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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS RESEARCH UK LIMITED (f/k/a GW RESEARCH LIMITED), **Plaintiff,** **v.** **APOTEX INC., INVAGEN PHARMACEUTICALS, INC., CIPLA LTD., CIPLA USA, INC., API PHARMA TECH LLC, LUPIN LTD., TARO PHARMACEUTICAL INDUSTRIES LTD., ASCENT PHARMACEUTICALS, INC., ZENARA PHARMA PRIVATE LTD., and BIOPHORE PHARMA, INC.,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Jazz Pharmaceuticals Research UK Limited ("Jazz"), formerly known as GW Research Limited, by its undersigned attorneys, for its Complaint against defendants Apotex Inc. ("Apotex"), InvaGen Pharmaceuticals, Inc. ("InvaGen"), Cipla Ltd., Cipla USA, Inc. ("Cipla USA") (Cipla Ltd. and Cipla USA, together, "Cipla"), API Pharma Tech LLC ("API Pharma"), Lupin Ltd. ("Lupin"), Taro Pharmaceutical Industries Ltd. ("Taro"), Ascent Pharmaceuticals,

Inc. ("Ascent"), and Zenara Pharma Private Ltd. ("Zenara"), and Biophore Pharma, Inc. ("Biophore") (Apotex, InvaGen, Cipla, API Pharma, Lupin, Taro, Ascent, Zenara, and Biophore, collectively, "Defendants"), alleges 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 the Defendants' filing of their respective Abbreviated New Drug Applications ("ANDAs") Nos. 217699 ("Apotex's ANDA"), 217522 ("InvaGen's ANDA"), 217871 ("Lupin's ANDA"), 217930 ("Taro's ANDA"), 217994 ("Ascent's ANDA"), and 217910 ("Biophore's and Zenara's ANDA"), with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of Jazz's cannabidiol oral solution drug product prior to the expiration of United States Patent No. 11,963,937 ("the '937 patent"), owned by Jazz.

The Parties

2. Plaintiff Jazz is a biopharmaceutical company focused on discovering, developing, and commercializing novel therapeutics from its proprietary cannabinoid product platform in a broad range of disease areas. One such product, Epidiolex® (cannabidiol) oral solution, is approved in patients one-year and older for the treatment of seizures associated with Lennox-Gastaut Syndrome ("LGS"), Dravet Syndrome ("DS"), and Tuberous Sclerosis Complex ("TSC"), all of which are rare diseases characterized by severe early-onset epilepsy. Epidiolex® is the first and only plant-derived cannabinoid medicine approved by the FDA.

3. Jazz is a corporation existing under the laws of the United Kingdom, having a principal place of business in Cambridge, UK.

4. On information and belief, Apotex is a corporation organized and existing under the laws of Canada, having a principal place of business at 150 Signet Drive, Toronto, Ontario, M9L 1T9 Canada.

5. On information and belief, InvaGen is a corporation organized and existing under the laws of New York, having a principal place of business at 7 Oser Avenue, Hauppauge, New York 11788. On further information and belief, InvaGen is an indirect, 100% wholly owned subsidiary of Cipla Ltd.

6. On information and belief, Cipla Ltd. is a corporation organized and existing under the laws of India, having a principal place of business at Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, 400 013, India.

7. On information and belief, Cipla USA is a corporation organized and existing under the laws of Delaware, having a principal place of business at 10 Independence Boulevard, Suite 300, Warren, New Jersey 07059. On further information and belief, Cipla USA is a 100% fully owned subsidiary of InvaGen.

8. On information and belief, API Pharma is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 7 Deer Park Drive, Suite M1, Princeton Corporate Plaza, Monmouth Junction, New Jersey 08852.

9. On information and belief, Lupin is a corporation organized and existing under the laws of India, having a principal place of business at B/4 Laxmi Towers, Bandra Kurla Complex, Bandra (E), Mumbai, 400 051, India.

10. On information and belief, Taro is a corporation organized and existing under the laws of Israel, having a principal place of business at 14 Hakitor Street, Haifa Bay 26247, Israel.

11. On information and belief, Ascent is a corporation organized and existing under the laws of New York, having a principal place of business at 400 South Technology Drive, Central Islip, New York.

12. On information and belief, Zenara is a corporation organized and existing under the laws of India, having a principal place of business at Plot No. 83/B, 84 & 87-96, Phase III, IDA Cherlapally, Hyderabad 500051, India.

13. On information and belief, Biophore is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 1 Deerpark Drive, Suite F8, Monmouth Junction, NJ 08852.

The Patent-in-Suit

14. On April 23, 2024, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '937 patent, entitled "Use of Cannabinoids in the Treatment of Epilepsy" to Jazz as assignee. The face of the '937 patent identifies Geoffrey Guy, Stephen Wright, and Orrin Devinsky as the inventors. A copy of the '937 patent is attached hereto as Exhibit A.

The Epidiolex® Drug Product

15. Jazz 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 cannabidiol 100 mg/mL oral solution ("NDA No. 210365"), which is sold under the trade name Epidiolex®. Epidiolex® is approved in patients one year of age and older for the treatment of seizures associated with LGS, DS, or TSC, all of which are rare diseases characterized by severe early-onset epilepsy. Epidiolex® is the first and only plant-derived cannabinoid medicine approved by the FDA. The claims of the '937 patent cover, *inter alia*, cannabidiol pharmaceutical compositions and methods of using Epidiolex® to treat LGS and/or DS.

16. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '937 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Epidiolex®.

Jurisdiction and Venue: Apotex

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

18. As set forth in Paragraphs 19-23 below, the Court has personal jurisdiction over Apotex by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

20. On information and belief, Apotex 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.

21. On information and belief, this Judicial District will be a destination for the generic version of Jazz's cannabidiol oral solution drug product for which Apotex seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 217699 ("Apotex's Proposed Product").

22. Apotex has consented to personal jurisdiction in this Court in numerous recent actions arising out of its ANDA filings and has filed counterclaims in such cases. *See, e.g., Amgen Inc. v. Apotex Inc.*, No. 22-cv-03827 (D.N.J.); *Supernus Pharms., Inc. v. Apotex Inc. et al.*, No. 20-cv-07870 (D.N.J.); *Boehringer Ingelheim Pharms., Inc. et al. v. Apotex Inc. et al.*, No. 18-cv-11350 (D.N.J.); *Pantheon Softgels Inc. et al. v. Apotex Inc. et al.*, No. 17-cv-13819 (D.N.J.); *Merck Sharp & Dohme Corp. v. Apotex Inc. et al.*, No. 17-cv-5399 (D.N.J.); *Dexcel*

Pharma Techs. Ltd. et al. v. Apotex Corp. et al., No. 17-cv-2423 (D.N.J.). Apotex has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

23. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, Apotex's Proposed Product, and Apotex's ANDA, Apotex did not contest personal jurisdiction or venue.

