMENT OF PRIORITY

This application is a continuation-in-part of and claims priority to U.S. patent application Ser. No. 18/176,855, filed Mar. 1, 2023, which is a continuation of U.S. patent application Ser. No. 18/148,682, filed Dec. 30, 2022, now U.S. Pat. No. 11,771,666, the entire contents of each of which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to methods of administering solriamfetol to a lactating subject while reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject.

BACKGROUND OF THE INVENTION

Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor that has received marketing approval in the US for improving wakefulness in adult subjects with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA). Solriamfetol has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others.

Pharmacokinetic studies have demonstrated rapid absorption and high oral bioavailability of solriamfetol with dose-proportional exposure (maximum serum concentration and area under the concentration-time curve [AUC]) in animals tested.

The present invention overcomes shortcomings in the art by providing methods of administering solriamfetol to a lactating subject while reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject.

SUMMARY OF THE INVENTION

The present invention relates to the development of methods of reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject. The invention additionally related to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol.

Accordingly, one aspect of the invention relates to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5) hours after administering the solriamfetol to the subject, thereby reducing exposure to solriamfetol in the infant.

Another aspect of the invention relates to a method for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject, thereby decreasing the potential for adverse events from solriamfetol in the infant. In some embodiments, the daily dose of solriamfetol is 150 mg.

An aspect of the invention relates to a method treating a disorder treatable with solriamfetol in a subject producing breast milk for feeding an infant, comprising: administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and reducing exposure to solriamfetol and/or decreasing the potential for adverse events in the infant fed breast milk from the subject comprising feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject. The disorder treatable with solriamfetol can be, without limitation, narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, attention deficit/hyperactivity disorder, cognitive impairment or binge eating disorder.

Another aspect of the invention relates to a method of avoiding exposing an infant of a nursing mother being treated with solriamfetol to peak concentrations of solriamfetol excreted in breast milk, such method comprising not feeding the infant breast milk obtained within at least about 3.5 hours (e.g., at least about 4 or 5 hours) of the mother receiving an oral once-daily dose of solriamfetol, wherein the T_max of solriamfetol excreted in the breast milk is approximately 1.1 hour.

A further aspect of the invention relates to a method of reducing the exposure to solriamfetol from breast milk, in an infant receiving breast milk from a nursing mother being treated with a once-daily dose of solriamfetol of about 37.5 mg to about 300 mg for a disorder amenable to treatment with solriamfetol, such method comprising feeding the infant breast milk obtained from the mother at least about 5 hours after administering the solriamfetol to the mother, wherein the exposure to solriamfetol in the infant is reduced by at least about 50% compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol.

An additional aspect of the invention relates to a method of treating excessive daytime sleepiness in a lactating mother, with an infant at risk of adverse events from the mother's excessive daytime sleepiness, and who wishes to breastfeed the infant, said method comprising: (a) determining the Epworth Sleepiness Scale (ESS) total score of the mother and if the mother experiences sleep attacks while caring for the infant; (b) providing the mother with an ESS total score of 15 or greater and who experiences sleep attacks while caring for the infant a starting dose of solriamfetol of 37.5 mg once daily if the excessive daytime sleepiness is associated with obstructive sleep apnea, or 75 mg once daily if the excessive daytime sleepiness is associated with narcolepsy, and doubling the dose at intervals of at least 3 days up to 150 mg once daily, wherein the elimination half-life of solriamfetol in plasma in the postpartum or lactating mother is about 5 hours; and (c) feeding the infant breast milk obtained from the mother at least about 3.5 hours (e.g., 4 or 5 hours) after administration of the solriamfetol to the mother, thereby avoiding exposing the infant to the maximum concentrations of solriamfetol in the breast milk, wherein the median T_max of solriamfetol excreted in the breast milk is approximately 1.1 hours.

In some embodiments, the method provides a daily infant dose of solriamfetol of about 0.3 mg or lower. In some embodiments, the method achieves a relative infant dose of less than about 9% of the subject weight-adjusted dose. In

some embodiments, the method achieves a relative infant dose of less than about 5% of the subject weight-adjusted dose.

In some embodiments, the infant does not experience agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure.

In some embodiments, the subject is from 1 day to 24 months postpartum or from 10 days to 12 months (52 weeks) postpartum.

In some embodiments, the subject is being treated with solriamfetol for narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, attention deficit/hyperactivity disorder, cognitive impairment, or binge eating disorder.

In some embodiments, the subject is a woman between the ages of 18 and 45 years.

In some embodiments, the adverse events are one or more of agitation, insomnia, anorexia, or reduced weight gain.

Methods of treating a disorder amenable to treatment with solriamfetol in a subject who is breastfeeding an infant are provided comprising orally administering solriamfetol at a daily dose of between about 37.5 mg and 300 mg to the subject.

These and other aspects of the invention are set forth in more detail in the description of the invention below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Time course of mean solriamfetol breast milk and plasma concentration-time profiles on linear and semi-logarithmic scales.

FIG. **2**. Mean breast milk cumulative solriamfetol amount-time profiles on linear scale following a single-dose administration of solriamfetol 150 mg tablet.

DETAILED DESCRIPTION

The present invention will now be described in more detail with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. In addition, any references cited herein are incorporated by reference in their entireties.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents, patent publications and other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

As used in the description of the invention and the appended claims, the singular forms "a," "an," and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

The term "about," as used herein when referring to a measurable value such as an amount of polypeptide, dose, time, temperature, enzymatic activity or other biological activity and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount.

As used herein, the transitional phrase "consisting essentially of" (and grammatical variants) is to be interpreted as encompassing the recited materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. Thus, the term "consisting essentially of" as used herein should not be interpreted as equivalent to "comprising."

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, prevention or delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Pharmaceutically acceptable carrier" (sometimes referred to as a "carrier") refers to a carrier or excipient that is useful in preparing a pharmaceutical or therapeutic composition that is generally safe and non-toxic and includes a carrier that is acceptable for veterinary and/or human pharmaceutical or therapeutic use. The terms "carrier" or "pharmaceutically acceptable carrier" can include, but are not limited to, phosphate buffered saline solution, water, emulsions (such as an oil/water or water/oil emulsion) and/or various types of wetting agents. As used herein, the term "carrier" encompasses, but is not limited to, any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations and as described further herein.

The term "modulate," "modulates," or "modulation" refers to enhancement (e.g., an increase) or inhibition (e.g., a decrease) in the specified level or activity.

The term "enhance" or "increase" refers to an increase in the specified parameter of at least about 1.25-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 8-fold, 10-fold, twelve-fold, or even fifteen-fold and/or can be expressed in the enhancement and/or increase of a specified level and/or activity of at least about 1%, 5%, 10%, 15%, 25%, 35%, 40%, 50%, 60%, 75%, 80%, 90%, 95% or more.

"Inhibit" or "reduce" or grammatical variations thereof as used herein refers to a decrease or diminishment in the

specified level or activity of at least about 1, 5, 10, 15%, 25%, 35%, 40%, 50%, 60%, 75%, 80%, 90%, 95% or more. In particular embodiments, the inhibition or reduction results in little or essentially no detectible activity (at most, an insignificant amount, e.g., less than about 10% or even 5%).

"Treat," "treating" and similar terms as used herein in the context of treating a subject refer to providing medical and/or surgical management of a subject. Treatment may include, but is not limited to, administering an agent or composition (e.g., a pharmaceutical composition) to a subject. Treatment is typically undertaken in an effort to alter the course of a disease (which term is used to indicate any disease, disorder, syndrome, or undesirable condition warranting or potentially warranting therapy) in a manner beneficial to the subject. The effect of treatment may include reversing, alleviating, reducing severity of, delaying the onset of, curing, inhibiting the progression of, and/or reducing the likelihood of occurrence or recurrence of the disease or one or more symptoms or manifestations of the disease. A therapeutic agent may be administered to a subject who has a disease or is at increased risk of developing a disease relative to a member of the general population. In some embodiments a therapeutic agent may be administered to a subject who has had a disease but no longer shows evidence of the disease. The agent may be administered e.g., to reduce the likelihood of recurrence of evident disease. A therapeutic agent may be administered prophylactically, i.e., before development of any symptom or manifestation of a disease. "Prophylactic treatment" refers to providing medical and/or surgical management to a subject who has not developed a disease or does not show evidence of a disease in order, e.g., to reduce the likelihood that the disease will occur, delay the onset of the disease, or to reduce the severity of the disease should it occur. The subject may have been identified as being at risk of developing the disease (e.g., at increased risk relative to the general population or as having a risk factor that increases the likelihood of developing the disease.

Grammatical variations of "administer," "administration," and "administering" to a subject include any route of introducing or delivering to a subject an agent. Administration can be carried out by any suitable route, including oral, topical, intravenous, subcutaneous, transcutaneous, transdermal, intramuscular, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, by inhalation, via an implanted reservoir, parenteral (e.g., subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intraperitoneal, intrahepatic, intralesional, and intracranial injections or infusion techniques), and the like. "Concurrent administration," "administration in combination," "simultaneous administration," or "administered simultaneously" as used herein, means that the compounds are administered at the same point in time, overlapping in time, or one following the other. In the latter case, the two compounds are administered at times sufficiently close that the results observed are indistinguishable from those achieved when the compounds are administered at the same point in time. "Systemic administration" refers to the introducing or delivering to a subject an agent via a route which introduces or delivers the agent to extensive areas of the subject's body (e.g., greater than 50% of the body), for example through entrance into the circulatory or lymph systems. By contrast, "local administration" refers to the introducing or delivery to a subject an agent via a route which introduces or delivers the agent to the area or area immediately adjacent to the point of administration and does not introduce the agent systemically in a therapeutically significant amount. For example, locally administered agents are easily detectable in the local vicinity of the point of administration but are undetectable or detectable at negligible amounts in distal parts of the subject's body. Administration includes self-administration and the administration by another.

"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., Remington's Pharmaceutical Science; 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

"Bioavailability," as used herein, refers to the estimated area under the curve, or AUC of the active drug in systemic circulation after oral administration with a dosage form as disclosed herein when compared with the AUC of the active drug in systemic circulation after intravenous administration of the active drug. The AUC is affected by the extent to which the drug is absorbed in the GI tract.

Products are considered to be "bioequivalent" if the relative mean C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$ of the test product to reference product is within 80% to 125%.

The term "$AUC_{(0\text{-}t)}$" means the area under the plasma concentration curve from time 0 to time t.

The term "$AUC_{(0\text{-}\infty)}$" or "$AUC_{0\text{-}inf}$" means the area under the plasma concentration time curve from time 0 to infinity.

"C_{max}" refers to the maximum milk or plasma concentration of solriamfetol.

"T_{max}" refers to the time to maximum milk or plasma concentration for a given drug.

"$t_{1/2}$" refers to the time to reduce the milk and plasma concentration by 50% during the terminal elimination phase of the drug.

Milk:plasma ratio means AUC in breast milk divided by AUC in plasma.

"A_{milk}" means the amount excreted in breast milk over 72 hours.

"Vd/F" means the apparent volume of distribution in plasma.

"CL/F" is the apparent oral clearance in plasma.

AUC0-t is the area under the concentration-time curve from time 0 to the time t of the last quantifiable concentration (milk and plasma).

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after

apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift. It is also understood that EDS is medically distinct from fatigue and disorders associated with fatigue.

The present invention is based, in part, on methods of using Sunosi® (referred to herein as solriamfetol (also known as (R)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride, and previously known as JZP-110, ADX-N05, R228060, and YKP10A)) in lactating subjects with a disorder amenable to treatment with solriamfetol while reducing the potential for adverse effects in infants fed the subject's breast milk. Solriamfetol is approved by the FDA for administration at doses equivalent to 37.5 mg, 75 mg, and 150 mg of APC (corresponding to 44.7 mg, 89.3 mg, and 178.5 mg of APC hydrochloride, respectively). Administration of solriamfetol to subjects expressing breast milk presents challenges. In a nonclinical study in rats, solriamfetol was detected in breast milk, with solriamfetol milk concentrations higher than solriamfetol plasma concentrations. It is desirable to reduce or minimize any adverse effects from the daily dose received by an infant fed breast milk from a subject treated with solriamfetol. In addition, it is desirable to identify methods that allow for the safety and tolerability of solriamfetol in nursing subjects.

Accordingly, one aspect of the invention relates to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject, thereby reducing exposure to solriamfetol in the infant.

One aspect of the invention comprises methods for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and feeding the infant breast milk from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject, thereby decreasing the potential for adverse events from solriamfetol in the infant. In an embodiment, the adverse event is one or more of agitation, insomnia, anorexia, or reduced weight gain.

Another aspect of the invention relates to a method of avoiding exposing an infant of a nursing mother being treated with solriamfetol to peak concentrations of solriamfetol excreted in breast milk, such method comprising not feeding the infant breast milk obtained within at least about 3.5 hours (e.g., within at least about 4 or 5 hours) of the mother receiving an oral once-daily dose of solriamfetol, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hour. In clinical studies, the range of T_{max} was 1 hour to 3 hours. Thus, waiting at least 3.5 hours after solriamfetol administration ensures avoidance of the T_{max} even for outlier subjects.

A further aspect of the invention relates to a method of reducing the exposure to solriamfetol from breast milk, in an infant receiving breast milk from a nursing mother being treated with a once-daily dose of solriamfetol of about 37.5 mg to about 300 mg for a disorder amenable to treatment with solriamfetol, such method comprising feeding the infant breast milk obtained from the mother at least about 5 hours (e.g., at least 6, 7, 8, 9, or 10 hours) after administering the solriamfetol to the mother, wherein the exposure to solriamfetol in the infant is reduced by at least about 50% (e.g., at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90%) compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol. In some embodiments, the resulting relative infant dose is about 2% or lower of the maternal weight-adjusted dose. In some embodiments, the once-daily dose of solriamfetol is 150 mg and the daily amount of solriamfetol passed to the infant through the breast milk is about 0.3 mg or lower. In some embodiments, the once-daily dose of solriamfetol is 75 mg and the daily amount of solriamfetol passed to the infant through the breast milk is about 0.15 mg or lower. In some embodiments, the breast milk is obtained from the mother at least about 10 hours (e.g., about 2 half-lives) after administering the solriamfetol to the mother and the exposure to solriamfetol in the infant is reduced by at least about 75% compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol. In some embodiments, the resulting relative infant dose is about 1% or lower of the maternal weight-adjusted dose.

One aspect of the invention relates to a method for treating a disorder treatable with solriamfetol in a subject producing breast milk for feeding an infant, comprising administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and reducing exposure to solriamfetol and/or decreasing the potential for adverse events in the infant fed breast milk from the subject, comprising feeding the infant breast milk obtained from the subject at least about 2 hours (e.g., at least about 3, 4, or 5 hours) after administering the solriamfetol to the subject. In one embodiment, the method reduces solriamfetol in the infant and the infant does not experience agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure. In one embodiment, the adverse events are one or more of agitation, insomnia, anorexia, or reduced weight gain.

A "disorder amenable to treatment with solriamfetol" or a "disorder treatable with solriamfetol" refers to any disorder in which administration of solriamfetol to a subject results in the treatment of one or more symptoms of the disorder in the subject. Example disorders amenable to treatment with solriamfetol include narcolepsy, cataplexy, excessive daytime sleepiness, obstructive sleep apnea, shift work disorder, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit hyperactivity disorder (ADHD), cognitive impairment and/or cognitive dysfunction, Parkinson's disease, restless legs syndrome, depression, bipolar disorder, obesity, or binge eating disorder. In some embodiments, the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease. In some embodiments, the disorders amenable to treatment with solriamfetol include narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, cognitive impairment, attention deficit/hyperactivity disorder, or binge eating disorder. In some embodiments, solriamfetol is administered to improve wakefulness. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/

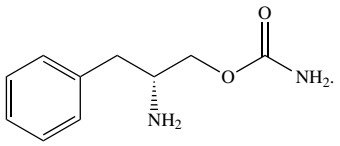
0018414. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift. It is also understood that EDS is medically distinct from fatigue and disorders associated with fatigue.

In some embodiments, the cause of the EDS may be, without limitation, central nervous system (CNS) pathologic abnormalities, stroke, narcolepsy, idiopathic CNS hypersomnia; sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder (ADHD), Alzheimer's disorder, major depression, bipolar disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work disorder, or sedating drugs.