24. In the alternative, this Court has personal jurisdiction over Apotex because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Jazz's claims arise under federal law; (b) Apotex is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Apotex 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 Apotex satisfies due process.

25. At least because, on information and belief, Apotex is a foreign company, venue is proper in this Judicial District pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Jurisdiction and Venue: InvaGen, Cipla, and API Pharma

26. This Court has jurisdiction over the subject matter of Count II against InvaGen, Cipla, and API Pharma pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

27. As set forth in Paragraphs 28-38 below, the Court has personal jurisdiction over InvaGen by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

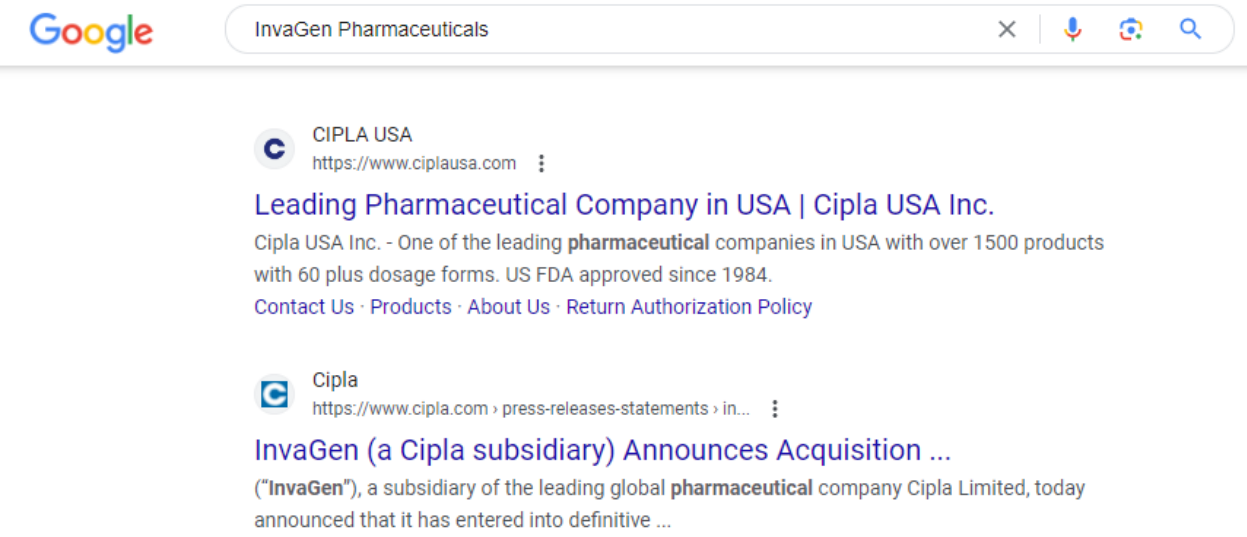
28. On information and belief, InvaGen, alone or in concert with Cipla Ltd. and/or Cipla USA, purposefully has conducted and continues to conduct business in this Judicial District.

29. On information and belief, InvaGen 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.

30. On information and belief, this Judicial District will be a destination for the generic version of Jazz's cannabidiol oral solution drug product for which InvaGen seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 217522 ("InvaGen's Proposed Product").

31. On information and belief, InvaGen will work in concert with API Pharma, Cipla Ltd., and/or Cipla USA toward the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including InvaGen's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the '937 patent.

32. On information and belief, InvaGen conducts business in this Judicial District through its wholly owned subsidiary, Cipla USA. On information and belief, InvaGen does not maintain its own website. Potential customers who search the internet for "InvaGen Pharmaceuticals" are instead directed to the webpage of Cipla USA:



33. In recent filings with the Patent Trial and Appeal Board, InvaGen represented that it "has a 100% fully owned subsidiary named Cipla USA Inc.," and that Cipla USA was a "real party-in-interest" to InvaGen's Petition for Inter Partes Review. *See* Petition for Inter Partes Review of U.S. Patent No. 10,828,310, *InvaGen Pharmaceuticals, Inc. v. Bayer Pharma*, Case IPR2022-01515 (P.T.A.B. Sept. 8, 2022).

34. On information and belief, Cipla USA acts at the direction, and for the benefit, of InvaGen, and is an agent / alter ego of InvaGen.

35. On information and belief, InvaGen 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. 0450360045.

36. InvaGen has consented to personal jurisdiction in this Court in recent actions arising out of its ANDA filings and has filed counterclaims in such cases. *See, e.g.*, *Sumitomo Dainippon Pharma Co., Ltd. v. Aurobindo Pharma Ltd. et al.*, No. 18-cv-2620 (D.N.J.). InvaGen has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

37. Further, InvaGen has previously submitted to the jurisdiction of this Court and has availed itself of the legal protections of the State of New Jersey, having previously transferred a case into this Judicial District by stating that "personal jurisdiction exists in New Jersey over both InvaGen and [its co-defendant]." *Roxane Labs., Inc. v. Camber Pharms., Inc.*, No. 14-cv-4042, ECF No. 28 at 18 (D.N.J. Apr. 4, 2014).

38. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, InvaGen's ANDA, and InvaGen's Proposed Product, InvaGen stipulated that it would not contest personal jurisdiction or venue. *See id.* at ECF No. 45.

39. For at least the foregoing reasons set forth above in Paragraphs 28-38, venue is proper in this Judicial District with respect to InvaGen pursuant to 28 U.S.C. § 1400(b).

40. As set forth in Paragraphs 41-47 below, the Court has personal jurisdiction over Cipla USA by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

41. On information and belief, Cipla USA, alone or at the direction of Cipla Ltd. and/or InvaGen, purposefully has conducted and continues to conduct business in this Judicial District.

42. On information and belief, Cipla USA, 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.

43. On information and belief, Cipla USA will work in concert with API Pharma, Cipla Ltd., and/or InvaGen toward the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including

InvaGen's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the '937 patent.

44. On information and belief, Cipla USA maintains a physical place of business in this Judicial District, in at least Warren, New Jersey. *See* https://www.ciplausa.com/about-us (last visited, June 20, 2024).

45. On information and belief, Cipla USA 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. 0450318628.

46. On information and belief, Cipla USA is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler operating in New Jersey under the registration number 5005183.

47. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), Cipla USA stipulated that it would not contest personal jurisdiction or venue. *See id.* at ECF No. 45.

48. For at least the foregoing reasons set forth above in Paragraphs 41-47, venue is proper in this Judicial District with respect to Cipla USA pursuant to 28 U.S.C. § 1400(b).

49. As set forth in Paragraphs 50-59 below, the Court has personal jurisdiction over Cipla Ltd. by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

50. On information and belief, Cipla Ltd., alone or through its indirect, wholly owned subsidiaries Cipla USA and InvaGen, purposefully has conducted and continues to conduct business in this Judicial District.

51. On information and belief, Cipla Ltd., alone or through its indirect, wholly owned subsidiaries Cipla USA and InvaGen, 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.

52. On information and belief, Cipla Ltd. will work in concert with API Pharma, Cipla USA, and/or InvaGen toward the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including InvaGen's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the '937 patent.

53. On information and belief, InvaGen acts at the direction, and for the benefit, of Cipla Ltd., and is an agent/alter ego of Cipla Ltd.

54. On information and belief, Cipla Ltd. considers ANDAs owned by InvaGen amongst the ANDAs owned by Cipla Ltd. *See* Cipla Ltd. 2022 Annual Report at 63 (available at https://www.cipla.com/sites/default/files/Annual-Report-2021-22-single-page.pdf (last visited, June 20, 2024)); *see also id.* at 116 (figures "include ANDAs owned by Cipla and InvaGen Pharmaceuticals Inc.").

55. On information and belief, Cipla Ltd. "includes" revenues raised by InvaGen in its own year-over-year sales figures for the North American region. *See id.* at 115.

56. On information and belief, several individuals are directors of both Cipla Ltd. and InvaGen. *Id.* at 172 (identifying "Ms Punita Lal," "Mr P R Ramesh," and "Mr Robert Stewart" as "Independent Directors" of both InvaGen and Cipla Ltd.).

57. On information and belief, Cipla Ltd. "has given guarantees in favor of various banks" in connection with loans obtained by InvaGen. *See id.* at 256, 268.

58. This Court has personal jurisdiction over Cipla Ltd. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, InvaGen; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey, including through, directly or indirectly, InvaGen. On information and belief, InvaGen acts at the direction, and for the benefit, of Cipla Ltd., and is controlled and/or dominated by Cipla Ltd.

59. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), Cipla Ltd. stipulated that it would not contest personal jurisdiction or venue. *See id.* at ECF No. 45.

60. In the alternative, this Court has personal jurisdiction over Cipla Ltd. because the requirements of Fed. R. Civ. P. 4(k)(2) are met as (a) Jazz's claims arise under federal law; (b) Cipla Ltd. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Cipla 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, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Cipla Ltd. satisfies due process.

61. At least because, on information and belief, Cipla Ltd. is a foreign company, venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

62. As set forth in Paragraphs 63-69 below, the Court has personal jurisdiction over API Pharma by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

64. On information and belief, API Pharma 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, API Pharma will work in concert with Cipla USA, Cipla Ltd., and/or InvaGen toward the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including InvaGen's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the '937 patent.

66. On information and belief, API Pharma is incorporated in New Jersey and maintains a physical place of business in this Judicial District, in at least Monmouth Junction, New Jersey. *See* https://www.apipharmatech.com/about-us/vision-mission/ (last visited, June 20, 2024).

67. On information and belief, API Pharma 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. 0450081108.

68. On information and belief, API Pharma is registered with the State of New Jersey's Department of Health as a drug manufacturer operating in New Jersey under the registration number 5005711.

69. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), API Pharma stipulated that it would not contest personal jurisdiction or venue. *See id.* at ECF No. 45.

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

Jurisdiction and Venue: Lupin

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

72. As set forth in Paragraphs 73-77 below, the Court has personal jurisdiction over Lupin by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

74. On information and belief, Lupin 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.

75. On information and belief, this Judicial District will be a destination for the generic version of Jazz's cannabidiol oral solution drug product for which Lupin seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 217871 ("Lupin's Proposed Product").

76. On information and belief, Lupin maintains a physical place of business in this Judicial District, in at least Somerset, New Jersey. Lupin's website states that its "first and only commercial manufacturing facility in the United States is located in Somerset, New Jersey. Lupin's New Jersey facility encompasses all functional areas of pharmaceutical manufacturing including quality control, packaging, production, quality assurance, regulatory affairs, research and development, formulation, and technical services." *See* https://www.lupin.com/US/lupin-u-s-locations/ (last visited, June 20, 2024). Lupin's most recent annual report, specifically points

to both "research" and "manufacturing" activities in New Jersey when describing the company's "Global Footprint." *See* https://www.lupin.com/wp-content/uploads/2023/07/integrated-report-consolidated.pdf (last visited, June 20, 2024).

77. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, Lupin's ANDA, and Lupin's Proposed Product, Lupin did not contest personal jurisdiction or venue.

78. In the alternative, this Court has personal jurisdiction over Lupin because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Jazz's claims arise under federal law; (b) Lupin is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Lupin 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 Lupin satisfies due process.

79. At least because, on information and belief, Lupin is a foreign company, venue is proper in this Judicial District pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Jurisdiction and Venue: Taro

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

81. As set forth in Paragraphs 82-88 below, the Court has personal jurisdiction over Taro by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

83. On information and belief, Taro 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.

84. On information and belief, this Judicial District will be a destination for the generic version of Jazz's cannabidiol oral solution drug product for which Taro seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 217930 ("Taro's Proposed Product").

85. On information and belief, Taro maintains a physical place of business in this Judicial District, in at least Cranbury, New Jersey. On information and belief, Taro Pharmaceuticals USA, Inc. ("Taro USA") is an indirect, wholly owned subsidiary of Taro. On information and belief, Taro maintains a physical place of business in Cranbury through its wholly owned subsidiary, Taro USA.

86. Taro has consented to personal jurisdiction in this Court in recent actions arising out of its ANDA filings and has filed counterclaims in such cases. *See, e.g., Horizon Therapeutics, LLC v. Taro Pharm. Indus. Ltd. et al.*, No. 22-cv-04663 (D.N.J.). Taro has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

87. Taro's Notice Letter consents to jurisdiction in the State of New Jersey by directing that "service of process for Taro in connection with the Taro ANDA" is to be carried out in Princeton, New Jersey.

88. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, Taro's ANDA, and Taro's Proposed Product, Taro did not contest personal jurisdiction or venue.

89. In the alternative, this Court has personal jurisdiction over Taro because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Jazz's claims arise under federal law; (b) Taro is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Taro 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 Taro satisfies due process.

90. At least because, on information and belief, Taro is a foreign company, venue is proper in this Judicial District pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Jurisdiction and Venue: Ascent

91. This Court has jurisdiction over the subject matter of Count V against Ascent pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

92. As set forth in Paragraphs 93-98 below, the Court has personal jurisdiction over Ascent by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

94. On information and belief, Ascent 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.

95. On information and belief, this Judicial District will be a destination for the generic version of Jazz's cannabidiol oral solution drug product for which Ascent seeks FDA

approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 217994 ("Ascent's Proposed Product").

96. On information and belief, Ascent has registered with the State of New Jersey's Department of Health as a drug wholesaler and manufacturer operating in New Jersey under the registration number 5005459.