In certain embodiments, solriamfetol structure is given below as formula I:

(I)



Methods for producing solriamfetol and related compounds can be found in U.S. Pat. Nos. 10,829,443, 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

In one embodiment, the methods detailed herein provide an infant fed breast milk from a subject to whom solriamfetol is administered does not experience adverse events, e.g., agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure. Monitoring the infant for agitation, insomnia, anorexia, or reduced weight gain can be performed. For example, monitoring and/or detecting weight loss, reduced weight gain, reduction in number of feedings or lessened intake, reduction in volume of milk ingested can be performed. Monitoring increase in agitation and/or insomnia in the infant, including a reduction of sleeping hours and/or time to fall asleep and stay asleep can also be performed to identify changes in the infant. In some embodiments, the monitoring for changes in the infant is performed at 3 or more hours subsequent to administering of the solriamfetol dose and subsequent to initiation of infant feeding with breast milk from the subject, for example at 3 hours, 4, hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours or more subsequent to administering of the solriamfetol dose. Monitoring for any changes experienced by the infant (e.g., agitation, insomnia, anorexia, or reduced weight gain) can be performed over the time period in which solriamfetol is administered to the subject, which may be over days, weeks, or months, with monitoring over any interval in that time frame, including hourly, daily, weekly, monthly or any time range therein.

In one embodiment, the method provides a daily infant dose of solriamfetol of about 0.4 mg or lower, e.g., about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.335 mg, about 0.33 mg, about 0.32 mg, about 0.21 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, about 0.01 mg, or lower. The daily infant dose means the daily dose that was received by the infant through feeding of breast milk.

In some embodiments, the subject is orally administered a once-daily dose of solriamfetol of about 150 mg and the daily infant dose of solriamfetol is reduced to about 0.3 mg or lower due to the waiting period after administration. In some embodiments, the subject is orally administered a once-daily dose of solriamfetol of about 75 mg and the daily infant dose of solriamfetol is reduced to about 0.15 mg or lower due to the waiting period after administration. In some embodiments, the subject is orally administered a once-daily dose of solriamfetol of about 37.5 mg and the daily infant dose of solriamfetol is reduced to about 0.08 mg or lower due to the waiting period after administration.

In one embodiment, the method provides a daily infant dose of solriamfetol of about 0.2 mg/kg (based on a nominal infant weight of 6 kg) or lower, e.g., about 0.19 mg/kg, about 0.18 mg/kg, about 0.17 mg/kg, about 0.16 mg/kg, about 0.15 mg/kg, about 0.14 mg/kg, about 0.13 mg/kg, about 0.12 mg/kg, about 0.11 mg/kg, about 0.10 mg/kg, about 0.09 mg/kg, about 0.08 mg/kg, about 0.07 mg/kg, about 0.06 mg/kg, about 0.05 mg/kg, about 0.04 mg/kg, about 0.03 mg/kg, about 0.02 mg/kg, about 0.01 mg/kg, or lower.

In one embodiment, the method provides a cumulative median infant dose of solriamfetol over 72 hours after a single dose of about 0.7 mg or lower, e.g., about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.355 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, or lower.

In some embodiments, the method provides a cumulative median infant dose of solriamfetol after a single dose of about 75%-80% after 8 hours of the total excreted in 72 hours, e.g., about 75%, 76%, 77%, 78%, 79%, or 80%. In some embodiments, the method provides a cumulative median infant dose of solriamfetol after a single dose of

about 95%-100% after 24 hours of the total excreted in 72 hours, e.g., about 95%, 96%, 97%, 98%, 99%, or 100%.

In some embodiments, breast milk for feeding of the infant is expressed or produced from the subject at 2 or more hours, 2.5 or more hours, 3 or more hours, 3.5 or more hours, 4 or more hours, 4.5 or more hours, or 5 or more hours, for example at 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 5.5 hours, 6 hours, 6.5 hours, 7 hours, 7.5 hours, 8 hours, 8.5 hours, 9 hours, 9.5 hours, 10 hours or more, subsequent to administering of the solriamfetol dose to the subject. In some embodiments, the breast milk produced from the subject for infant feeding in the methods detailed herein occurs at about the mean elimination half-life of solriamfetol or later, i.e., at about 5 hours, subsequent to administration of the solriamfetol. In some embodiments, the breast milk produced from the subject for infant feeding in the methods detailed herein occurs at about 2-4 times the median T_{max} of solriamfetol or later, i.e., at about 2 hours, 2.5 hours, 3 hours, 3.5 hours, or 4 hours subsequent to administration of the solriamfetol.

In some embodiments, the breastfeeding of the infant is performed at 3 or more hours, 4 or more hours, or 5 or more hours subsequent to administering of the solriamfetol dose to the subject. In some embodiments, the breast milk for feeding the infant is obtained from the subject at 3 or more hours, 4 or more hours, or 5 or more hours subsequent to administering of the solriamfetol dose to the subject.

In some embodiments, the subject refrains from breastfeeding the infant during the waiting period (e.g., the 2 or more hours). In other embodiments, the breast milk produced during the waiting period is expressed and not fed to the infant, e.g., wherein the expressed milk is discarded.

In some embodiments, the method achieves a relative infant dose, the percentage of the weight-adjusted subject dose excreted in breast milk over 24 hours, of less than about 10%, less than about 9.5%, less than about 9%, less than about 8.5%, less than about 8%, less than about 7.5%, less than about 7%, less than about 6.5%, less than about 6%, less than about 5.5%, less than about 5%, less than about 4.9%, less than about 4.8%, less than about 4.7%, less than about 4.6%, less than about 4.5%, less than about 4.4%, less than about 4.3%, less than about 4.2%, less than about 4.1%, less than about 4.0%, less than about 3.9%, less than about 3.8%, less than about 3.7%, less than about 3.6%, less than about 3.5%, less than about 3.4%, less than about 3.3%, less than about 3.2%, less than about 3.1%, less than about 3.0%, less than about 2.9%, less than about 2.8%, less than about 2.7%, less than about 2.6%, less than about 2.5%, less than about 2.4%, less than about 2.3%, less than about 2.2%, less than about 2.1%, less than about 2.0%, less than about 1.9%, less than about 1.8%, less than about 1.7%, less than about 1.6%, less than about 1.5%, less than about 1.4%, less than about 1.3%, less than about 1.2%, less than about 1.1%, less than about 1.0%, of the subject weight-adjusted dose.

In some embodiments, the cumulative median amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.335 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, or about 0.01 mg over 72 hours.

In some embodiments, the cumulative median amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, or about 0.01 mg over 24 hours.

In some embodiments, the cumulative median amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, about 0.59 mg, about 0.58 mg, about 0.57 mg, about 0.56 mg, about 0.55 mg, about 0.54 mg, about 0.53 mg, about 0.52 mg, about 0.51 mg, about 0.50 mg, about 0.49 mg, about 0.48 mg, about 0.47 mg, about 0.46 mg, about 0.45 mg, about 0.44 mg, about 0.43 mg, about 0.42 mg, about 0.41 mg, about 0.40 mg, about 0.39 mg, about 0.38 mg, about 0.37 mg, about 0.36 mg, about 0.35 mg, about 0.34 mg, about 0.33 mg, about 0.32 mg, about 0.31 mg, about 0.30 mg, about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, about 0.14 mg, about 0.13 mg, about 0.12 mg, about 0.11 mg, about 0.10 mg, about 0.09 mg, about 0.08 mg, about 0.07 mg, about 0.06 mg, about 0.05 mg, about 0.04 mg, about 0.03 mg, about 0.02 mg, or about 0.01 mg over 8 hours.

A daily dose of about 1 to about 2000 mg of solriamfetol or a pharmaceutically acceptable salt thereof may be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 1-1000 mg, e.g., about 20-500 mg, in single or divided doses, is administered. In some embodiments, the daily dose may be about 0.01 to about 150 mg/kg body weight, e.g., about 0.2 to about 18 mg/kg body weight. In some embodiments, the

dose contains about 1 mg to about 1000 mg of the drug or any range or value therein, e.g., about 10 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

For example, in certain such embodiments, the total amount of drug may be selected from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, or any range therein.

In one embodiment of the invention, solriamfetol is administered to the subject as needed to treat a disorder. The compound can be administered continuously or intermittently. In one embodiment, the compound is administered to the subject more than once a day, e.g., 2, 3, or 4 times per day, or once every 1, 2, 3, 4, 5, 6, or 7 days. In another embodiment, the compound is administered to the subject no more than once a week, e.g., no more than once every two weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or longer. In a further embodiment, the compound is administered using two or more different schedules, e.g., more frequently initially (for example to build up to a certain level, e.g., once a day or more) and then less frequently (e.g., once a week or less). In other embodiments, the compound can be administered by any discontinuous administration regimen. In one example, the compound can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days, or longer. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule.

The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, solriamfetol is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Further agents include, without limitation, stimulants, antipsychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302.

The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults, and geriatric subjects. In some embodiments, the subject is postpartum, In some embodiments, the subject is a woman between the ages of 18 and 45 years.

Suitable subjects are generally lactating mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. The human subject can be a lactating individual who is breastfeeding an infant frequently or on a regular basis. In some embodiments, the human subject is a woman. The woman may be between about 18 and 45 years of age. The term "breastfeeding" may also be referred to as chestfeeding, or grammatical variations thereof, refers to delivering breast milk of the individual directly to an infant, extracting breast milk from the individual using a device and subsequently delivering to an infant, extracting breast milk from the individual using a device and storing the breast milk for a period of time and subsequently delivering the stored breast milk to the infant, or a combination thereof.

The subject of the present disclosure can be in lactation, for example, an individual who is lactating (e.g., producing breast milk), nursing or breastfeeding. The subject can be in lactation after pregnancy, i.e., post-partum, or via induced lactation (e.g., with metoclopramide, oral contraceptives, herbal medications, stimulation via pumping, or any combination thereof.).

In some embodiments, the subject is between 1 day and 24 months postpartum, between about 1 day and 12 months postpartum, between about 10 days and 12 months (52 weeks) postpartum, or between about 15 weeks to about 37 weeks postpartum. In some embodiments, the subject expresses mature milk, which typically occurs about 10 to about 30 days (e.g., about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days) postpartum, or about 10 to about 20 days postpartum, or about 10 to about 20 days after beginning of milk expression in induced lactation. Infancy starts at birth and ends around the age of 2 years; accordingly, the infant stage being fed breast milk includes the breastfeeding period.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing a disorder amenable to treatment with solriamfetol, is suspected of having a disorder amenable to treatment with solriamfetol, and/or is anticipated to experience a disorder amenable to treatment with solriamfetol, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment.

In some embodiments, the subject is a mother whose disease or disorder is putting her baby at risk of adverse events from the maternal condition (e.g., she falls asleep while caring for the baby), and who wishes to breastfeed. Surveys have shown that at least 60% of women with narcolepsy report difficulties caring for their babies because of their symptoms, and are afraid of being impaired by their disease as it relates to caring for their babies.

Thus, one aspect of the invention relates to a method of treating excessive daytime sleepiness in a lactating mother, with an infant at risk of adverse events from the mother's excessive daytime sleepiness, and who wishes to breastfeed the infant, said method comprising: (a) determining the Epworth Sleepiness Scale (ESS) total score of the mother and if the mother experiences sleep attacks while caring for the infant; (b) providing the mother with an ESS total score of 15 or greater and who experiences sleep attacks while caring for the infant a starting dose of solriamfetol of 37.5 mg once daily if the excessive daytime sleepiness is associated with obstructive sleep apnea, or 75 mg once daily if the excessive daytime sleepiness is associated with narcolepsy, and doubling the dose at intervals of at least 3 days up to 150 mg once daily, wherein the elimination half-life of

solriamfetol in plasma in the postpartum or lactating mother is about 5 hours; and (c) feeding the infant breast milk obtained from the mother at least about 3.5 hours (e.g., 4 or 5 hours) after administration of the solriamfetol to the mother, thereby avoiding exposing the infant to the maximum concentrations of solriamfetol in the breast milk, wherein the median T_{max} of solriamfetol excreted in the breast milk is approximately 1.1 hours.

The method selects subjects suitable for treatment based on disease severity, interference with infant care, and desire of the mother to provide the infant the developmental and health benefits of breastfeeding

The ESS is a subjective sleepiness test that is well known in the art and routinely used to measure the sleepiness level of a subject. The scale is intended to measure daytime sleepiness through the use of a short questionnaire that asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives. The scores for the eight questions are added together to obtain a single number that estimates the subject's average sleep propensity (ASP). A number in the 0-10 range is considered to be normal while 11-12 indicates mild excessive sleepiness, 13-15 indicates moderate excessive sleepiness, and 16 or higher indicates severe excessive sleepiness. Narcolepsy patients have an average score of about 17. Obstructive sleep apnea (OSA) patients with excessive sleepiness have an average score of about 15.

A "sleep attack," as used herein, refers to a strong urge to sleep, often followed by a period of sleep in which you cannot control when you fall asleep. These periods can last from a few seconds to a half hour.

In some embodiments, the lactating mother experiences a reduction in the ESS total score of 5 or more, e.g., 6, 7, 8, 9, or 10 or more.

In some embodiments, the lactating mother experiences a reduction in the frequency of sleep attacks while holding, feeding, nursing, or otherwise caring for the infant. The reduction in frequency may be at least about 10$, 20%, 30%, 40%, or 50% relative to an untreated mother.

In some embodiments, the lactating mother experiences a reduction in automatic movements (the movement of parts of the body such as their hands while sleeping) while caring for the infant. The reduction in automatic movements may be at least about 10%, 20%, 30%, 40%, or 50% relative to an untreated mother.

Having described the present invention, the same will be explained in greater detail in the following examples, which are included herein for illustration purposes only, and which are not intended to be limiting to the invention.

EXAMPLES

Example 1. Phase 4 Clinical Trial in Breastfeeding Subjects

A Phase 4, open-label, single-dose study to evaluate the pharmacokinetics (PK) of solriamfetol in the breast milk and plasma of healthy postpartum women following oral administration of a 150 mg solriamfetol tablet.

The study was conducted in 6 healthy adult lactating women who were between 15 and 37 weeks postpartum and were administered a single oral dose of SUNOSI 150 mg. SUNOSI was excreted in breast milk with a milk to plasma AUC ratio of approximately 2:1. The median T_{max} for SUNOSI in breast milk was approximately 1.1 hours, and the mean elimination half-life in breast milk was approximately 5.0 hours. The average amount that would be passed to the infant was estimated to be 0.59 mg over 24 hours, which is about 4.0% of the maternal dose on a weight-adjusted basis. The data from the lactation study indicate that SUNOSI is transferred to breastmilk in nursing mothers, with the relative infant dose (RID) is approximately 4% of the maternal weight-adjusted dosage. Data to assess the effects of SUNOSI on a breastfed infant or on milk production is not provided. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition. Breastfed infants should be monitored for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Solriamfetol had a short systemic elimination half-life of 5.0 to 7.6 hours, and with once daily dosing the estimated accumulation ratio of 1.06 was marginally higher than 1, indicating essentially no accumulation with repeated dosing. Therefore, a single therapeutic dose of solriamfetol was administered in this study. Since the objective of this study was to evaluate solriamfetol PK in breast milk and plasma, as well as to estimate the daily drug dose received by the infant from breast milk, the highest approved therapeutic dose of 150 mg solriamfetol was administered.

The subjects were between 10 days and 52 weeks postpartum. The lower time limit of 10 days postpartum represented a time after which mature milk was developed (US FDA 2019). The upper time limit of 52 weeks postpartum was chosen based on a prospective study that showed that fat, total solids, and "energy" (kcal/dL) were all statistically increased in breast milk collected 12 to 18 months postpartum (N=25) compared with breast milk collected 1 to 12 months postpartum (N=35) (Czosnykowska Lukacka 2018). Also, there was a paucity of data regarding breast milk nutrient composition at >12 months postpartum (Wu 2018). The study included frequent maternal milk sample collections during a 72-hour period postdose to enable detection of the potential presence of solriamfetol in breast milk. Plasma concentrations of solriamfetol were also evaluated during the same time period to assess solriamfetol's potential accumulation in breast milk relative to the plasma.

Subjects were instructed to refrain from breastfeeding their infants for 72 hours postdose. Based on the drug's short half-life, this period (10×half-life) was expected to be of sufficient duration for complete elimination of solriamfetol from both the systemic circulation and breast milk.

Pharmacokinetic Results

All subjects in the PK Population were included in the PK analysis. Pharmacokinetic Population was defined as all subjects who received study drug and provided postdose breast milk or plasma PK data for at least one collection interval or time point. Subject 1003, 1004, and 1007 had multiple protocol deviations documented with regards to the timing of food consumption, however, these deviations are not likely to impact solriamfetol PK and these subjects were included in the descriptive statistics or PK parameter analysis. Furthermore, the PK of solriamfetol in fed versus fasted subjects satisfied the criteria for bioequivalence, indicating that solriamfetol can be taken regardless of food intake.

The mean plasma and breast milk solriamfetol concentration time profiles are shown in FIG. **1**. FIG. **1** shows the time course of mean plasma and breast milk solriamfetol concentrations on Day 1 following a single-dose administration of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. After reaching maximum solriamfetol concentrations approximately 1.00 to 3.00

hours after oral administration, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol concentrations in breast milk were approximately 2-fold higher than plasma concentrations

The mean breast milk cumulative solriamfetol amount-time profiles are shown in FIG. **2**. FIG. **2** shows the mean breast milk cumulative solriamfetol amount-time profiles following a single-dose administration of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. Arithmetic mean±SD amount excreted in breast milk over 72 hours was 0.6880±0.4672 mg. However, near complete excretion was observed within 24 hours of dosing.

No subjects had Rsq adjusted values <0.700, or % AUCex >20%, therefore Lambda_z and AUC0-inf related parameters were all considered reliable and included in descriptive statistics.

Table 1 summarizes the plasma and breast milk PK parameters for solriamfetol following single-dose administration.

Solriamfetol exposure was approximately 2-fold higher, on average, in breast milk than plasma with geometric mean C_{max} of 1861 vs 892.5 ng/mL, AUC_{0-t} of 12770 vs 6236 h*ng/mL, and AUC_{0-inf} of 12940 vs 6340 h*ng/mL, respectively. The geometric mean milk:plasma ratio was 2.047.

Plasma solriamfetol t_{max} (from 0.98 to 3.02 hours, median 1.25 hours) was similar to breast milk (from 1.00 to 3.00 hours, median 1.12 hours).

The geometric mean solriamfetol $t_{1/2}$ appear similar between plasma (4.751 hours) and breast milk (4.869 hours). Furthermore, the geometric mean plasma solriamfetol CL/F was 23.66 L/h and V_z/F was 162.2 L. Geometric mean A_{milk} was 0.5651 mg, with a daily and relative infant dose of 0.5856 mg and 4.030%, respectively.

TABLE 1

Summary of Pharmacokinetic Parameters for Solriamfetol in Plasma and Breast Milk (Pharmacokinetic Population)

Pharmacokinetic	Arithmetic Mean (CV %) [Geometric Mean]	
Parameters	Plasma (N = 6)	Breast Milk (N = 6)
AUC_{0-inf} (h*ng/mL)	6543 (27.7) [6340]	13850 (41.0) [12940]
AUC_{0-t} (h*ng/ml)	6439 (27.9) [6236]	13700 (41.4) [12770]
C_{max} (ng/ml)	905.2 (18.0) [892.5]	2068 (48.7) [1861]
t_{max} (h)[a]	1.25 (0.98, 3.02)	1.12 (1.00, 3.00)
Lambda_z (1/h)	0.1478 (19.1) [0.1459]	0.1446 (18.8) [1424]
$t_{1/2}$ (h)	4.804 (15.2) [4.751]	4.954 (21.4) [4.869]
CL/F (L/h)	24.40 (26.8) [23.66]	NC
V_z/F (L)	168.9 (31.9) [162.2]	NC
Milk:Plasma Ratio	NC	2.136 (35.8) [2.047]
A_{milk} (mg)	NC	0.6880 (67.9) [0.5651]
Daily Infant Dose (mg)	NC	0.6927 (63.5) [0.5856]
Relative Infant Dose (%)	NC	4.602 (60.6) [4.030]

NC = not calculated.

Note:

CV % was based on the arithmetic mean.

[a]Median (min, max).

Pharmacokinetic Conclusion

Solriamfetol t_{max} for both plasma and breast milk were similar and ranged between 1 to 3 hours. After reaching maximum solriamfetol concentrations, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol breast milk exposure (C_{max} and AUCs) was 2-fold higher than plasma. Furthermore, the geometric mean milk:plasma ratio was 2.047. The solriamfetol $t_{1/2}$ appeared similar in plasma and breast milk at approximately 5 hours.

This study was exclusively in post-partum women, a very different population than the ones for the studies reported in the Pharmacokinetics section of the current Sunosi® label which were healthy male and female patients who were not postpartum. The Sunosi® label reports oral bioavailability of solriamfetol is approximately 95% with peak plasma concentration of solriamfetol occurs at a median T_{max} of 2 hours (range 1.25 to 3.0 hours) post-dose under fasted conditions healthy male and female patients who were not postpartum. Indeed, while the median T_{max} reported for healthy male and female patients who were not postpartum is reported in the label as 2 hours, the T_{max} in the present lactation study is 1 hour. Similarly, the apparent mean elimination plasma half-life is 7.1 hours for healthy male and female patients who were not postpartum on the Sunosi® label compared to 4.8 hours in plasma and 4.95 hours in breast milk in the present lactation study.

CL/F and were determined for plasma solriamfetol only. Arithmetic mean of CL/F was 24.40 L/h and was 168.9 L. A_{milk},daily infant dose, and relative infant dose were determined for breast milk solriamfetol only. Arithmetic mean of was 0.6880 mg, daily infant dose was 0.6927 mg, and relative infant dose was 4.602% Safety Results

Adverse Events: The overall summary of Treatment Emergent Adverse Events (TEAEs) is summarized in Table 2. A total of 3 (50%) subjects had at least 1 AE; of 2 (33.3%) subjects had TEAEs related to the study drug and 1 (16.7%) subject had TEAE unrelated to the study drug. The mild TEAEs were reported in 2 (33.3%) subjects and moderate TEAEs were reported in 1 (16.7%) subject. No SAEs were reported in the study. None of the subjects discontinued due to TEAEs.

TABLE 2

Overall Summary of Treatment Emergent Adverse Events (Safety Population)

Category	Solriamfetol 150 mg (N = 6) n (%)
Subjects with at least 1 AE	3 (50.0)
Subjects with an	
AE considered related to study drug	2 (33.3)
AE considered unrelated to study drug	1 (16.7)
Subjects with[a]	
SAE	0
SAE considered related to study drug	0
SAE considered unrelated to study drug	0
Subjects who discontinued due to	
AE	0
AE considered related to study drug	0
AE considered unrelated to study drug	0
Subjects with[a]	
Mild AE	2 (33.3)
Moderate AE	1 (16.7)
Severe AE	0
Life-threatening AE	0
Fatal AE	0

AE = adverse event; N = number of subjects exposed; SAE = serious adverse event.

Note:

Percentages are based on N

[a]Subjects reporting an adverse event in more than one category were counted only once for the category.

Out of 3 subjects reporting TEAEs, 1 subject had dizziness and headache (SOC: Nervous system disorder), 1 subject had agitation (SOC: Psychiatric disorder), and 1 subject had an event of headache (SOC: Nervous system

disorder) (Table 3). A total of 4 TEAEs were reported where 3 TEAEs (dizziness, headache, and agitation) were mild and 1 TEAE (headache) was moderate in intensity. All the 3 mild TEAEs were related to the study drug and the moderate TEAE was unrelated to the study drug. All the TEAEs were resolved.

TABLE 3

Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Safety Population)

System Organ Class (SOC) Preferred Term (PT)	Solriamfetol 150 mg (N = 6) n (%)
Nervous system disorders	2 (33.3)
Dizziness	1 (16.7)
Headache	2 (33.3)
Psychiatric disorders	1 (16.7)
Agitation	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

A subject with multiple adverse events within a primary system organ class was counted only once.

A subject with multiple occurrences of an AE was counted only once in the AE category

System organ classes are presented in alphabetical order; preferred terms are presented within system organ class in alphabetical order

Adverse events were coded using the MedDRA coding dictionary, MedDRA180 Mixed

Vital Signs: There were no major changes in vital sign parameters from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4. The summary of clinically notable vital signs at any post-baseline visit are summarized in Table 4.

TABLE 4

Summary of Clinically Notable Vital Signs at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
Systolic blood pressure (mmHg)	Blood pressure change by > 20% from the study baseline value/recordings	1 (16.7)
Diastolic blood pressure (mmHg)	Average diastolic blood pressure ≥ 95 mmHg or ≤ 60 mmHg	2 (33.3)
Pulse rate (beats/min)	Pulse change by > 20% from the study baseline value/recordings	2 (33.3)
Body temperature (C)	Change in body temperature > 1.8% from the subjects baseline temperature recordings	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

Baseline was defined as the last non-missing measurement taken prior to dosing. All post-baseline assessments, including unscheduled, were considered for this summary.

There were no major changes in ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. No abnormal clinically significant ECG findings were reported.

The summary of clinically notable ECG findings at any post-baseline visit are summarized in Table 5.

TABLE 5

Summary of Clinically Notable Electrocardiograms at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
ECG mean heart rate (bpm)	Ventricular rate ≥ 100 beats/min or ≤ 60 beats/min	2 (33.3)
PR interval, single beat (msec)	PR interval ≥ 200 msec or ≤ 120 msec	2 (33.3)
QRS duration, single beat (msec)	QRS duration ≥ 100 msec or ≤ 80 msec	4 (66.7)
QT interval, single beat (msec)	QT interval ≥ 440 msec or ≤ 350 msec	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

Baseline was defined as the last non-missing measurement taken prior to dosing. All post-baseline assessments, including unscheduled, were considered for this summary.

None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

Safety Conclusions

Overall, 6 subjects were enrolled in the safety analysis and treated with the single oral dose of Solriamfetol which was safe and well tolerated.

Out of 6 subject 3 (50%) subjects had at least 1 AE. Out of 3 subjects reporting TEAEs: 1 subject had dizziness and headache (SOC: Nervous system disorder) both of mild intensity and were related to study drug; 1 subject had agitation (SOC: Psychiatric disorder) of mild intensity and was related to study drug; 1 subject had an event of headache (SOC: Nervous system disorder) of moderate intensity and was not related to study drug. No SAEs, deaths, or other significant AEs were reported in the study. None of the subjects discontinued due to TEAEs. None of the subjects had abnormal, clinically significant laboratory findings. There were no major changes in vital sign from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4 and ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

Discussion

The instant study was a Phase 4, open-label, single-dose study to evaluate the PK of solriamfetol in the breast milk and plasma of healthy postpartum women following oral administration of a 150 mg solriamfetol tablet. A total of 6 subjects were enrolled and were included in both PK and safety analysis. All the 6 subjects had completed the study. There were no premature discontinuations reported in the study.

The primary objective (PK) of this study was to assess the PK of solriamfetol in plasma and breast milk after single oral dose of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. Solriamfetol exposure was approximately 2-fold higher, on average, in breast milk than plasma with geometric mean C_{max} of 1861 vs 892.5 ng/mL, AUC_{0-t} of 12770 vs 6236 h*ng/mL, and AUC_{0-inf} of 12940 vs 6340 h*ng/mL, respectively. The geometric mean milk:plasma ratio was 2.047. Plasma solriamfetol t_{max} (from 0.98 to 3.02 h, median 1.25 h) was similar to breast milk (from 1.00 to 3.00 hours, median 1.12 hours). The geometric mean solriamfetol $t_{1/2}$ appeared similar between plasma (4.751 hours) and breast milk (4.869 hours). Furthermore, the geometric mean plasma solriamfetol CL/F was 23.66 L/h

and V_z/F was 162.2 L. Geometric mean A_{milk} was 0.5651 mg, with a daily and relative infant dose of 0.5856 mg and 4.030%, respectively.

The secondary objective of study was to assess the safety and tolerability of the solriamfetol in healthy postpartum women. Overall, the study drug was safe and well tolerated.

No SAEs, deaths, or other significant AEs were reported in the study. None of the subjects discontinued due to TEAEs. Out of 6 subjects, 3 subjects reported adverse events. All AE (dizziness, headache, and agitation) were of mild intensity except 1 AE (headache) was of moderate intensity.

None of the subjects had abnormal or clinically significant laboratory findings. There were no major changes in vital sign from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4 and ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

Conclusion

Solriamfetol T_{max} for both plasma and breast milk were similar and ranged between 1 to 3 hours. After reaching maximum solriamfetol concentrations, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol breast milk exposure (C_{max}, AUCs) was 2-fold higher than plasma. Furthermore, the geometric mean milk:plasma ratio was 2.047. Solriamfetol $t_{1/2}$ appeared similar in plasma and breast milk at approximately 5 hours. Solriamfetol was safe and well tolerated.

Further analysis of the data indicate that the daily infant dose is 0.112 mg/kg (based on nominal infant weight of 6 kg) and the relative infant dose (RID) is approximately 5.5% of the maternal weight-adjusted dosage. Data are insufficient to determine effects of solriamfetol on a breastfed infant or its effects on milk production.

The cumulative median amount excreted in breast milk was 0.67 mg over 72 hours, which is about 5.5% of the maternal dose on a weight-adjusted basis. Of the total amount of solriamfetol excreted in breast milk over 72 hours, approximately 78% and 98% were excreted by 8 and 24 hours, respectively, with an apparent mean elimination half-life in breast milk of about 5 hours.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for solriamfetol and any potential adverse effects on the breastfed infant from solriamfetol or from the underlying maternal condition.

Infants exposed to solriamfetol should be monitored for signs of agitation, insomnia, and reduced weight gain.

Methodology

On Day −1, eligible subjects underwent the baseline procedures. On Day 1, 2 hours after a light breakfast, subjects were to receive a single dose of solriamfetol 150 mg with 240 mL of water. Subjects had to fast for approximately 4 hours after the first dose; water was allowed except for 1 hour before and 1 hour after dosing with the study drug.

Pharmacokinetic analysis of breast milk obtained from both breasts (by pumping) was evaluated prior to dose administration and at intervals up to 72 hours postdose. Blood samples were also collected for plasma solriamfetol quantitation and PK analysis predose and at timepoints up to 72 hours postdose. Solriamfetol breast milk and plasma concentrations were measured using validated bioanalytical methods. Safety was assessed throughout the study by 12-lead ECG, vital sign measurements, the Columbia-Suicide Severity Rating Scale (C-SSRS), and the incidence of adverse events (AE).

The study drug was yellow, film-coated tablets that contained the excipients hydroxypropyl cellulose and magnesium stearate and a polymer film coat (Opadry®).

The total overall study duration (first subject screened to safety follow-up of last subject) was approximately 11 months.

Vital signs (blood pressure, pulse rate, temperature, and respiratory rate) were measured with the subject in a seated or supine position and resting for at least 5 minutes prior to taking the measurement. The dominant arm was used for blood pressure and pulse rate measurements. On Day 1, vital signs were collected at predose, and at approximately 2 (blood pressure and pulse) and 4 hours (blood pressure and pulse) postdose.

12-lead ECG was taken with the subject in a supine position and resting for at least 10 minutes prior to taking the measurement. On Day 1, ECGs were collected predose and at approximately 2 hours postdose.

Subjects must fast for at least 8 hours before chemistry and hematology blood draws. All clinical laboratory tests were performed at Screening only (rescreening is permitted).

Screening/Baseline C-SSRS version at Screening, and since Last Visit version on Day −1 and Day 2 (or at ET).

Breast milk collection occurred at −2 to 0 (prior to dose), 0-2, 2-4, 4-8, 8-12, 12-18, 24-32, 32-40, 40-48 and 48-72 hours postdose on Days 1-4.

Blood samples for plasma PK evaluation were collected at the following time points: Predose, 1, 1.5, 3, 6, 8.5, 10, 13, 15, 21, 24, 28, 36, 44, and 72 hours following dosing on Day 1. General study methodology is outlined in Table 6.

TABLE 6

Screening	Check-in (Baseline)	Study drug dosing	Check-out	Safety Follow-up	Lactation Follow-up
		PK sampling			
Days −21 to −2	Day −1	Day 1	Day 4	Days 9-11	Days 39-41

Standardized meals include meals as needed on Day −1, a light breakfast approximately 2.5 hours before dosing on Day 1 (to be completed approximately 2 hours before dosing) followed by lunch approximately 4 hours after dosing, dinner approximately 8 hours after dosing, and a snack approximately 11 hours after dosing, and standardized meals thereafter.