97. Ascent has consented to personal jurisdiction in this Court in recent actions arising out of its ANDA filings and has filed counterclaims in such cases. *See, e.g., Tris Pharma, Inc. v. Ascent Pharm., Inc.*, No. 21-cv-12867 (D.N.J.). Ascent has purposefully availed itself of the rights, benefits, and privileges of New Jersey by asserting counterclaims in this Court.

98. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, Ascent's ANDA, and Ascent's Proposed Product, Ascent did not contest personal jurisdiction or venue.

99. For at least the foregoing reasons set forth above in Paragraphs 93-98, venue is proper in this Judicial District with respect to Ascent pursuant to 28 U.S.C. § 1400(b).

Jurisdiction and Venue: Biophore and Zenara

100. This Court has jurisdiction over the subject matter of Count VI against Biophore and Zenara pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

101. As set forth in Paragraphs 102-107 below, the Court has personal jurisdiction over Biophore by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

103. On information and belief, Biophore 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.

104. On information and belief, this Judicial District will be a destination for the generic version of Jazz's cannabidiol oral solution drug product for which Biophore and Zenara seek FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 217910 ("Biophore's and Zenara's Proposed Product").

105. On information and belief, Biophore is incorporated in the state of New Jersey and maintains a physical place of business in this Judicial District, in at least Monmouth Junction, New Jersey.

106. On information and belief, Biophore 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. 0400378257.

107. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, Biophore's and Zenara's Proposed Product, and Biophore's and Zenara's ANDA, Biophore did not contest personal jurisdiction or venue.

108. For at least the foregoing reasons set forth above in Paragraphs 102-107, venue is proper in this Judicial District with respect to Biophore pursuant to 28 U.S.C. § 1400(b).

109. As set forth in Paragraphs 110-113 below, the Court has personal jurisdiction over Zenara by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

111. On information and belief, Zenara 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.

112. On information and belief, this Judicial District will be a destination for Biophore's and Zenara's Proposed Product.

113. In *Jazz Pharm. Research UK Ltd. v. Teva Pharm., Inc., et al.*, No. 23-cv-00018 (MEF)(AME) (D.N.J.), involving the same parties, Biophore's and Zenara's Proposed Product, and Biophore's and Zenara's ANDA, Zenara did not contest personal jurisdiction or venue.

114. In the alternative, this Court has personal jurisdiction over Zenara because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Jazz's claims arise under federal law; (b) Zenara is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Zenara 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 Zenara satisfies due process.

115. At least because, on information and belief, Zenara is a foreign company, venue is proper in this Judicial District pursuant to 28 U.S.C. § 1391(c)(3) and 28 U.S.C. § 1400(b).

Acts Giving Rise To Count I Against Apotex

116. Pursuant to Section 505 of the FFDCA, Apotex filed ANDA No. 217699 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Apotex's Proposed Product, before the '937 patent expires.

117. No earlier than November 28, 2022, Apotex sent written notice of a Paragraph IV Certification ("Apotex's Notice Letter") to Jazz. According to Apotex's Notice Letter, Apotex

filed 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 Apotex's Proposed Product before expiration of the patents listed in the Orange Book with respect to Epidiolex®.

118. On information and belief, in connection with the filing of its ANDA as described above, Apotex 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 Apotex's Proposed Product before the expiration of the Orange Book patents with respect to Epidiolex®, one of which is the '937 patent.

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

Acts Giving Rise To Count II Against InvaGen, Cipla, and API Pharma

120. Pursuant to Section 505 of the FFDCA, API Pharma filed ANDA No. 217522 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of InvaGen's Proposed Product, before the '937 patent expires.

121. No earlier than December 2, 2022, InvaGen sent written notice of a Paragraph IV Certification ("InvaGen's First Notice Letter") to Jazz. No earlier than October 26, 2023, InvaGen sent written notice of a second Paragraph IV Certification ("InvaGen's Second Notice Letter") to Jazz. No earlier than December 4, 2023, InvaGen sent written notice of a third Paragraph IV Certification ("InvaGen's Third Notice Letter") to Jazz. No earlier than April 12, 2024, InvaGen sent written notice of a fourth Paragraph IV Certification ("InvaGen's Fourth Notice Letter") to Jazz. According to InvaGen's Notice Letters, API Pharma filed 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 InvaGen's Proposed Product before expiration of the patents listed in the Orange Book with respect to Epidiolex®.

122. On information and belief, in connection with the filing of the ANDA as described above, API Pharma 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 InvaGen's Proposed Product before the expiration of the Orange Book patents with respect to Epidiolex®, one of which is the '937 patent.

123. According to InvaGen's First Notice Letter, after the FDA had received API Pharma's Paragraph IV Certification, API Pharma transferred ownership of ANDA No. 217522 to InvaGen "in accordance with 21 CFR § 314.72(a)(1)."

124. On information and belief, and as evidenced by the facts set forth in Paragraphs 26-69 and 120-123 above, following FDA approval of ANDA No. 217522, InvaGen, Cipla, and API Pharma will act in concert to make, use, offer to sell, or sell InvaGen's Proposed Product throughout the United States, or import such a generic product into the United States.

125. On information and belief, and as evidenced by the facts set forth in Paragraphs 26-69 and 120-124 above, following FDA approval of ANDA No. 217522, InvaGen, Cipla, and API Pharma intend to directly benefit from sales of InvaGen's Proposed Product.

Acts Giving Rise to Count III Against Lupin

126. Pursuant to Section 505 of the FFDCA, Lupin filed ANDA No. 217871 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Lupin's Proposed Product, before the '937 patent expires.

127. No earlier than December 2, 2022, Lupin sent written notice of a Paragraph IV Certification ("Lupin's First Notice Letter") to Jazz. No earlier than July 7, 2023, Lupin sent written notice of a second Paragraph IV Certification ("Lupin's Second Notice Letter") to Jazz. According to Lupin's Notice Letters, Lupin filed 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 Lupin's Proposed Product before expiration of the patents listed in the Orange Book with respect to Epidiolex®.

128. On information and belief, in connection with the filing of its ANDA as described above, Lupin 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 Lupin's Proposed Product before the expiration of the Orange Book patents with respect to Epidiolex®, one of which is the '937 patent.

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

Acts Giving Rise to Count IV Against Taro

130. Pursuant to Section 505 of the FFDCA, Taro filed ANDA No. 217930 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Taro's Proposed Product, before the '937 patent expires.