Record was from 30 days prior to screening through the Safety Follow Up telephone call 5 to 7 days after check-out from the study facility (at Day 4 or ET).

Adverse events were monitored throughout the study by safety assessments, observations, and subject reporting, including the Safety FU telephone call 5-7 days (i.e., Days 9-11) after check-out from the study facility on Day 4, or ET.

Breast milk collection: Solriamfetol concentration in breast milk and plasma was evaluated based on samples collected prior to and postdose on Days 1 to 4. Breast milk was collected from both breasts, using electronic breast pumps, during the following intervals: From −2 to 0 at predose and at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, 24 to 32, 32 to 40, 40 to 48, and 48 to 72 hours postdose on Day 1. The midpoint of each breast milk collection interval was used as the time variable.

Breast milk was collected as often as needed during the assigned intervals; however, at the end of each interval, breast milk was pumped from both breasts and collected. At

the end of each collection interval, all milk expressed from both breasts during that interval was pooled. The milk was thoroughly mixed by gently inverting the collection vessel 10 times to ensure homogeneity in milk composition. The weight and volume of the collected milk during each interval was also recorded.

Serial blood samples (4 mL) were collected and dispensed into labeled K2EDTA tubes. The actual time of blood collection for all samples was recorded on the eCRF. Solriamfetol concentration in breast milk and plasma were determined using a validated bioanalytical method (LC-MS/MS) at Origin Bioanalytical Laboratory. The analytical range (lower limit of quantitation [LLOQ] to upper limit of quantitation) for plasma solriamfetol was 8.42 to 4210.00 ng/mL, and breast milk solriamfetol was 10.0 to 8000 ng/mL.

Pharmacokinetic parameters were derived with Phoenix® WinNonlin® Version 8.3 (Certara, Inc., Princeton, New Jersey, USA) and/or SAS© Version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Criteria for Subjects: Each subject who met the following criteria were enrolled in the study: Healthy adult female 18 to 50 years of age, inclusive, at the time of consent; At least 50 kg body weight and body mass index (BMI) within 18 to 35 kg/m^2 inclusive; Postpartum between 10 days and 52 weeks, inclusive, after delivery of a normal, healthy infant by the time of dosing, and actively lactating from both breasts; If breastfeeding, agreed to withhold breastfeeding their infant(s) from approximately 2 hours before dosing to approximately 72-hours after dosing and resumed breastfeeding after completion of study Day 4 procedures or would have made a decision to wean their infants before enrollment in the study; Agreed not to use nicotine-containing products including tobacco (cigarettes, cigars, chewing tobacco, snuff), e-cigarettes, and nicotine lozenge/gum/patch within 3 days prior to check-in on Day −1, and for the duration of the study; Had used a medically acceptable method of contraception for at least the 2 months prior to dosing on Day 1, and consented to use a medically acceptable method of contraception throughout the entire study period and for 30 days after the study was completed; Agreed to comply with study-specified diet while in the study; Able to understand and comply with study requirements; Ensured that their breastfed infant(s) was able to feed from a bottle before study participation begins; Agreed to ensure nutrition was available for their infant(s) through stored breast milk, or alternative nutritional sources as necessary, for the duration of the study; Participants who: Were fully vaccinated for at least 14 days after the last (or only) dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 [COVID-19]) vaccine; or Elected not to be vaccinated prior to the study, with Participant who chooses not to be fully vaccinated prior to the start of the study did not receive any dose of the COVID-19 vaccine and remained on the study.

Clinical laboratory tests including hematology, serum chemistry, urinalysis, and thyroid panel, were collected at Screening only.

A complete physical examination included, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight were also measured and recorded. At Screening and Baseline/Randomization visits, BMI was calculated by the site in order to verify eligibility.

Vital signs included oral temperature, pulse rate, respiratory rate, and BP. Clinically significant abnormal vital signs results reported during Screening/Randomization were recorded as medical history and those reported after study drug were recorded as AEs.

Blood pressure and pulse measurements were assessed with the subject in a seated or supine position and resting for at least 5 minutes prior to taking the measurement. The dominant arm was used for blood pressure and pulse rate measurements. On Day 1, vital signs were collected at predose, and at approximately 2 (blood pressure and pulse) and 4 hours (blood pressure and pulse) postdose.

The 12-lead ECGs were collected at Screening, Day −1 until Day 4. Single 12-lead ECG was obtained using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT, and corrected QT interval (QTc) intervals. Any abnormal safety assessments including ECG readings considered clinically significant in the medical and scientific judgment of the investigator were reported as an AE. The investigator had to review the ECG and document it in the source documents. Clinically significant abnormal ECG results reported during Screening were recorded as medical history and those reported after study drug were recorded as AEs.

All laboratory tests were to be performed in accordance with Laboratory Manual. The tests detailed in Table 7 were performed by the central laboratory. Additional tests might be performed at any time during the study as determined necessary by the investigator or required by local regulations.

All laboratory tests with abnormal values considered clinically significant during the study or within 14 days after the last dose of study drug (and considered by the investigator to be related to study drug) were repeated until the values return to normal or Baseline or were no longer considered clinically significant by the investigator or medical monitor. If clinically significant values did not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology were to be identified.

TABLE 7

Safety Laboratory Test	
Hematology:	Serum Chemistry:
Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential (absolute count and percent)	Albumin (ALB)
	Alkaline phosphatase (ALK-P)
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Blood urea nitrogen (BUN)
Urinalysis:	Calcium (Ca)
Appearance	Carbon dioxide (CO2)
Bilirubin	Chloride (Cl)
Color	Creatinine
Glucose	Creatine kinase
Ketones	Glucose
Nitrite	Phosphorus
Occult blood	Potassium (K)
pH	Sodium (Na)
Protein	Total bilirubin
Specific gravity	Direct bilirubin
Urobilinogen	Total cholesterol
Leukocyte esterase	Total protein
	Triglycerides
	Uric acid

TABLE 7-continued

Safety Laboratory Test	
Drug Screening:	Pregnancy *:
Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opiates, phencyclidine) Breath alcohol test	Serum at Screening Urine at Baseline (Day -1)

ALB = albumin; ALK-P = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; CO2 - carbon dioxide; Cl = chlorine; K = potassium; Na = sodium; WBC = white blood cell count.
*Pregnancy screening required for all subjects in the study.

Statistical/Analytical

Unless otherwise specified, continuous data was summarized using descriptive statistics comprising of the number of subjects exposed (N) and with data to be summarized (n), mean, standard deviation (SD), median, minimum (min), maximum (max), geometric mean (Geo-mean), coefficient of variation (CV %), and geometric coefficient of variation (CV %). Categorical variables were presented using counts and percentages. Analyses and summary outputs were generated using SAS® Version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

The PK Population consisted of all subjects who received study drug and provided postdose breast milk or plasma PK data for at least one collection interval or time point. This population was used for evaluable PK concentration data and PK parameter summaries and listings. The Safety Population consisted of all subjects who received the dose of study drug.

This population was used for demographic and baseline characteristics and for safety data summaries and listings.

Pharmacokinetic concentrations and parameters were summarized using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (CV %), median, min, max, Geometric mean (Geo-mean) and the geometric coefficient of variation (Geo-CV %). For the PK parameter t_{max}, only n, median, minimum, and maximum was presented.

Subjects with partial data were evaluated on a case-by-case basis to determine if sufficient data was available for reliable calculation of PK parameters. In case of an incomplete milk collection (partial/spilt sample with inaccurate information of the total milk volume of the by-interval samples), the by-interval recovery was listed but not included in the summary, and cumulative recovery was only reported through the most recent prior complete milk collection. By-interval data during which a subject was unable to lactate (produce any milk), was treated as an amount of zero (for the affected interval) in the summation of cumulative recovery calculation.

Plasma and milk concentrations were summarized using descriptive statistics.

Concentrations that were below the lower limit of quantitation (BLQ) were treated as follows for the computation of descriptive statistics:

The summary statistics at a time with one or more BLQ values were calculated by assigning ½ LLOQ to all values less than LLOQ. If the calculated arithmetic (and geometric) mean value was BLQ, then SD and CV % were presented as "ND.", and the mean was presented as "BLQ. However, since a high proportion of BLQ values may have affected the SD; if more than 50% of values were imputed, then no mean was calculated for that time point and again a value of BLQ was presented only for the mean value. Within the summary statistics, any minimum, or median values that were calculated to be BLQ were presented as BLQ within the summary presentation.

Concentrations collected outside of the protocol allowed sampling windows were included in descriptive statistics, unless the PK scientist observed that the deviation was substantial enough to impact descriptive statistics. In this case, the excluded concentrations were identified in the CSR.

For plotting arithmetic mean concentration profiles: The arithmetic mean value at a time with one or more BLQ values were calculated by assigning ½ LLOQ to all values BLQ. If the calculated mean value was BLQ, then that time point was plotted as zero in the mean pharmacokinetic profiles. However, since a high proportion of BLQ values may have affected the SD; if more than 50% of values were imputed, then no mean was calculated for that time point and again a value of zero plotted. A line with a label of LLOQ in the concentration axis was overlaid to show the level of LLOQ.

Safety analyses were based on the Safety Population. The secondary endpoints for evaluating subject safety and tolerance were the incidence of reported AEs and the laboratory test results for all subjects.

Adverse events: Adverse events recorded in the electronic case report forms (eCRFs) were coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as any event with onset date on or after the first dose of study drug or any ongoing event that worsened in severity after the date of the first dose of study drug or any event that was present at baseline but was subsequently considered drug-related by the investigator through the end of the study. The incidence of TEAEs were presented by severity, relationship to study drug, start and end date, seriousness, and outcome. The investigator assessed the severity and relatedness of each AE to study drug. Columbia-Suicide Severity Rating Scale (C-SSRS) data were summarized at scheduled visits and were listed. Other safety analyses were performed as appropriate.

12 Lead ECG: The number and percentage of subjects who had the following postbaseline clinically notable ECG interval abnormality was summarized: Ventricular rate >100 beats/min or ≤60 beats/min; PR interval ≥200 msec or ≤120 msec; QRS duration ≥100 msec or ≤80 msec; QT interval ≥440 msec or ≤350 msec; QTc Bazett and QTc Fredericia ≥470 msec or ≤330 msec; RR interval ≥1200 msec or ≤600 msec; and QTc Bazette and QTc Fredericia increase from study Baseline Value >30 msec.

Vital Signs: The following clinically notable vital sign abnormalities were presented: Average systolic blood pressure ≥150 mmHg or ≤80 mmHg; Average diastolic blood pressure ≥95 mmHg or ≤60 mmHg; Average heart rate ≥120 bpm or ≤50 bpm; Respiratory rate <10 breaths/min or >24 breaths/min; Body temperature >37.9° C. or <35.5° C.; Systolic and diastolic blood pressure change by >20% from the study baseline value/recordings; Pulse change by >20% from the study baseline value/recordings; Change in body weight by ≥7% from subject's baseline value (weight loss/weight gain); and Change in body temperature >1.8% from the subject's baseline temperature recordings.

Physical Examination: Physical examination data for each subject was presented in a listing. A clinically significant adverse change (i.e., worsening) of a physical examination finding after screening was recorded as an AE.

Disposition of Subjects. A total of 6 subjects were enrolled and treated in the study. All 6 subjects had com-

pleted the study. There were no premature discontinuations reported in the study. All 6 subjects received the study drug (safety population) and provided post-dose breast milk or plasma PK data for at least one collection interval or time point (PK population). All 6 subjects were females and belonged to not Hispanic or Latino ethnicity. The mean (SD) of age, weight, height, and BMI of the overall population was 28.7 (5.54) years, 79.15 (12.162) kg, 168.62 (6.013) cm, and 27.90 (4.513) kg/m^2, respectively.

TABLE 8

Demographics and Baseline Characteristics (Safety Population)

Characteristic	Solriamfetol 150 mg (N = 6)
Age (years)	
n	6
Mean (SD)	28.7 (5.54)
Median	29.5
Min, Max	21, 35
Gender, n (%)	
Female	6 (100%)
Missing	0
Race, n (%)	
White	3 (50.0)
Black or African American	3 (50.0)
Missing	0
Ethnicity, n (%)	
Not Hispanic or Latino	6 (100%)
Missing	0
Height (cm)	
n	6
Mean (SD)	168.62 (6.013)
Median	170.00
Min, Max	160.0, 177.5
Weight (kg)	
n	6
Mean (SD)	79.15 (12.162)
Median	77.90
Min, Max	64.1, 99.1
BMI (kg/m^2)	
n	6
Mean (SD)	27.90 (4.513)
Median	27.95
Min, Max	22.4, 34.3

BMI = body mass index; N = number of subjects exposed
Note:
Percentages are based on N.

Prior and Concomitant Medication: Two subjects had taken medications during the study for AEs. One subject received acetaminophen and other received ibuprofen.

Medical and Surgical History: A total of 5 of 6 subjects had the medical and surgical history. Of these subjects, 1 subject had the medical history of appendectomy, C-section, and tubal ligation. One subject had asthma and C-section. One subject had cholelithiasis, pancreatitis, and gall bladder removal. One subject had umbilical hernia repair, heartburn, and C-section, and 1 subject had natural childbirth and hip pain dur to natural childbirth.

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The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent appli-

cations, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A method of reducing the exposure to solriamfetol from breast milk, in an infant receiving breast milk from a nursing human mother being treated with a once-daily dose of solriamfetol of about 150 mg for a disorder amenable to treatment with solriamfetol, the method comprising feeding the infant breast milk obtained from the mother at least about 5 hours after administering the solriamfetol to the mother, wherein the exposure to solriamfetol in the infant is reduced by at least about 50% compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol, and wherein a daily infant dose of solriamfetol is reduced to about 0.3 mg or lower.

2. The method of claim **1**, wherein the resulting relative infant dose is about 2% or lower of the once-daily dose of about 150 mg solriamfetol.

3. The method of claim **1**, wherein the breast milk is obtained from the mother at least about 7 hours after administering the solriamfetol to the mother.

4. The method of claim **1**, wherein the breast milk is obtained from the mother at least about 10 hours after administering the solriamfetol to the mother.

5. The method of claim **1**, wherein the infant does not experience agitation due to exposure to the solriamfetol.

6. The method of claim **1**, wherein the infant does not experience insomnia due to exposure to the solriamfetol.

7. The method of claim **1**, wherein the infant does not experience anorexia and/or reduced weight gain due to exposure to the solriamfetol.

8. The method of claim **1**, wherein the mother is being treated with solriamfetol for excessive daytime sleepiness, narcolepsy, obstructive sleep apnea, shift work disorder, attention deficit hyperactivity disorder, Parkinson's disease, binge eating disorder, or cognitive impairment.

9. The method of claim **8**, wherein the excessive daytime sleepiness is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

10. The method of claim **8**, wherein the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

11. The method of claim **1**, wherein the mother is being treated with solriamfetol to improve wakefulness.

12. The method of claim **1**, wherein the mother is from about 1 day to about 24 months postpartum.

13. The method of claim **1**, wherein the mother is from about 10 days to about 52 weeks postpartum.

14. The method of claim **1**, wherein the mother is between the ages of 18 and 45 years.

15. A method of reducing the exposure to solriamfetol from breast milk, in an infant receiving breast milk from a nursing human mother being treated with a once-daily dose of solriamfetol of about 75 mg for a disorder amenable to treatment with solriamfetol, the method comprising feeding the infant breast milk obtained from the mother at least about 5 hours after administering the solriamfetol to the mother, wherein the exposure to solriamfetol in the infant is reduced by at least about 50% compared to the exposure that would result with feeding the infant breast milk obtained from the mother less than 5 hours after administration of the solriamfetol, and wherein a daily infant dose of solriamfetol is reduced to about 0.15 mg or lower.

16. The method of claim **15**, wherein the resulting relative infant dose is about 2% or lower of the once-daily dose of about 75 mg solriamfetol.

17. The method of claim **15**, wherein the breast milk is obtained from the mother at least about 7 hours after administering the solriamfetol to the mother.

18. The method of claim **15**, wherein the breast milk is obtained from the mother at least about 10 hours after administering the solriamfetol to the mother.

19. The method of claim **15**, wherein the infant does not experience agitation due to exposure to the solriamfetol.

20. The method of claim **15**, wherein the infant does not experience insomnia due to exposure to the solriamfetol.

21. The method of claim **15**, wherein the infant does not experience anorexia and/or reduced weight gain due to exposure to the solriamfetol.

22. The method of claim **15**, wherein the mother is being treated with solriamfetol for excessive daytime sleepiness, narcolepsy, obstructive sleep apnea, shift work disorder, attention deficit hyperactivity disorder, Parkinson's disease, binge eating disorder, or cognitive impairment.

23. The method of claim **22**, wherein the excessive daytime sleepiness is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

24. The method of claim **22**, wherein the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, or Parkinson's disease.

25. The method of claim **15**, wherein the mother is being treated with solriamfetol to improve wakefulness.

26. The method of claim **15**, wherein mother is from about 1 day to about 24 months postpartum.

27. The method of claim **15**, wherein mother is from about 10 days to about 52 weeks postpartum.

28. The method of claim **15**, wherein the mother is between the ages of 18 and 45 years.

* * * * *

EXHIBIT G

US012064411B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 12,064,411 B1**
(45) **Date of Patent: *Aug. 20, 2024**

(54) **METHODS OF ADMINISTERING SOLRIAMFETOL TO LACTATING WOMEN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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A61K 9/00	(2006.01)
A61P 43/00	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/27*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61P 43/00*** (2018.01)

(58) **Field of Classification Search**
CPC A61K 31/27; A61P 43/00
See application file for complete search history.

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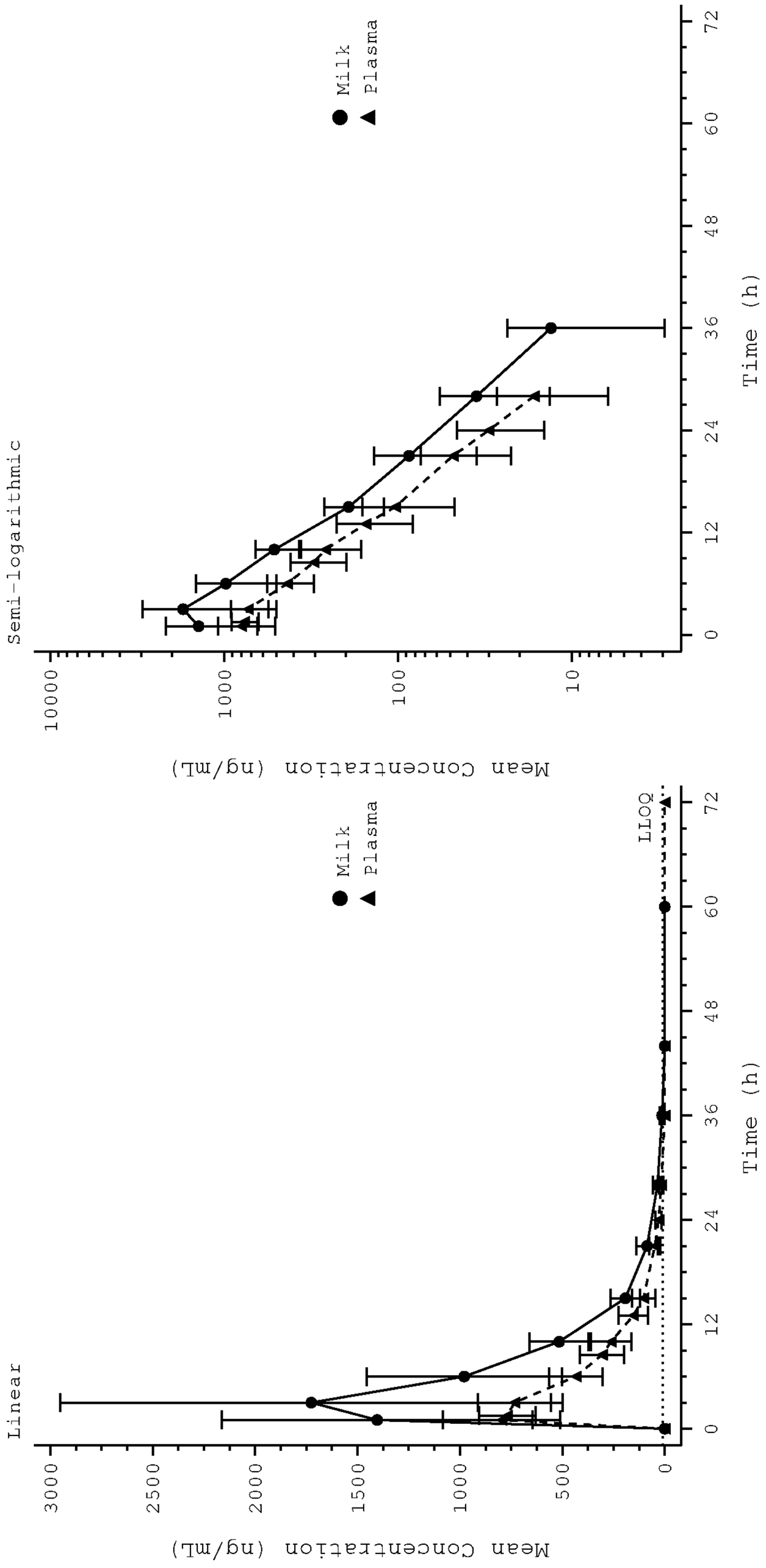
(57) **ABSTRACT**

Provided herein according to some embodiments is a method for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby decreasing potential for adverse events from solriamfetol in an infant.

18 Claims, 2 Drawing Sheets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Semi-logarithmic
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1000
100
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Mean Concentration (ng/mL)
0
12
24
36
48
60
72
Time (h)
Milk
Plasma
LLOQ
Linear
3000
2500
2000
1500
1000
500
0
Mean Concentration (ng/mL)
0
12
24
36
48
60
72
Time (h)

FIG. 1

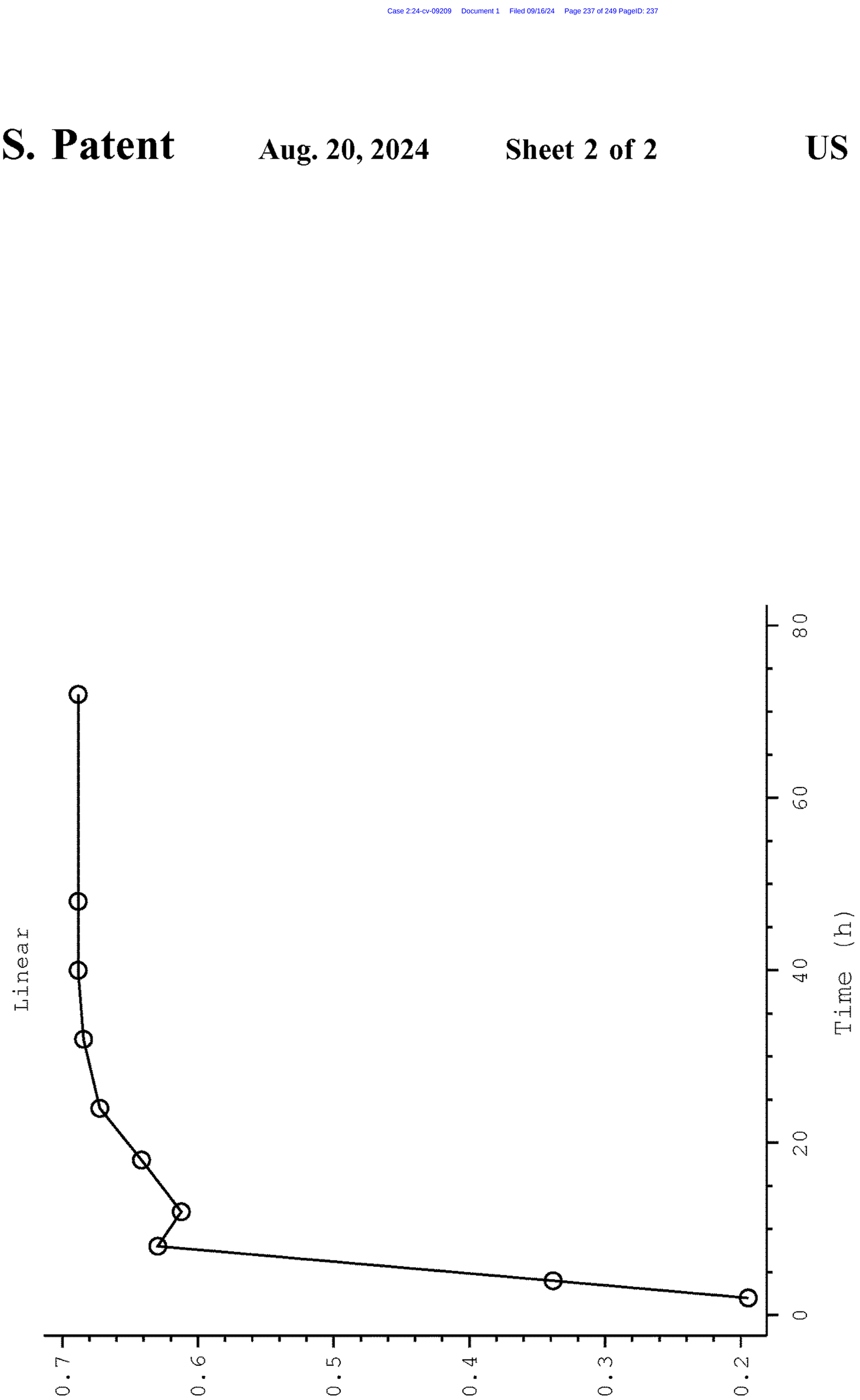


FIG. 2

METHODS OF ADMINISTERING SOLRIAMFETOL TO LACTATING WOMEN

STATEMENT OF PRIORITY

This application is a continuation of and claims priority to U.S. application Ser. No. 18/148,682 filed Dec. 30, 2022.

FIELD OF THE INVENTION

The present invention relates to methods of administering solriamfetol to a lactating subject while reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject.

BACKGROUND OF THE INVENTION

Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor that has received marketing approval in the US for improving wakefulness in adult subjects with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA). Solriamfetol has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others.

Pharmacokinetic studies have demonstrated rapid absorption and high oral bioavailability of solriamfetol with dose-proportional exposure (maximum serum concentration and area under the concentration-time curve [AUC]) in animals tested.

The present invention overcomes shortcomings in the art by providing methods of administering solriamfetol to a lactating subject while reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject.

SUMMARY OF THE INVENTION

The present invention relates to the development of methods of reducing the potential for adverse events from solriamfetol in an infant fed breast milk from the subject. The invention additionally related to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol.

Accordingly, one aspect of the invention relates to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby reducing exposure to solriamfetol in the infant.

Another aspect of the invention relates to a method for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising: administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby decreasing the potential for adverse events from solriamfetol in the infant. In some embodiments, the daily dose of solriamfetol is 150 mg.

An aspect of the invention relates to a method treating a disorder treatable with solriamfetol in a subject producing breast milk for feeding an infant, comprising: administering

solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and reducing exposure to solriamfetol and/or decreasing the potential for adverse events in the infant fed breast milk from the subject comprising feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject. The disorder treatable with solriamfetol can be, without limitation, narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, attention deficit/hyperactivity disorder, cognitive impairment or binge eating disorder.

In some embodiments, the method provides a daily infant dose of solriamfetol of about 0.3 mg or lower. In some embodiments, the method achieves a relative infant dose of less than about 9% of the subject weight-adjusted dose. In some embodiments, the method achieves a relative infant dose of less than about 5% of the subject weight-adjusted dose.

In some embodiments, the infant does not experience agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure.

In some embodiments, the subject is from 1 day to 24 months postpartum or from 10 days to 12 months postpartum.

In some embodiments, the subject is being treated with solriamfetol for narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, attention deficit/hyperactivity disorder, cognitive impairment, or binge eating disorder.

In some embodiments, the subject is a woman between the ages of 18 and 45 years.

In some embodiments, the adverse events are one or more of agitation, insomnia, anorexia, or reduced weight gain.

Methods of treating a disorder amenable to treatment with solriamfetol in a subject who is breastfeeding an infant are provided comprising orally administering solriamfetol at a daily dose of between about 37.5 mg and 300 mg to the subject.

These and other aspects of the invention are set forth in more detail in the description of the invention below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Time course of mean solriamfetol breast milk and plasma concentration-time profiles on linear and semi-logarithmic scales.

FIG. **2**. Mean breast milk cumulative solriamfetol amount-time profiles on linear scale following a single-dose administration of solriamfetol 150 mg tablet.

DETAILED DESCRIPTION

The present invention will now be described in more detail with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. In addition, any references cited herein are incorporated by reference in their entireties.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents, pat-

ent publications and other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

As used in the description of the invention and the appended claims, the singular forms "a," "an," and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

The term "about," as used herein when referring to a measurable value such as an amount of polypeptide, dose, time, temperature, enzymatic activity or other biological activity and the like, is meant to encompass variations of ±10%, ±5%, ±1%, ±0.5%, or even ±0.1% of the specified amount.

As used herein, the transitional phrase "consisting essentially of" (and grammatical variants) is to be interpreted as encompassing the recited materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. Thus, the term "consisting essentially of" as used herein should not be interpreted as equivalent to "comprising."

The term "therapeutically effective amount" or "effective amount," as used herein, refers to that amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (e.g., in one or more symptoms), delay or reduction in the progression of the condition, prevention or delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, etc., as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, e.g., at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

"Pharmaceutically acceptable carrier" (sometimes referred to as a "carrier") refers to a carrier or excipient that is useful in preparing a pharmaceutical or therapeutic composition that is generally safe and non-toxic and includes a carrier that is acceptable for veterinary and/or human pharmaceutical or therapeutic use. The terms "carrier" or "pharmaceutically acceptable carrier" can include, but are not limited to, phosphate buffered saline solution, water, emulsions (such as an oil/water or water/oil emulsion) and/or various types of wetting agents. As used herein, the term "carrier" encompasses, but is not limited to, any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, stabilizer, or other material well known in the art for use in pharmaceutical formulations and as described further herein.

The term "modulate," "modulates," or "modulation" refers to enhancement (e.g., an increase) or inhibition (e.g., a decrease) in the specified level or activity.

The term "enhance" or "increase" refers to an increase in the specified parameter of at least about 1.25-fold, 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 8-fold, 10-fold, twelve-fold, or even fifteen-fold and/or can be expressed in the enhancement and/or increase of a specified level and/or activity of at least about 1%, 5%, 10%, 15%, 25%, 35%, 40%, 50%, 60%, 75%, 80%, 90%, 95% or more.

"Inhibit" or "reduce" or grammatical variations thereof as used herein refers to a decrease or diminishment in the specified level or activity of at least about 1, 5, 10, 15%, 25%, 35%, 40%, 50%, 60%, 75%, 80%, 90%, 95% or more. In particular embodiments, the inhibition or reduction results in little or essentially no detectible activity (at most, an insignificant amount, e.g., less than about 10% or even 5%).

"Treat," "treating" and similar terms as used herein in the context of treating a subject refer to providing medical and/or surgical management of a subject. Treatment may include, but is not limited to, administering an agent or composition (e.g., a pharmaceutical composition) to a subject. Treatment is typically undertaken in an effort to alter the course of a disease (which term is used to indicate any disease, disorder, syndrome, or undesirable condition warranting or potentially warranting therapy) in a manner beneficial to the subject. The effect of treatment may include reversing, alleviating, reducing severity of, delaying the onset of, curing, inhibiting the progression of, and/or reducing the likelihood of occurrence or recurrence of the disease or one or more symptoms or manifestations of the disease. A therapeutic agent may be administered to a subject who has a disease or is at increased risk of developing a disease relative to a member of the general population. In some embodiments a therapeutic agent may be administered to a subject who has had a disease but no longer shows evidence of the disease. The agent may be administered e.g., to reduce the likelihood of recurrence of evident disease. A therapeutic agent may be administered prophylactically, i.e., before development of any symptom or manifestation of a disease. "Prophylactic treatment" refers to providing medical and/or surgical management to a subject who has not developed a disease or does not show evidence of a disease in order, e.g., to reduce the likelihood that the disease will occur, delay the onset of the disease, or to reduce the severity of the disease should it occur. The subject may have been identified as being at risk of developing the disease (e.g., at increased risk relative to the general population or as having a risk factor that increases the likelihood of developing the disease.