131. No earlier than December 5, 2022, Taro sent written notice of a Paragraph IV Certification ("Taro's First Notice Letter") to Jazz. No earlier than June 23, 2023, Taro sent written notice of a second Paragraph IV Certification ("Taro's Second Notice Letter") to Jazz. No earlier than September 15, 2023, Taro sent written notice of a third Paragraph IV

Certification ("Taro's Third Notice Letter") to Jazz. No earlier than December 7, 2023, Taro sent written notice of a fourth Paragraph IV Certification ("Taro's Fourth Notice Letter") to Jazz. No earlier than February 29, 2024, Taro sent written notice of a fifth Paragraph IV Certification ("Taro's Fifth Notice Letter") to Jazz. According to Taro's Notice Letters, Taro filed 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 Taro's Proposed Product before expiration of the patents listed in the Orange Book with respect to Epidiolex®.

132. On information and belief, in connection with the filing of its ANDA as described above, Taro provided written certifications 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 Taro's Proposed Product before the expiration of the Orange Book patents with respect to Epidiolex®, one of which is the '937 patent.

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

Acts Giving Rise to Count V Against Ascent

134. Pursuant to Section 505 of the FFDCA, Ascent filed ANDA No. 217994 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Ascent's Proposed Product, before the '937 patent expires.

135. No earlier than December 6, 2022, Ascent sent written notice of a Paragraph IV Certification ("Ascent's First Notice Letter") to Jazz. No earlier than November 14, 2023, Ascent sent written notice of a second Paragraph IV Certification ("Ascent's Second Notice Letter") to Jazz. According to Ascent's Notice Letters, Ascent filed 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 Ascent's Proposed Product before expiration of the patents listed in the Orange Book with respect to Epidiolex®.

136. On information and belief, in connection with the filing of its ANDA as described above, Ascent 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 Ascent's Proposed Product before the expiration of the Orange Book patents with respect to Epidiolex®, one of which is the '937 patent.

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

Acts Giving Rise to Count VI Against Biophore and Zenara

138. Pursuant to Section 505 of the FFDCA, Biophore and Zenara filed ANDA No. 217910 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Biophore's and Zenara's Proposed Product, before the '937 patent expires.

139. No earlier than December 6, 2022, Biophore and Zenara sent written notice of a Paragraph IV Certification ("Biophore's and Zenara's First Notice Letter") to Jazz. No earlier than June 2, 2023, Biophore and Zenara sent written notice of a second Paragraph IV Certification ("Biophore's and Zenara's Second Notice Letter") to Jazz. According to Biophore's and Zenara's Notice Letters, Biophore and Zenara filed 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 Biophore's and Zenara's Proposed Product before expiration of the patents listed in the Orange Book with respect to Epidiolex®.

140. Biophore's and Zenara's Notice Letters collectively refer to both Biophore and Zenara as "Zenara" and state that these two entities "collectively . . . filed an Abbreviated New Drug Application ('ANDA') under 21 U.S.C. § 355(j) to obtain approval from the U.S. Food & Drug Administration ('FDA') to market cannabidiol oral solution, 100 mg/mL . . . prior to the expiration of [certain of the patents listed in the Orange Book with respect to Epidiolex®]."

141. On information and belief, in connection with the filing of their ANDA as described above, Biophore and Zenara provided written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), indicating that they seek to obtain approval of its ANDA to engage in the commercial manufacture, use, or sale of Biophore's and Zenara's Proposed Product before the expiration of the Orange Book patents with respect to Epidiolex®, one of which is the '937 patent.

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

Count I: Infringement of the '937 Patent by Apotex

143. Jazz repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

144. Apotex's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Apotex's Proposed Product, prior to the expiration of the '937 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.

145. A justiciable controversy exists between the parties hereto as to the infringement of the '937 patent.

146. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex will infringe one or more claims of the '937 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Apotex's Proposed Product in the United States.

147. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex will induce infringement of one or more claims of the '937 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Apotex's Proposed Product in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex will intentionally encourage acts of direct infringement with knowledge of the '937 patent and knowledge that its acts are encouraging infringement.

148. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex will contributorily infringe one or more claims of the '937 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Apotex's Proposed Product in the United States. On information and belief, Apotex knew and knows that Apotex's Proposed Product is designed for a use that infringes one or more claims of the '937 patent, and Apotex's Proposed Product lacks a substantial non-infringing use.

149. Failure to enjoin Apotex's infringement of the '937 patent will substantially and irreparably damage Jazz.

150. Jazz does not have an adequate remedy at law.

Count II: Infringement of the '937 Patent by InvaGen, Cipla and API Pharma

151. Jazz repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

152. The submission of ANDA No. 217522 to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of InvaGen's Proposed Product, prior to the expiration of the '937 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.

153. A justiciable controversy exists between the parties hereto as to the infringement of the '937 patent.

154. Unless enjoined by this Court, upon FDA approval of InvaGen's ANDA, InvaGen, Cipla, and API Pharma will infringe one or more claims of the '937 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing InvaGen's Proposed Product in the United States.

155. Unless enjoined by this Court, upon FDA approval of InvaGen's ANDA, InvaGen, Cipla, and/or API Pharma will induce infringement of one or more claims of the '937 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing InvaGen's Proposed Product in the United States. On information and belief, upon FDA approval of InvaGen's ANDA, InvaGen, Cipla and/or API Pharma will intentionally encourage acts of direct infringement with knowledge of the '937 patent and knowledge that their acts are encouraging infringement.

156. Unless enjoined by this Court, upon FDA approval of InvaGen's ANDA, InvaGen, Cipla, and/or API Pharma will contributorily infringe one or more claims of the '937 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell,

selling, and/or importing InvaGen's Proposed Product in the United States. On information and belief, InvaGen, Cipla, and/or API Pharma knew and knows that InvaGen's Proposed Product is designed for a use that infringes one or more claims of the '937 patent, and InvaGen's Proposed Product lacks a substantial non-infringing use.

157. Failure to enjoin InvaGen's, Cipla's, and API Pharma's infringement of the '937 patent will substantially and irreparably damage Jazz.

158. Jazz does not have an adequate remedy at law.

Count III: Infringement of the '937 Patent by Lupin

159. Jazz repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

160. Lupin's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Lupin's Proposed Product, prior to the expiration of the '937 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.

161. A justiciable controversy exists between the parties hereto as to the infringement of the '937 patent.

162. Unless enjoined by this Court, upon FDA approval of Lupin's ANDA, Lupin will infringe one or more claims of the '937 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Lupin's Proposed Product in the United States.

163. Unless enjoined by this Court, upon FDA approval of Lupin's ANDA, Lupin will induce infringement of one or more claims of the '937 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Lupin's

Proposed Product in the United States. On information and belief, upon FDA approval of Lupin's ANDA, Lupin will intentionally encourage acts of direct infringement with knowledge of the '937 patent and knowledge that its acts are encouraging infringement.

164. Unless enjoined by this Court, upon FDA approval of Lupin's ANDA, Lupin will contributorily infringe one or more claims of the '937 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Lupin's Proposed Product in the United States. On information and belief, Lupin knew and knows that Lupin's Proposed Product is designed for a use that infringes one or more claims of the '937 patent, and Lupin's Proposed Product lacks a substantial non-infringing use.