Grammatical variations of "administer," "administration," and "administering" to a subject include any route of introducing or delivering to a subject an agent. Administration can be carried out by any suitable route, including oral, topical, intravenous, subcutaneous, transcutaneous, transdermal, intramuscular, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, by inhalation, via an implanted reservoir, parenteral (e.g., subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intraperitoneal, intrahepatic, intralesional, and intracranial injections or infusion techniques), and the like. "Concurrent administration," "administration in combination," "simultaneous administration," or "administered simultaneously" as used herein, means that the compounds

are administered at the same point in time, overlapping in time, or one following the other. In the latter case, the two compounds are administered at times sufficiently close that the results observed are indistinguishable from those achieved when the compounds are administered at the same point in time. "Systemic administration" refers to the introducing or delivering to a subject an agent via a route which introduces or delivers the agent to extensive areas of the subject's body (e.g., greater than 50% of the body), for example through entrance into the circulatory or lymph systems. By contrast, "local administration" refers to the introducing or delivery to a subject an agent via a route which introduces or delivers the agent to the area or area immediately adjacent to the point of administration and does not introduce the agent systemically in a therapeutically significant amount. For example, locally administered agents are easily detectable in the local vicinity of the point of administration but are undetectable or detectable at negligible amounts in distal parts of the subject's body. Administration includes self-administration and the administration by another.

"Pharmaceutically acceptable," as used herein, means a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, e.g., Remington's Pharmaceutical Science; 21st ed. 2005).

"Concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds "concurrently" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

"Bioavailability," as used herein, refers to the estimated area under the curve, or AUC of the active drug in systemic circulation after oral administration with a dosage form as disclosed herein when compared with the AUC of the active drug in systemic circulation after intravenous administration of the active drug. The AUC is affected by the extent to which the drug is absorbed in the GI tract.

Products are considered to be "bioequivalent" if the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test product to reference product is within 80% to 125%.

The term "$AUC_{(0-t)}$" means the area under the plasma concentration curve from time 0 to time t.

The term "$AUC_{(0-\infty)}$" or "AUC_{0-inf}" means the area under the plasma concentration time curve from time 0 to infinity.

"C_{max}" refers to the maximum milk or plasma concentration of solriamfetol.

"T_{max}" refers to the time to maximum milk or plasma concentration for a given drug.

"$t_{1/2}$" refers to the time to reduce the milk and plasma concentration by 50% during the terminal elimination phase of the drug.

Milk:plasma ratio means AUC in breast milk divided by AUC in plasma.

"A_{milk}" means the amount excreted in breast milk over 72 hours.

"Vd/F" means the apparent volume of distribution in plasma.

"CL/F" is the apparent oral clearance in plasma.

AUC0-t is the area under the concentration-time curve from time 0 to the time t of the last quantifiable concentration (milk and plasma).

The present invention is based, in part, on methods of using Sunosi® (referred to herein as solriamfetol (also known as (R)-2-amino-3-phenylpropyl carbamate (APC), and previously known as JZP-110, ADX-N05, R228060, and YKP10A)) in lactating subjects with a disorder amenable to treatment with solriamfetol while reducing the potential for adverse effects in infants fed the subject's breast milk. Administration of solriamfetol to subjects expressing breast milk presents challenges. In a nonclinical study in rats, solriamfetol was detected in breast milk, with solriamfetol milk concentrations higher than solriamfetol plasma concentrations. It is desirable to reduce or minimize any adverse effects from the daily dose received by an infant fed breast milk from a subject treated with solriamfetol. In addition, it is desirable to identify methods that allow for the safety and tolerability of solriamfetol in nursing subjects.

Accordingly, one aspect of the invention relates to a method of reducing exposure to solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising orally administering the solriamfetol to the subject at a daily dose of about 37.5 mg to about 300 mg; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby reducing exposure to solriamfetol in the infant.

One aspect of the invention comprises methods for decreasing the potential for adverse events from solriamfetol in an infant fed breast milk obtained from a subject treated with solriamfetol comprising administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and feeding the infant breast milk from the subject at least about 5 hours after administering the solriamfetol to the subject, thereby decreasing the potential for adverse events from solriamfetol in the infant. In an embodiment, the adverse event is one or more of agitation, insomnia, anorexia, or reduced weight gain.

One aspect of the invention relates to a method for treating a disorder treatable with solriamfetol in a subject producing breast milk for feeding an infant, comprising administering solriamfetol orally at a daily dose of between 37.5 mg and 300 mg to the subject; and reducing exposure to solriamfetol and/or decreasing the potential for adverse events in the infant fed breast milk from the subject, comprising feeding the infant breast milk obtained from the subject at least about 5 hours after administering the solriamfetol to the subject. In one embodiment, the method reduces solriamfetol in the infant and the infant does not experience agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure. In one embodiment, the adverse events are one or more of agitation, insomnia, anorexia, or reduced weight gain.

A "disorder amenable to treatment with solriamfetol" or a "disorder treatable with solriamfetol" refers to any disorder in which administration of solriamfetol to a subject results in the treatment of one or more symptoms of the disorder in the

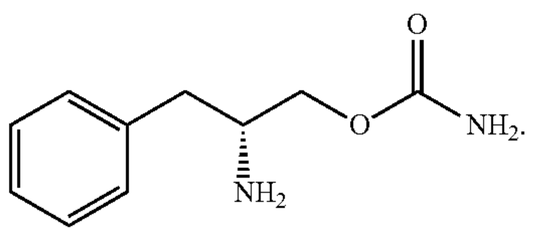
subject. Example disorders amenable to treatment with solriamfetol include narcolepsy, cataplexy, excessive daytime sleepiness, obstructive sleep apnea, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder (ADHD), cognitive impairment and/or cognitive dysfunction, restless legs syndrome, depression, bipolar disorder, obesity, or binge eating disorder. In some embodiments, the disorders amenable to treatment with solriamfetol include narcolepsy, excessive daytime sleepiness, obstructive sleep apnea, cognitive impairment, attention deficit/hyperactivity disorder, or binge eating disorder. See, for example, U.S. Pat. Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

"Excessive daytime sleepiness" or "EDS" refers to persistent sleepiness at a time when the individual would be expected to be awake and alert, even during the day after apparently adequate or even prolonged nighttime sleep. EDS may be the result of a sleep disorder or a symptom of another underlying disorder such as narcolepsy, sleep apnea, circadian rhythm sleep disorder, or idiopathic hypersomnia. While the name includes "daytime," it is understood that the sleepiness may occur at other times that the subject should be awake, such as nighttime or other times, e.g., if the subject is working nightshift. It is also understood that EDS is medically distinct from fatigue and disorders associated with fatigue.

In some embodiments, the cause of the EDS may be, without limitation, central nervous system (CNS) pathologic abnormalities, stroke, narcolepsy, idiopathic CNS hypersomnia; sleep deficiency, sleep apnea, obstructive sleep apnea, insufficient nocturnal sleep, chronic pain, acute pain, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, attention deficit hyperactivity disorder (ADHD), Alzheimer's disorder, major depression, bipolar disorder, cardiac ischemia; misalignments of the body's circadian pacemaker with the environment, jet lag, shift work, or sedating drugs.

In certain embodiments, solriamfetol structure is given below as formula I:

(I)



Methods for producing solriamfetol and related compounds can be found in U.S. Pat. Nos. 10,829,443, 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated by reference in their entireties for all purposes.

In one embodiment, the methods detailed herein provide an infant fed breast milk from a subject to whom solriamfetol is administered does not experience adverse events, e.g., agitation, insomnia, anorexia, or reduced weight gain due to solriamfetol exposure. Monitoring the infant for agitation, insomnia, anorexia, or reduced weight gain can be performed. For example, monitoring and/or detecting weight loss, reduced weight gain, reduction in number of feedings or lessened intake, reduction in volume of milk ingested can be performed. Monitoring increase in agitation and/or insomnia in the infant, including a reduction of sleeping hours and/or time to fall asleep and stay asleep can also be performed to identify changes in the infant. In some embodiments, the monitoring for changes in the infant is performed at 3 or more hours subsequent to administering of the solriamfetol dose and subsequent to initiation of infant feeding with breast milk from the subject, for example at 3 hours, 4, hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours or more subsequent to administering of the solriamfetol dose. Monitoring for any changes experienced by the infant (e.g., agitation, insomnia, anorexia, or reduced weight gain) can be performed over the time period in which solriamfetol is administered to the subject, which may be over days, weeks, or months, with monitoring over any interval in that time frame, including hourly, daily, weekly, monthly or any time range therein.

In one embodiment, the method provides a daily infant dose of solriamfetol of about 0.3 mg or lower, e.g., about 0.29 mg, about 0.28 mg, about 0.27 mg, about 0.26 mg, about 0.25 mg, about 0.24 mg, about 0.23 mg, about 0.22 mg, about 0.21 mg, about 0.20 mg, about 0.19 mg, about 0.18 mg, about 0.17 mg, about 0.16 mg, about 0.15 mg, or lower. The daily infant dose means the daily dose that was received by the infant through feeding of breast milk.

In some embodiments, breast milk for feeding of the infant is expressed or produced from the subject at 3 or more hours, 4 or more hours, or 5 or more hours, for example at 3 hours, 4, hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours or more, subsequent to administering of the solriamfetol dose to the subject. In some embodiments, the breast milk produced from the subject for infant feeding in the methods detailed herein occurs at about the mean elimination half-life of solriamfetol or later, i.e., at about 5 hours, subsequent to administration of the solriamfetol. In some embodiments, the breastfeeding of the infant is performed at 3 or more hours, 4 or more hours, or 5 or more hours subsequent to administering of the solriamfetol dose to the subject. In some embodiments, the breast milk for feeding the infant is obtained from the subject at 3 or more hours, 4 or more hours, or 5 or more hours subsequent to administering of the solriamfetol dose to the subject.

In some embodiments, the method achieves a relative infant dose, the percentage of the weight-adjusted subject dose excreted in breast milk over 24 hours, of less than about 10%, less than about 9.5%, less than about 9%, less than about 8.5%, less than about 8%, less than about 7.5%, less than about 7%, less than about 6.5%, less than about 6%, less than about 5.5%, less than about 5%, less than about 4.9%, less than about 4.8%, less than about 4.7%, less than about 4.6%, less than about 4.5%, less than about 4.4%, less than about 4.3%, less than about 4.2%, less than about 4.1%, or about 4.0% of the subject weight-adjusted dose.

In some embodiments, the average amount of solriamfetol that would be passed to an infant feeding from the breast milk produced by the subject treated with solriamfetol according to the methods disclosed herein is less than about 0.70 mg, about 0.69 mg, about 0.68 mg, about 0.67 mg, about 0.66 mg, about 0.65 mg, about 0.64 mg, about 0.63 mg, about 0.62 mg, about 0.61 mg, about 0.60 mg, or about 0.59 mg over 24 hours.

A daily dose of about 1 to about 2000 mg of solriamfetol or a pharmaceutically acceptable salt thereof may be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 1-1000 mg, e.g., about 20-500 mg, in single or divided doses, is administered. In some embodiments, the daily dose may be about

0.01 to about 150 mg/kg body weight, e.g., about 0.2 to about 18 mg/kg body weight. In some embodiments, the dose contains about 1 mg to about 1000 mg of the drug or any range or value therein, e.g., about 10 mg to about 500 mg, e.g., about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg. For example, in certain such embodiments, the total amount of drug may be selected from about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, or any range therein.

In one embodiment of the invention, solriamfetol is administered to the subject as needed to treat a disorder. The compound can be administered continuously or intermittently. In one embodiment, the compound is administered to the subject more than once a day, e.g., 2, 3, or 4 times per day, or once every 1, 2, 3, 4, 5, 6, or 7 days. In another embodiment, the compound is administered to the subject no more than once a week, e.g., no more than once every two weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or longer. In a further embodiment, the compound is administered using two or more different schedules, e.g., more frequently initially (for example to build up to a certain level, e.g., once a day or more) and then less frequently (e.g., once a week or less). In other embodiments, the compound can be administered by any discontinuous administration regimen. In one example, the compound can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days, or longer. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

In one aspect of the invention, solriamfetol is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Further agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Pat. Nos. 8,952,062 and 9,050,302.

The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. Human subjects include neonates, infants, juveniles, adults, and geriatric subjects. In some embodiments, the subject is postpartum, In some embodiments, the subject is a woman between the ages of 18 and 45 years.

Suitable subjects are generally lactating mammalian subjects. The term "mammal" as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (e.g., rats or mice), etc. The human subject can be a lactating individual who is breastfeeding an infant frequently or on a regular basis. In some embodiments, the human subject is a woman. The woman may be between about 18 and 45 years of age. The term "breastfeeding" may also be referred to as chest-feeding, or grammatical variations thereof, refers to delivering breast milk of the individual directly to an infant, extracting breast milk from the individual using a device and subsequently delivering to an infant, extracting breast milk from the individual using a device and storing the breast milk for a period of time and subsequently delivering the stored breast milk to the infant, or a combination thereof.

The subject of the present disclosure can be in lactation, for example, an individual who is lactating (e.g., producing breast milk), nursing or breastfeeding. The subject can be in lactation after pregnancy, i.e., post-partum, or via induced lactation (e.g., with metoclopramide, oral contraceptives, herbal medications, stimulation via pumping, or any combination thereof.).

In some embodiments, the subject is between 1 day and 24 months postpartum, between about 1 day and 12 months postpartum, or between about 10 days and 12 months postpartum. In some embodiments, the subject expresses mature milk, which typically occurs about 10 to about 30 days (e.g., about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days) postpartum, or about 10 to about 20 days postpartum, or about 10 to about 20 days after beginning of milk expression in induced lactation. Infancy starts at birth and ends around the age of 2 years; accordingly, the infant stage being fed breast milk includes the breastfeeding period.

The subject can be a subject "in need of" the methods of the present invention, e.g., in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing a disorder amenable to treatment with solriamfetol, is suspected of having a disorder amenable to treatment with solriamfetol, and/or is anticipated to experience a disorder amenable to treatment with solriamfetol, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment.

Having described the present invention, the same will be explained in greater detail in the following examples, which are included herein for illustration purposes only, and which are not intended to be limiting to the invention.

EXAMPLES

Example 1. Phase 4 Clinical Trial in Breastfeeding Subjects

A Phase 4, open-label, single-dose study to evaluate the pharmacokinetics (PK) of solriamfetol in the breast milk and plasma of healthy postpartum women following oral administration of a 150 mg solriamfetol tablet.

The study was conducted in 6 healthy adult lactating women who were between 15 and 37 weeks postpartum and were administered a single oral dose of SUNOSI 150 mg. SUNOSI was excreted in breast milk with a milk to plasma AUC ratio of approximately 2:1. The median T_{max} for SUNOSI in breast milk was approximately 1.1 hours, and the mean elimination half-life in breast milk was approximately 5.0 hours. The average amount that would be passed to the infant was estimated to be 0.59 mg over 24 hours,

which is about 4.0% of the maternal dose on a weight-adjusted basis. The data from the lactation study indicate that SUNOSI is transferred to breastmilk in nursing mothers, with the relative infant dose (RID) is approximately 4% of the maternal weight-adjusted dosage. Data to assess the effects of SUNOSI on a breastfed infant or on milk production is not provided. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition. Breastfed infants should be monitored for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

Solriamfetol had a short systemic elimination half-life of 5.0 to 7.6 hours, and with once daily dosing the estimated accumulation ratio of 1.06 was marginally higher than 1, indicating essentially no accumulation with repeated dosing. Therefore, a single therapeutic dose of solriamfetol was administered in this study. Since the objective of this study was to evaluate solriamfetol PK in breast milk and plasma, as well as to estimate the daily drug dose received by the infant from breast milk, the highest approved therapeutic dose of 150 mg solriamfetol was administered.

The subjects were between 10 days and 52 weeks postpartum. The lower time limit of 10 days postpartum represented a time after which mature milk was developed (US FDA 2019). The upper time limit of 52 weeks postpartum was chosen based on a prospective study that showed that fat, total solids, and "energy" (kcal/dL) were all statistically increased in breast milk collected 12 to 18 months postpartum (N=25) compared with breast milk collected 1 to 12 months postpartum (N=35) (Czosnykowska Lukacka 2018). Also, there was a paucity of data regarding breast milk nutrient composition at >12 months postpartum (Wu 2018). The study included frequent maternal milk sample collections during a 72-hour period postdose to enable detection of the potential presence of solriamfetol in breast milk. Plasma concentrations of solriamfetol were also evaluated during the same time period to assess solriamfetol's potential accumulation in breast milk relative to the plasma.

Subjects were instructed to refrain from breastfeeding their infants for 72 hours postdose. Based on the drug's short half-life, this period (10× half-life) was expected to be of sufficient duration for complete elimination of solriamfetol from both the systemic circulation and breast milk.