165. Failure to enjoin Lupin's infringement of the '937 patent will substantially and irreparably damage Jazz.

166. Jazz does not have an adequate remedy at law.

Count IV: Infringement of the '937 Patent by Taro

167. Jazz repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

168. Taro's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Taro's Proposed Product, prior to the expiration of the '937 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.

169. A justiciable controversy exists between the parties hereto as to the infringement of the '937 patent.

170. Unless enjoined by this Court, upon FDA approval of Taro's ANDA, Taro will infringe one or more claims of the '937 patent under 35 U.S.C. § 271(a), including at least claim

1, by making, using, offering to sell, selling, and/or importing Taro's Proposed Product in the United States.

171. Unless enjoined by this Court, upon FDA approval of Taro's ANDA, Taro will induce infringement of one or more claims of the '937 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Taro's Proposed Product in the United States. On information and belief, upon FDA approval of Taro's ANDA, Taro will intentionally encourage acts of direct infringement with knowledge of the '937 patent and knowledge that its acts are encouraging infringement.

172. Unless enjoined by this Court, upon FDA approval of Taro's ANDA, Taro will contributorily infringe one or more claims of the '937 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Taro's Proposed Product in the United States. On information and belief, Taro knew and knows that Taro's Proposed Product is designed for a use that infringes one or more claims of the '937 patent, and Taro's Proposed Product lacks a substantial non-infringing use.

173. Failure to enjoin Taro's infringement of the '937 patent will substantially and irreparably damage Jazz.

174. Jazz does not have an adequate remedy at law.

Count V: Infringement of the '937 Patent by Ascent

175. Jazz repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

176. Ascent's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Ascent's Proposed Product, prior to

the expiration of the '937 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.

177. A justiciable controversy exists between the parties hereto as to the infringement of the '937 patent.

178. Unless enjoined by this Court, upon FDA approval of Ascent's ANDA, Ascent will infringe one or more claims of the '937 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Ascent's Proposed Product in the United States.

179. Unless enjoined by this Court, upon FDA approval of Ascent's ANDA, Ascent will induce infringement of one or more claims of the '937 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Ascent's Proposed Product in the United States. On information and belief, upon FDA approval of Ascent's ANDA, Ascent will intentionally encourage acts of direct infringement with knowledge of the '937 patent and knowledge that its acts are encouraging infringement.

180. Unless enjoined by this Court, upon FDA approval of Ascent's ANDA, Ascent will contributorily infringe one or more claims of the '937 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Ascent's Proposed Product in the United States. On information and belief, Ascent knew and knows that Ascent's Proposed Product is designed for a use that infringes one or more claims of the '937 patent, and Ascent's Proposed Product lacks a substantial non-infringing use.

181. Failure to enjoin Ascent's infringement of the '937 patent will substantially and irreparably damage Jazz.

182. Jazz does not have an adequate remedy at law.

Count VI: Infringement of the '937 Patent by Biophore and Zenara

183. Jazz repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

184. Biophore's and Zenara's submission of their ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Biophore's and Zenara's Proposed Product, prior to the expiration of the '937 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.

185. A justiciable controversy exists between the parties hereto as to the infringement of the '937 patent.

186. Unless enjoined by this Court, upon FDA approval of Biophore's and Zenara's ANDA, Biophore and Zenara will infringe one or more claims of the '937 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Biophore's and Zenara's Proposed Product in the United States.

187. Unless enjoined by this Court, upon FDA approval of Biophore's and Zenara's ANDA, Biophore and Zenara will induce infringement of one or more claims of the '937 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Biophore's and Zenara's Proposed Product in the United States. On information and belief, upon FDA approval of Biophore's and Zenara's ANDA, Biophore and Zenara will intentionally encourage acts of direct infringement with knowledge of the '937 patent and knowledge that their acts are encouraging infringement.

188. Unless enjoined by this Court, upon FDA approval of Biophore's and Zenara's ANDA, Biophore and Zenara will contributorily infringe one or more claims of the '937 patent

under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Biophore's and Zenara's Proposed Product in the United States. On information and belief, Biophore and Zenara knew and know that Biophore's and Zenara's Proposed Product is designed for a use that infringes one or more claims of the '937 patent, and Biophore's and Zenara's Proposed Product lacks a substantial non-infringing use.

189. Failure to enjoin Biophore's and Zenara's infringement of the '937 patent will substantially and irreparably damage Jazz.

190. Jazz does not have an adequate remedy at law.

PRAYER FOR RELIEF AGAINST APOTEX

WHEREFORE, Plaintiff Jazz respectfully requests the following relief:

(A) A Judgment that Apotex infringed one or more claims of the '937 patent by submitting ANDA No. 217699;

(B) A Judgment that Apotex has infringed, and that Apotex's making, using, offering to sell, selling, or importing Apotex's Proposed Product will infringe one or more claims of the '937 patent;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 217699 be a date no earlier than the later of the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Apotex and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Apotex's Proposed Product until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Apotex, its officers, agents, attorneys and employees, and those acting in privity or

concert with them, from practicing any method claimed in the '937 patent, or from actively inducing or contributing to the infringement of any claim of the '937 patent, until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Apotex's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of the '937 patent;

(G) To the extent that Apotex has committed any acts with respect to the methods claimed in the '937 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Jazz damages for such acts;

(H) If Apotex engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Apotex's Proposed Product prior to the expiration of the '937 patent, a Judgment awarding damages to Jazz resulting from such infringement, together with interest;

(I) A Judgment declaring that the '937 patent remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Jazz 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 INVAGEN, CIPLA, AND API PHARMA

WHEREFORE, Plaintiff Jazz respectfully requests the following relief:

(A) A Judgment that InvaGen, Cipla, and/or API Pharma infringed one or more claims of the '937 patent by submitting ANDA No. 217522;

(B) A Judgment that InvaGen, Cipla, and/or API Pharma have infringed, and that InvaGen's, Cipla's, and API Pharma's making, using, offering to sell, selling, or importing InvaGen's Proposed Product will infringe one or more claims of the '937 patent;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 217522 be a date no earlier than the later of the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining InvaGen, Cipla, and API Pharma, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing InvaGen's Proposed Product until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining InvaGen, Cipla, and API Pharma, and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any method claimed in the '937 patent, or from actively inducing or contributing to the infringement of any claim of the '937 patent, until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of InvaGen's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of the '937 patent;

(G) To the extent that InvaGen, Cipla, and/or API Pharma have committed any acts with respect to the methods claimed in the '937 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Jazz damages for such acts;

(H) If InvaGen, Cipla, and/or API Pharma engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of InvaGen's Proposed Product prior to the expiration of the '937 patent, a Judgment awarding damages to Jazz resulting from such infringement, together with interest;

(I) A Judgment declaring that the '937 patent remains valid and enforceable;

(J) A Judgment that this case is exceptional pursuant to 35 U.S.C. § 285 and awarding Jazz 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 LUPIN

WHEREFORE, Plaintiff Jazz respectfully requests the following relief:

(A) A Judgment that Lupin infringed one or more claims of the '937 patent by submitting ANDA No. 217871;

(B) A Judgment that Lupin has infringed, and that Lupin's making, using, offering to sell, selling, or importing Lupin's Proposed Product will infringe one or more claims of the '937 patent;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 217871 be a date no earlier than the later of the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Lupin and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Lupin's Proposed Product until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Lupin, its officers, agents, attorneys and employees, and those acting in privity or

concert with them, from practicing any method claimed in the '937 patent, or from actively inducing or contributing to the infringement of any claim of the '937 patent, until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Lupin's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of the '937 patent;

(G) To the extent that Lupin has committed any acts with respect to the methods claimed in the '937 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Jazz damages for such acts;

(H) If Lupin engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Lupin's Proposed Product prior to the expiration of the '937 patent, a Judgment awarding damages to Jazz resulting from such infringement, together with interest;

(I) A Judgment declaring that the '937 patent remains valid and enforceable;

(J) A Judgment that this case is exceptional pursuant to 35 U.S.C. § 285 and awarding Jazz 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 TARO

WHEREFORE, Plaintiff Jazz respectfully requests the following relief:

(A) A Judgment that Taro infringed one or more claims of the '937 patent by submitting ANDA No. 217930;

(B) A Judgment that Taro has infringed, and that Taro's making, using, offering to sell, selling, or importing Taro's Proposed Product will infringe one or more claims of the '937 patent;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 217930 be a date no earlier than the later of the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Taro and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Taro's Proposed Product until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Taro, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any method claimed in the '937 patent, or from actively inducing or contributing to the infringement of any claim of the '937 patent, until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Taro's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of the '937 patent;

(G) To the extent that Taro has committed any acts with respect to the methods claimed in the '937 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Jazz damages for such acts;

(H) If Taro engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Taro's Proposed Product prior to the expiration of the '937 patent, a Judgment awarding damages to Jazz resulting from such infringement, together with interest;

(I) A Judgment declaring that the '937 patent remains valid and enforceable;

(J) A Judgment that this case is exceptional pursuant to 35 U.S.C. § 285 and awarding Jazz 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 ASCENT

WHEREFORE, Plaintiff Jazz respectfully requests the following relief:

(A) A Judgment that Ascent infringed one or more claims of the '937 patent by submitting ANDA No. 217994;

(B) A Judgment that Ascent has infringed, and that Ascent's making, using, offering to sell, selling, or importing Ascent's Proposed Product will infringe one or more claims of the '937 patent;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 217994 be a date no earlier than the later of the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Ascent and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Ascent's Proposed Product until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Ascent, its officers, agents, attorneys and employees, and those acting in privity or

concert with them, from practicing any method claimed in the '937 patent, or from actively inducing or contributing to the infringement of any claim of the '937 patent, until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Ascent's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of the '937 patent;

(G) To the extent that Ascent has committed any acts with respect to the methods claimed in the '937 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Jazz damages for such acts;

(H) If Ascent engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Ascent's Proposed Product prior to the expiration of the '937 patent, a Judgment awarding damages to Jazz resulting from such infringement, together with interest;

(I) A Judgment declaring that the '937 patent remains valid and enforceable;

(J) A Judgment that this case is exceptional pursuant to 35 U.S.C. § 285 and awarding Jazz 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 BIOPHORE AND ZENARA

WHEREFORE, Plaintiff Jazz respectfully requests the following relief:

(A) A Judgment that Biophore and Zenara infringed one or more claims of the '937 patent by submitting ANDA No. 217910;

(B) A Judgment that Biophore and Zenara have infringed, and that Biophore's and Zenara's making, using, offering to sell, selling, or importing Biophore's and Zenara's Proposed Product will infringe one or more claims of the '937 patent;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 217910 be a date no earlier than the later of the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Biophore and Zenara and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Biophore's and Zenara's Proposed Product until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Biophore and Zenara, their officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any method claimed in the '937 patent, or from actively inducing or contributing to the infringement of any claim of the '937 patent, until after the expiration of the '937 patent, or any later expiration of exclusivity to which Jazz is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Biophore's and Zenara's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of the '937 patentt;

(G) To the extent that Biophore and Zenara have committed any acts with respect to the methods claimed in the '937 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Jazz damages for such acts;

(H) If Biophore and Zenara engage in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Biophore's and Zenara's Proposed Product prior to the expiration of the '937 patent, a Judgment awarding damages to Jazz resulting from such infringement, together with interest;

(I) A Judgment declaring that the '937 patent remains valid and enforceable;

(J) A Judgment that this case is exceptional pursuant to 35 U.S.C. § 285 and awarding Jazz 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: July 3, 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 *Jazz Pharmaceuticals Research UK Limited v. Teva Pharm., Inc., et al.*, Civil Action No. 23-cv-00018 (MEF)(AME) (D.N.J.); *Jazz Pharmaceuticals Research UK Limited v. Teva Pharm., Inc., et al.*, Civil Action No. 23-cv-03914 (MEF)(AME) (D.N.J.); and *Jazz Pharmaceuticals Research UK Limited v. Apotex Inc. et al.*, Civil Action No. 23-cv-23141 (MEF)(AME) (D.N.J.) are related to the matter in controversy because the matter in controversy involves the same Plaintiff, some of the same Defendants, related patents with common inventors, and because Defendants are seeking FDA approval to market a generic version of the same pharmaceutical product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: July 3, 2024

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EXHIBIT A

US011963937B2

(12) **United States Patent**
Guy et al.