Pharmacokinetic Results

All subjects in the PK Population were included in the PK analysis. Pharmacokinetic Population was defined as all subjects who received study drug and provided postdose breast milk or plasma PK data for at least one collection interval or time point. Subject 1003, 1004, and 1007 had multiple protocol deviations documented with regards to the timing of food consumption, however, these deviations are not likely to impact solriamfetol PK and these subjects were included in the descriptive statistics or PK parameter analysis. Furthermore, the PK of solriamfetol in fed versus fasted subjects satisfied the criteria for bioequivalence, indicating that solriamfetol can be taken regardless of food intake.

The mean plasma and breast milk solriamfetol concentration time profiles are shown in FIG. **1**. FIG. **1** shows the time course of mean plasma and breast milk solriamfetol concentrations on Day 1 following a single-dose administration of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. After reaching maximum solriamfetol concentrations approximately 1.00 to 3.00 hours after oral administration, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol concentrations in breast milk were approximately 2-fold higher than plasma concentrations

The mean breast milk cumulative solriamfetol amount-time profiles are shown in FIG. **2**. FIG. **2** shows the mean breast milk cumulative solriamfetol amount-time profiles following a single-dose administration of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. Arithmetic mean±SD amount excreted in breast milk over 72 hours was 0.6880±0.4672 mg. However, near complete excretion was observed within 24 hours of dosing.

No subjects had Rsq adjusted values <0.700, or % AUCex>20%, therefore Lambda_z and AUC0-inf related parameters were all considered reliable and included in descriptive statistics.

Table 1 summarizes the plasma and breast milk PK parameters for solriamfetol following single-dose administration.

Solriamfetol exposure was approximately 2-fold higher, on average, in breast milk than plasma with geometric mean C_{max} of 1861 vs 892.5 ng/mL, AUC_{0-t} of 12770 vs 6236 h*ng/ml, and AUC_{0-inf} of 12940 vs 6340 h*ng/ml, respectively. The geometric mean milk:plasma ratio was 2.047.

Plasma solriamfetol t_{max} (from 0.98 to 3.02 hours, median 1.25 hours) was similar to breast milk (from 1.00 to 3.00 hours, median 1.12 hours).

The geometric mean solriamfetol $t_{1/2}$ appear similar between plasma (4.751 hours) and breast milk (4.869 hours). Furthermore, the geometric mean plasma solriamfetol CL/F was 23.66 L/h and V_z/F was 162.2 L. Geometric mean A_{milk} was 0.5651 mg, with a daily and relative infant dose of 0.5856 mg and 4.030%, respectively.

TABLE 1

Summary of Pharmacokinetic Parameters for Solriamfetol in Plasma and Breast Milk (Pharmacokinetic Population)

	Arithmetic Mean (CV %) [Geometric Mean]	
Pharmacokinetic Parameters	Plasma (N = 6)	Breast Milk (N = 6)
AUC_{0-inf} (h * ng/ml)	6543 (27.7) [6340]	13850 (41.0) [12940]
AUC_{0-t} (h * ng/ml)	6439 (27.9) [6236]	13700 (41.4) [12770]
C_{max} (ng/mL)	905.2 (18.0) [892.5]	2068 (48.7) [1861]
t_{max} (h)[a]	1.25 (0.98, 3.02)	1.12 (1.00, 3.00)
Lambda_z (1/h)	0.1478 (19.1) [0.1459]	0.1446 (18.8) [1424]
$t_{1/2}$ (h)	4.804 (15.2) [4.751]	4.954 (21.4) [4.869]
CL/F (L/h)	24.40 (26.8) [23.66]	NC
V_z/F (L)	168.9 (31.9) [162.2]	NC
Milk:Plasma Ratio	NC	2.136 (35.8) [2.047]
A_{milk} (mg)	NC	0.6880 (67.9) [0.5651]
Daily Infant Dose (mg)	NC	0.6927 (63.5) [0.5856]
Relative Infant Dose (%)	NC	4.602 (60.6) [4.030]

NC = not calculated.

Note:

CV % was based on the arithmetic mean.

[a]Median (min, max).

Pharmacokinetic Conclusion

Solriamfetol t_{max} for both plasma and breast milk were similar and ranged between 1 to 3 hours. After reaching maximum solriamfetol concentrations, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol breast milk exposure (C_{max} and AUCs) was 2-fold higher than plasma. Furthermore, the geometric mean milk:plasma ratio was 2.047. The solriamfetol $t_{1/2}$ appeared similar in plasma and breast milk at approximately 5 hours. This study was exclusively in post-partum women, a very different population than the ones for the studies

reported in the Pharmacokinetics section of the current Sunosi® label which were healthy male and female patients who were not postpartum. The Sunosi® label reports oral bioavailability of solriamfetol is approximately 95% with peak plasma concentration of solriamfetol occurs at a median T_{max} of 2 hours (range 1.25 to 3.0 hours) post-dose under fasted conditions healthy male and female patients who were not postpartum. Indeed, while the median T_{max} reported for healthy male and female patients who were not postpartum is reported in the label as 2 hours, the T_{max} in the present lactation study is 1 hour. Similarly, the apparent mean elimination plasma half-life is 7.1 hours for healthy male and female patients who were not postpartum on the Sunosi® label compared to 4.8 hours in plasma and 4.95 hours in breast milk in the present lactation study.

CL/F and were determined for plasma solriamfetol only. Arithmetic mean of CL/F was 24.40 L/h and was 168.9 L. A_{milk}, daily infant dose, and relative infant dose were determined for breast milk solriamfetol only. Arithmetic mean of was 0.6880 mg, daily infant dose was 0.6927 mg, and relative infant dose was 4.602% Safety Results

Adverse Events: The overall summary of Treatment Emergent Adverse Events (TEAEs) is summarized in Table 2. A total of 3 (50%) subjects had at least 1 AE; of 2 (33.3%) subjects had TEAEs related to the study drug and 1 (16.7%) subject had TEAE unrelated to the study drug. The mild TEAEs were reported in 2 (33.3%) subjects and moderate TEAEs were reported in 1 (16.7%) subject. No SAEs were reported in the study. None of the subjects discontinued due to TEAEs.

TABLE 2

Overall Summary of Treatment Emergent Adverse Events (Safety Population)

Category	Solriamfetol 150 mg (N = 6) n (%)
Subjects with at least 1 AE	3 (50.0)
Subjects with an	
AE considered related to study drug	2 (33.3)
AE considered unrelated to study drug	1 (16.7)
Subjects with[a]	
SAE	0
SAE considered related to study drug	0
SAE considered unrelated to study drug	0
Subjects who discontinued due to	
AE	0
AE considered related to study drug	0
AE considered unrelated to study drug	0
Subjects with[a]	
Mild AE	2 (33.3)
Moderate AE	1 (16.7)
Severe AE	0
Life-threatening AE	0
Fatal AE	0

AE = adverse event;

N = number of subjects exposed;

SAE = serious adverse event.

Note:

Percentages are based on N

[a]Subjects reporting an adverse event in more than one category were counted only once for the category.

Out of 3 subjects reporting TEAEs, 1 subject had dizziness and headache (SOC: Nervous system disorder), 1 subject had agitation (SOC: Psychiatric disorder), and 1 subject had an event of headache (SOC: Nervous system disorder) (Table 3). A total of 4 TEAEs were reported where 3 TEAEs (dizziness, headache, and agitation) were mild and 1 TEAE (headache) was moderate in intensity. All the 3 mild TEAEs were related to the study drug and the moderate TEAE was unrelated to the study drug. All the TEAEs were resolved.

TABLE 3

Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term (Safety Population)

System Organ Class (SOC) Preferred Term (PT)	Solriamfetol 150 mg (N = 6) n (%)
Nervous system disorders	2 (33.3)
Dizziness	1 (16.7)
Headache	2 (33.3)
Psychiatric disorders	1 (16.7)
Agitation	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

A subject with multiple adverse events within a primary system organ class was counted only once.

A subject with multiple occurrences of an AE was counted only once in the AE category

System organ classes are presented in alphabetical order; preferred terms are presented within system organ class in alphabetical order

Adverse events were coded using the MedDRA coding dictionary, MedDRA180 Mixed

Vital Signs: There were no major changes in vital sign parameters from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4. The summary of clinically notable vital signs at any post-baseline visit are summarized in Table 4.

TABLE 4

Summary of Clinically Notable Vital Signs at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
Systolic blood pressure (mmHg)	Blood pressure change by >20% from the study baseline value/recordings	1 (16.7)
Diastolic blood pressure (mmHg)	Average diastolic blood pressure ≥95 mmHg or ≤60 mmHg	2 (33.3)
Pulse rate (beats/min)	Pulse change by >20% from the study baseline value/recordings	2 (33.3)
Body temperature (C.)	Change in body temperature >1.8% from the subjects baseline temperature recordings	1 (16.7)

N = number of subjects exposed.

Notes:

Percentages are based on N.

Baseline was defined as the last non-missing measurement taken prior to dosing. All post-baseline assessments, including unscheduled, were considered for this summary.

There were no major changes in ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. No abnormal clinically significant ECG findings were reported.

The summary of clinically notable ECG findings at any post-baseline visit are summarized in Table 5.

TABLE 5

Summary of Clinically Notable Electrocardiograms at Any Post-baseline Visit/Timepoint (Safety Population)

Parameter (Unit)	Criteria	Solriamfetol 150 mg (N = 6) n (%)
ECG mean heart rate (bpm)	Ventricular rate ≥100 beats/min or ≤60 beats/min	2 (33.3)
PR interval, single beat (msec)	PR interval ≥200 msec or ≤120 msec	2 (33.3)
QRS duration, single beat (msec)	QRS duration ≥100 msec or ≤80 msec	4 (66.7)
QT interval, single beat (msec)	QT interval ≥440 msec or ≤350 msec	1 (16.7)

N = number of subjects exposed.
Notes:
Percentages are based on N.
Baseline was defined as the last non-missing measurement taken prior to dosing. All post-baseline assessments, including unscheduled, were considered for this summary.

None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

Safety Conclusions

Overall, 6 subjects were enrolled in the safety analysis and treated with the single oral dose of Solriamfetol which was safe and well tolerated.

Out of 6 subject 3 (50%) subjects had at least 1 AE. Out of 3 subjects reporting TEAEs: 1 subject had dizziness and headache (SOC: Nervous system disorder) both of mild intensity and were related to study drug; 1 subject had agitation (SOC: Psychiatric disorder) of mild intensity and was related to study drug; 1 subject had an event of headache (SOC: Nervous system disorder) of moderate intensity and was not related to study drug. No SAEs, deaths, or other significant AEs were reported in the study. None of the subjects discontinued due to TEAEs. None of the subjects had abnormal, clinically significant laboratory findings. There were no major changes in vital sign from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4 and ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

DISCUSSION

The instant study was a Phase 4, open-label, single-dose study to evaluate the PK of solriamfetol in the breast milk and plasma of healthy postpartum women following oral administration of a 150 mg solriamfetol tablet. A total of 6 subjects were enrolled and were included in both PK and safety analysis. All the 6 subjects had completed the study. There were no premature discontinuations reported in the study.

The primary objective (PK) of this study was to assess the PK of solriamfetol in plasma and breast milk after single oral dose of solriamfetol 150 mg tablet in the morning 2 hours after completion of a light breakfast. Solriamfetol exposure was approximately 2-fold higher, on average, in breast milk than plasma with geometric mean C_{max} of 1861 vs 892.5 ng/ml, AUC_{0-t} of 12770 vs 6236 h*ng/ml, and AUC_{0-inf} of 12940 vs 6340 h*ng/ml, respectively. The geometric mean milk:plasma ratio was 2.047. Plasma solriamfetol t_{max} (from 0.98 to 3.02 h, median 1.25 h) was similar to breast milk (from 1.00 to 3.00 hours, median 1.12 hours). The geometric mean solriamfetol $t_{1/2}$ appeared similar between plasma

(4.751 hours) and breast milk (4.869 hours). Furthermore, the geometric mean plasma solriamfetol CL/F was 23.66 L/h and V_z/F was 162.2 L. Geometric mean A_{milk} was 0.5651 mg, with a daily and relative infant dose of 0.5856 mg and 4.030%, respectively.

The secondary objective of study was to assess the safety and tolerability of the solriamfetol in healthy postpartum women. Overall, the study drug was safe and well tolerated. No SAEs, deaths, or other significant AEs were reported in the study. None of the subjects discontinued due to TEAEs. Out of 6 subjects, 3 subjects reported adverse events. All AE (dizziness, headache, and agitation) were of mild intensity except 1 AE (headache) was of moderate intensity.

None of the subjects had abnormal or clinically significant laboratory findings. There were no major changes in vital sign from baseline to Day 1 2 hours and 4 hours, Day 2, Day 3, and Day 4 and ECG parameters from baseline to Day 1 predose and 2 hours, Day 2, Day 3, and Day 4. None of the subjects had reported any suicidal ideation or event under Columbia-Classification Algorithm for Suicide Assessment.

CONCLUSION

Solriamfetol T_{max} for both plasma and breast milk were similar and ranged between 1 to 3 hours. After reaching maximum solriamfetol concentrations, plasma and breast milk exposures followed a parallel monoexponential decline. Solriamfetol breast milk exposure (C_{max}, AUCs) was 2-fold higher than plasma. Furthermore, the geometric mean milk:plasma ratio was 2.047. Solriamfetol $t_{1/2}$ appeared similar in plasma and breast milk at approximately 5 hours. Solriamfetol was safe and well tolerated.

METHODOLOGY

On Day −1, eligible subjects underwent the baseline procedures. On Day 1, 2 hours after a light breakfast, subjects were to receive a single dose of solriamfetol 150 mg with 240 mL of water. Subjects had to fast for approximately 4 hours after the first dose; water was allowed except for 1 hour before and 1 hour after dosing with the study drug.

Pharmacokinetic analysis of breast milk obtained from both breasts (by pumping) was evaluated prior to dose administration and at intervals up to 72 hours postdose. Blood samples were also collected for plasma solriamfetol quantitation and PK analysis predose and at timepoints up to 72 hours postdose. Solriamfetol breast milk and plasma concentrations were measured using validated bioanalytical methods. Safety was assessed throughout the study by 12-lead ECG, vital sign measurements, the Columbia-Suicide Severity Rating Scale (C-SSRS), and the incidence of adverse events (AE).

The study drug was yellow, film-coated tablets that contained the excipients hydroxypropyl cellulose and magnesium stearate and a polymer film coat (Opadry®).

The total overall study duration (first subject screened to safety follow-up of last subject) was approximately 11 months.

Vital signs (blood pressure, pulse rate, temperature, and respiratory rate) were measured with the subject in a seated or supine position and resting for at least 5 minutes prior to taking the measurement. The dominant arm was used for blood pressure and pulse rate measurements. On Day 1, vital signs were collected at predose, and at approximately 2 (blood pressure and pulse) and 4 hours (blood pressure and pulse) postdose.

12-lead ECG was taken with the subject in a supine position and resting for at least 10 minutes prior to taking the measurement. On Day 1, ECGs were collected predose and at approximately 2 hours postdose.

Subjects must fast for at least 8 hours before chemistry and hematology blood draws. All clinical laboratory tests were performed at Screening only (rescreening is permitted).

Screening/Baseline C-SSRS version at Screening, and since Last Visit version on Day −1 and Day 2 (or at ET).

Breast milk collection occurred at −2 to 0 (prior to dose), 0-2, 2-4, 4-8, 8-12, 12-18, 24-32, 32-40, 40-48 and 48-72 hours postdose on Days 1-4.

Blood samples for plasma PK evaluation were collected at the following time points: Predose, 1, 1.5, 3, 6, 8.5, 10, 13, 15, 21, 24, 28, 36, 44, and 72 hours following dosing on Day 1. General study methodology is outlined in Table 6.

TABLE 6

Screening	Check-in (Baseline)	Study drug dosing	Check-out	Safety Follow-up	Lactation Follow-up
	---------PK sampling---------				
Days −21 to −2	Day −1	Day 1	Day 4	Days 9-11	Days 39-41

Standardized meals include meals as needed on Day −1, a light breakfast approximately 2.5 hours before dosing on Day 1 (to be completed approximately 2 hours before dosing) followed by lunch approximately 4 hours after dosing, dinner approximately 8 hours after dosing, and a snack approximately 11 hours after dosing, and standardized meals thereafter.

Record was from 30 days prior to screening through the Safety Follow Up telephone call 5 to 7 days after check-out from the study facility (at Day 4 or ET).

Adverse events were monitored throughout the study by safety assessments, observations, and subject reporting, including the Safety FU telephone call 5-7 days (i.e., Days 9-11) after check-out from the study facility on Day 4, or ET.

Breast milk collection: Solriamfetol concentration in breast milk and plasma was evaluated based on samples collected prior to and postdose on Days 1 to 4. Breast milk was collected from both breasts, using electronic breast pumps, during the following intervals: From −2 to 0 at predose and at 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 18, 18 to 24, 24 to 32, 32 to 40, 40 to 48, and 48 to 72 hours postdose on Day 1. The midpoint of each breast milk collection interval was used as the time variable.

Breast milk was collected as often as needed during the assigned intervals; however, at the end of each interval, breast milk was pumped from both breasts and collected. At the end of each collection interval, all milk expressed from both breasts during that interval was pooled. The milk was thoroughly mixed by gently inverting the collection vessel 10 times to ensure homogeneity in milk composition. The weight and volume of the collected milk during each interval was also recorded.

Serial blood samples (4 mL) were collected and dispensed into labeled K2EDTA tubes. The actual time of blood collection for all samples was recorded on the eCRF. Solriamfetol concentration in breast milk and plasma were determined using a validated bioanalytical method (LC-MS/MS) at Origin Bioanalytical Laboratory. The analytical range (lower limit of quantitation [LLOQ] to upper limit of quantitation) for plasma solriamfetol was 8.42 to 4210.00 ng/mL, and breast milk solriamfetol was 10.0 to 8000 ng/mL.

Pharmacokinetic parameters were derived with Phoenix® WinNonlin® Version 8.3 (Certara, Inc., Princeton, New Jersey, USA) and/or SAS® Version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Criteria for Subjects: Each subject who met the following criteria were enrolled in the study: Healthy adult female 18 to 50 years of age, inclusive, at the time of consent; At least 50 kg body weight and body mass index (BMI) within 18 to 35 kg/m^2 inclusive; Postpartum between 10 days and 52 weeks, inclusive, after delivery of a normal, healthy infant by the time of dosing, and actively lactating from both breasts; If breastfeeding, agreed to withhold breastfeeding their infant(s) from approximately 2 hours before dosing to approximately 72-hours after dosing and resumed breastfeeding after completion of study Day 4 procedures or would have made a decision to wean their infants before enrollment in the study; Agreed not to use nicotine-containing products including tobacco (cigarettes, cigars, chewing tobacco, snuff), e-cigarettes, and nicotine lozenge/gum/patch within 3 days prior to check-in on Day −1, and for the duration of the study; Had used a medically acceptable method of contraception for at least the 2 months prior to dosing on Day 1, and consented to use a medically acceptable method of contraception throughout the entire study period and for 30 days after the study was completed; Agreed to comply with study-specified diet while in the study; Able to understand and comply with study requirements; Ensured that their breastfed infant(s) was able to feed from a bottle before study participation begins; Agreed to ensure nutrition was available for their infant(s) through stored breast milk, or alternative nutritional sources as necessary, for the duration of the study; Participants who: Were fully vaccinated for at least 14 days after the last (or only) dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 [COVID-19]) vaccine; or Elected not to be vaccinated prior to the study, with Participant who chooses not to be fully vaccinated prior to the start of the study did not receive any dose of the COVID-19 vaccine and remained on the study.

Clinical laboratory tests including hematology, serum chemistry, urinalysis. and thyroid panel, were collected at Screening only.

A complete physical examination included, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight were also measured and recorded. At Screening and Baseline/Randomization visits, BMI was calculated by the site in order to verify eligibility.

Vital signs included oral temperature, pulse rate, respiratory rate, and BP. Clinically significant abnormal vital signs results reported during Screening/Randomization were recorded as medical history and those reported after study drug were recorded as AEs.

Blood pressure and pulse measurements were assessed with the subject in a seated or supine position and resting for at least 5 minutes prior to taking the measurement. The dominant arm was used for blood pressure and pulse rate measurements. On Day 1, vital signs were collected at predose, and at approximately 2 (blood pressure and pulse) and 4 hours (blood pressure and pulse) postdose.

The 12-lead ECGs were collected at Screening, Day −1 until Day 4. Single 12-lead ECG was obtained using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT, and corrected QT interval (QTc)

intervals. Any abnormal safety assessments including ECG readings considered clinically significant in the medical and scientific judgment of the investigator were reported as an AE. The investigator had to review the ECG and document it in the source documents. Clinically significant abnormal ECG results reported during Screening were recorded as medical history and those reported after study drug were recorded as AEs.

All laboratory tests were to be performed in accordance with Laboratory Manual. The tests detailed in Table 7 were performed by the central laboratory. Additional tests might be performed at any time during the study as determined necessary by the investigator or required by local regulations.

All laboratory tests with abnormal values considered clinically significant during the study or within 14 days after the last dose of study drug (and considered by the investigator to be related to study drug) were repeated until the values return to normal or Baseline or were no longer considered clinically significant by the investigator or medical monitor. If clinically significant values did not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology were to be identified.

TABLE 7

Safety Laboratory Test	
Hematology:	Serum Chemistry:
Complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential (absolute count and percent)	Albumin (ALB)
Urinalysis:	Alkaline phosphatase (ALK-P)
Appearance	Alanine aminotransferase (ALT)
Bilirubin	Aspartate aminotransferase (AST)
Color	Blood urea nitrogen (BUN)
Glucose	Calcium (Ca)
Ketones	Carbon dioxide (CO2)
Nitrite	Chloride (Cl)
Occult blood	Creatinine
pH	Creatine kinase
Protein	Glucose
Specific gravity	Phosphorus
Urobilinogen	Potassium (K)
Leukocyte esterase	Sodium (Na)
	Total bilirubin
	Direct bilirubin
	Total cholesterol
	Total protein
	Triglycerides
	Uric acid
Drug Screening:	Pregnancy*:
Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opiates, phencyclidine)	Serum at Screening
Breath alcohol test	Urine at Baseline (Day -1)

ALB = albumin;
ALK-P = alkaline phosphatase;
ALT = alanine aminotransferase;
AST = aspartate aminotransferase;
BUN = blood urea nitrogen;
Ca = calcium;
CBC = complete blood count;
CO2—carbon dioxide;
Cl = chlorine;
K = potassium;
Na = sodium;
WBC = white blood cell count.
*Pregnancy screening required for all subjects in the study.

Statistical/Analytical

Unless otherwise specified, continuous data was summarized using descriptive statistics comprising of the number of subjects exposed (N) and with data to be summarized (n), mean, standard deviation (SD), median, minimum (min), maximum (max), geometric mean (Geo-mean), coefficient of variation (CV %), and geometric coefficient of variation (CV %). Categorical variables were presented using counts and percentages. Analyses and summary outputs were generated using SAS® Version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

The PK Population consisted of all subjects who received study drug and provided postdose breast milk or plasma PK data for at least one collection interval or time point. This population was used for evaluable PK concentration data and PK parameter summaries and listings. The Safety Population consisted of all subjects who received the dose of study drug. This population was used for demographic and baseline characteristics and for safety data summaries and listings.

Pharmacokinetic concentrations and parameters were summarized using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (CV %), median, min, max, Geometric mean (Geo-mean) and the geometric coefficient of variation (Geo-CV %). For the PK parameter t_{max}, only n, median, minimum, and maximum was presented.

Subjects with partial data were evaluated on a case-by-case basis to determine if sufficient data was available for reliable calculation of PK parameters. In case of an incomplete milk collection (partial/spilt sample with inaccurate information of the total milk volume of the by-interval samples), the by-interval recovery was listed but not included in the summary, and cumulative recovery was only reported through the most recent prior complete milk collection. By-interval data during which a subject was unable to lactate (produce any milk), was treated as an amount of zero (for the affected interval) in the summation of cumulative recovery calculation.

Plasma and milk concentrations were summarized using descriptive statistics. Concentrations that were below the lower limit of quantitation (BLQ) were treated as follows for the computation of descriptive statistics:

The summary statistics at a time with one or more BLQ values were calculated by assigning ½ LLOQ to all values less than LLOQ. If the calculated arithmetic (and geometric) mean value was BLQ, then SD and CV % were presented as "ND.", and the mean was presented as "BLQ. However, since a high proportion of BLQ values may have affected the SD; if more than 50% of values were imputed, then no mean was calculated for that time point and again a value of BLQ was presented only for the mean value. Within the summary statistics, any minimum, or median values that were calculated to be BLQ were presented as BLQ within the summary presentation.

Concentrations collected outside of the protocol allowed sampling windows were included in descriptive statistics, unless the PK scientist observed that the deviation was substantial enough to impact descriptive statistics. In this case, the excluded concentrations were identified in the CSR.

For plotting arithmetic mean concentration profiles: The arithmetic mean value at a time with one or more BLQ values were calculated by assigning ½ LLOQ to all values BLQ. If the calculated mean value was BLQ, then that time point was plotted as zero in the mean pharmacokinetic profiles. However, since a high proportion of BLQ values may have affected the SD; if more than 50% of values were imputed, then no mean was calculated for that time point and again a value of zero plotted. A line with a label of LLOQ in the concentration axis was overlaid to show the level of LLOQ.

Safety analyses were based on the Safety Population. The secondary endpoints for evaluating subject safety and tolerance were the incidence of reported AEs and the laboratory test results for all subjects.

Adverse events: Adverse events recorded in the electronic case report forms (eCRFs) were coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as any event with onset date on or after the first dose of study drug or any ongoing event that worsened in severity after the date of the first dose of study drug or any event that was present at baseline but was subsequently considered drug-related by the investigator through the end of the study. The incidence of TEAEs were presented by severity, relationship to study drug, start and end date, seriousness, and outcome. The investigator assessed the severity and relatedness of each AE to study drug. Columbia-Suicide Severity Rating Scale (C-SSRS) data were summarized at scheduled visits and were listed. Other safety analyses were performed as appropriate.

12 Lead ECG: The number and percentage of subjects who had the following postbaseline clinically notable ECG interval abnormality was summarized: Ventricular rate≥100 beats/min or ≤60 beats/min; PR interval≥200 msec or ≤120 msec; QRS duration≥100 msec or ≤80 msec; QT interval≥440 msec or ≤350 msec; QTc Bazett and QTc Fredericia≥470 msec or ≤330 msec; RR interval≥1200 msec or ≤600 msec; and QTc Bazette and QTc Fredericia increase from study Baseline Value>30 msec.

Vital Signs: The following clinically notable vital sign abnormalities were presented: Average systolic blood pressure≥150 mmHg or ≤80 mmHg; Average diastolic blood pressure≥95 mmHg or ≤60 mmHg; Average heart rate≥120 bpm or ≤50 bpm; Respiratory rate<10 breaths/min or >24 breaths/min; Body temperature>37.9° C. or <35.5° C.; Systolic and diastolic blood pressure change by >20% from the study baseline value/recordings; Pulse change by >20% from the study baseline value/recordings; Change in body weight by ≥7% from subject's baseline value (weight loss/weight gain); and Change in body temperature>1.8% from the subject's baseline temperature recordings.

Physical Examination: Physical examination data for each subject was presented in a listing. A clinically significant adverse change (i.e., worsening) of a physical examination finding after screening was recorded as an AE.

Disposition of Subjects. A total of 6 subjects were enrolled and treated in the study. All 6 subjects had completed the study. There were no premature discontinuations reported in the study. All 6 subjects received the study drug (safety population) and provided post-dose breast milk or plasma PK data for at least one collection interval or time point (PK population). All 6 subjects were females and belonged to not Hispanic or Latino ethnicity. The mean (SD) of age, weight, height, and BMI of the overall population was 28.7 (5.54) years, 79.15 (12.162) kg, 168.62 (6.013) cm, and 27.90 (4.513) kg/m^2, respectively.

TABLE 8

Demographics and Baseline Characteristics (Safety Population)

Characteristic	Solriamfetol 150 mg (N = 6)
Age (years)	
n	6
Mean (SD)	28.7 (5.54)
Median	29.5
Min, Max	21, 35
Gender, n (%)	
Female	6 (100%)
Missing	0
Race, n (%)	
White	3 (50.0)
Black or African American	3 (50.0)
Missing	0
Ethnicity, n (%)	
Not Hispanic or Latino	6 (100%)
Missing	0
Height (cm)	
n	6
Mean (SD)	168.62 (6.013)
Median	170.00
Min, Max	160.0, 177.5
Weight (kg)	
n	6
Mean (SD)	79.15 (12.162)
Median	77.90
Min, Max	64.1, 99.1
BMI (kg/m^2)	
n	6
Mean (SD)	27.90 (4.513)
Median	27.95
Min, Max	22.4, 34.3

BMI = body mass index;
N = number of subjects exposed
Note:
Percentages are based on N.

TABLE 8-continued

Demographics and Baseline Characteristics (Safety Population)

Prior and Concomitant Medication: Two subjects had taken medications during the study for AEs. One subject received acetaminophen and other received ibuprofen.

Medical and Surgical History: A total of 5 of 6 subjects had the medical and surgical history. Of these subjects, 1 subject had the medical history of appendectomy, C-section, and tubal ligation. One subject had asthma and C-section. One subject had cholelithiasis, pancreatitis, and gall bladder removal. One subject had umbilical hernia repair, heartburn, and C-section, and 1 subject had natural childbirth and hip pain dur to natural childbirth.

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The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

What is claimed is:

1. A method of reducing the risk of insomnia in an infant fed breast milk obtained from a subject treated with solriamfetol, wherein the method provides a daily infant dose of solriamfetol of about 0.3 mg or lower, the method comprising:

orally administering the solriamfetol to the subject at a daily dose of about 150 mg; and

feeding the infant breast milk obtained from the subject at least about 5 hours after administering the solriamfetol to the subject;

thereby decreasing the potential for insomnia from solriamfetol in the infant.

2. The method of claim **1**, wherein the infant does not experience insomnia due to solriamfetol dose.

3. The method of claim **1**, wherein the subject is from 1 day to 24 months postpartum.

4. The method of claim **1**, wherein the subject is from 10 days to 12 months postpartum.

5. The method of claim **1**, wherein the subject is being treated with solriamfetol for excessive daytime sleepiness, narcolepsy, obstructive sleep apnea, shift work disorder, attention deficit hyperactivity disorder, depression, binge eating disorder, Parkinson's disease, or cognitive impairment.

6. The method of claim **5**, wherein the excessive daytime sleepiness is associated with narcolepsy, obstructive sleep apnea, shift work, major depression, or Parkinson's disease.

7. The method of claim **5**, wherein the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, Parkinson's disease, or attention deficit hyperactivity disorder.

8. The method of claim **1**, wherein the subject is being treated with solriamfetol to improve wakefulness.

9. The method of claim **1**, wherein the subject is a woman between the ages of 18 and 50 years.

10. A method of reducing the risk of insomnia in an infant fed breast milk obtained from a subject treated with solriamfetol, wherein the method provides a daily infant dose of solriamfetol of about 0.15 mg or lower, the method comprising:

orally administering the solriamfetol to the subject at a daily dose of about 75 mg; and

feeding the infant breast milk obtained from the subject at least about 5 hours after administering the solriamfetol to the subject;

thereby decreasing the potential for insomnia from solriamfetol in the infant.

11. The method of claim **10**, wherein the infant does not experience insomnia due to solriamfetol dose.

12. The method of claim **10**, wherein the subject is from 1 day to 24 months postpartum.

13. The method of claim **10**, wherein the subject is from 10 days to 12 months postpartum.

14. The method of claim **10**, wherein the subject is being treated with solriamfetol for excessive daytime sleepiness, narcolepsy, obstructive sleep apnea, shift work disorder, attention deficit hyperactivity disorder, depression, binge eating disorder, Parkinson's disease, or cognitive impairment.

15. The method of claim **14**, wherein the excessive daytime sleepiness is associated with narcolepsy, obstructive sleep apnea, shift work, major depression, or Parkinson's disease.

16. The method of claim **14**, wherein the cognitive impairment is associated with narcolepsy, obstructive sleep apnea, shift work, Parkinson's disease, or attention deficit hyperactivity disorder.

17. The method of claim **10**, wherein the subject is being treated with solriamfetol to improve wakefulness.

18. The method of claim **10**, wherein the subject is a woman between the ages of 18 and 50 years.

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