(10) **Patent No.: US 11,963,937 B2**
(45) **Date of Patent: *Apr. 23, 2024**

(54) **USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY**

(71) Applicant: **GW Research Limited**, Cambridge (GB)

(72) Inventors: **Geoffrey Guy**, Cambridge (GB); **Stephen Wright**, Altrincham (GB); **Orrin Devinsky**, New York, NY (US)

(73) Assignee: **GW Research Limited**, Cambridge (GB)

(*) 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.: **18/320,906**

(22) Filed: **May 19, 2023**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 17/472,016, filed on Sep. 10, 2021, now Pat. No. 11,701,330, which is a continuation of application No. 17/119,873, filed on Dec. 11, 2020, now Pat. No. 11,154,516, which is a continuation of application No. 16/791,940, filed on

(Continued)

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**

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A61K 31/36	(2006.01)
A61K 31/4015	(2006.01)
A61K 31/4166	(2006.01)
A61K 31/423	(2006.01)
A61K 31/444	(2006.01)
A61K 31/496	(2006.01)
A61K 31/515	(2006.01)
A61K 31/53	(2006.01)
A61K 31/55	(2006.01)
A61K 31/551	(2006.01)
A61K 31/5513	(2006.01)
A61K 31/5517	(2006.01)
A61K 31/7048	(2006.01)
A61K 36/185	(2006.01)
A61K 45/06	(2006.01)
A61K 47/10	(2017.01)

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(52) **U.S. Cl.**

CPC ***A61K 31/05*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 31/165*** (2013.01); ***A61K 31/19*** (2013.01); ***A61K 31/195*** (2013.01); ***A61K 31/197*** (2013.01); ***A61K 31/20*** (2013.01); ***A61K 31/27*** (2013.01); ***A61K 31/35*** (2013.01); ***A61K 31/352*** (2013.01); ***A61K 31/36*** (2013.01); ***A61K 31/4015*** (2013.01); ***A61K 31/4166*** (2013.01); ***A61K 31/423*** (2013.01); ***A61K 31/444*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/515*** (2013.01); ***A61K 31/53*** (2013.01); ***A61K 31/55*** (2013.01); ***A61K 31/551*** (2013.01); ***A61K 31/5513*** (2013.01); ***A61K 31/5517*** (2013.01); ***A61K 31/7048*** (2013.01); ***A61K 36/185*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/26*** (2013.01); ***A61K 47/44*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/05

See application file for complete search history.

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(74) *Attorney, Agent, or Firm* — COOLEY LLP

(57) **ABSTRACT**

The present disclosure relates to the use of cannabidiol (CBD) for the reduction of total convulsive seizure frequency in the treatment of "treatment-resistant epilepsy" (TRE). In particular, the disclosure relates to the use of CBD of treating TRE when the TRE is Dravet syndrome; myoclonic absence seizures or febrile infection related epilepsy syndrome (FIRES). The disclosure further relates to the use of CBD in combination with one or more anti-epileptic drugs (AEDs).

29 Claims, No Drawings

Related U.S. Application Data

Feb. 14, 2020, now abandoned, which is a continuation of application No. 15/948,412, filed on Apr. 9, 2018, now Pat. No. 10,603,288, which is a continuation of application No. 15/449,084, filed on Mar. 3, 2017, now Pat. No. 9,956,183, which is a continuation of application No. 15/284,766, filed on Oct. 4, 2016, now Pat. No. 9,949,936, which is a continuation of application No. 14/741,783, filed on Jun. 17, 2015, now Pat. No. 9,474,726.

(51) **Int. Cl.**

A61K 47/26	(2006.01)
A61K 47/44	(2017.01)

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USE OF CANNABINOIDS IN THE TREATMENT OF EPILEPSY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. patent application Ser. No. 17/472,016, filed Sep. 10, 2021; which is a Continuation of U.S. patent application Ser. No. 17/119,873, filed Dec. 11, 2020, now U.S. Pat. No. 11,154,516, issued Oct. 26, 2021; which is a Continuation of U.S. patent application Ser. No. 16/791,940, filed Feb. 14, 2020; which is a Continuation of U.S. patent application Ser. No. 15/948,412, filed Apr. 9, 2018, now U.S. Pat. No. 10,603,288, issued Mar. 31, 2020; which is a Continuation of U.S. patent application Ser. No. 15/449,084, filed Mar. 3, 2017, now U.S. Pat. No. 9,956,183, issued May 1, 2018; which is a Continuation of U.S. patent application Ser. No. 15/284,766, filed Oct. 4, 2016, now U.S. Pat. No. 9,949,936 issued Apr. 24, 2018; which is a Continuation of U.S. patent application Ser. No. 14/741,783, filed Jun. 17, 2015, now U.S. Pat. No. 9,474,726 issued Oct. 25, 2016; which claims the benefit of priority of GB 1506550.1, filed Apr. 17, 2015, and GB 1410771.8, filed Jun. 17, 2014, each of which incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to the use of cannabidiol (CBD) for the reduction of total convulsive seizure frequency in the treatment of "treatment-resistant epilepsy" (TRE). In one embodiment the patients suffering from TRE are children and young adults. CBD appears particularly effective when the TRE is Dravet syndrome; myoclonic absence seizures or febrile infection related epilepsy syndrome (FIRES). In these indications the reduction of total convulsive frequency has surprisingly been shown to be greater than 50%, through 70% to greater than 90% in a significant number of patients. Indeed a significant number of patients have been seizure free at the end of three months treatment.

Preferably the CBD used is in the form of a highly purified extract of *cannabis* such that the CBD is present at greater than 98% of the total extract (w/w) and the other components of the extract are characterised. In particular tetrahydrocannabinol (THC) has been substantially removed to a level of not more than 0.15% (w/w). Alternatively, it is a synthetically produced CBD.

In use the CBD is used concomitantly with one or more other anti-epileptic drugs (AED). Alternatively the CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form. Where the CBD is formulated for administration separately, sequentially or simultaneously it may be provided as a kit or together with instructions to administer the one or more components in the manner indicated.

BACKGROUND TO THE INVENTION

Epilepsy occurs in approximately 1% of the population worldwide, (Thurman et al., 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AED). However, 30% of this patient group, (Eadie et al., 2012), are unable to obtain

seizure freedom from the AED that are available and as such are termed as suffering from "treatment-resistant epilepsy" (TRE).

Treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2009).

Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment-resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

Childhood epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

One such childhood epilepsy is Dravet syndrome. Onset of Dravet syndrome almost always occurs during the first year of life with clonic and tonic-clonic seizures in previously healthy and developmentally normal infants (Dravet, 2011). Symptoms peak at about five months of age. Other seizures develop between one and four years of age such as prolonged focal dyscognitive seizures and brief absence seizures.

Seizures progress to be frequent and treatment-resistant, meaning that the seizures do not respond well to treatment. They also tend to be prolonged, lasting more than 5 minutes. Prolonged seizures may lead to status epilepticus, which is a seizure that lasts more than 30 minutes, or seizures that occur in clusters, one after another.

Prognosis is poor and approximately 14% of children die during a seizure, because of infection, or suddenly due to uncertain causes, often because of the relentless neurological decline. Patients develop intellectual disability and life-long ongoing seizures. Intellectual impairment varies from severe in 50% patients, to moderate and mild intellectual disability each accounting for 25% of cases.

There are currently no FDA approved treatments specifically indicated for Dravet syndrome. The standard of care usually involves a combination of the following anticonvulsants: clobazam, clonazepam, levetiracetam, topiramate and valproic acid.

Stiripentol is approved in Europe for the treatment of Dravet syndrome in conjunction with clobazam and valproic acid. In the US, stiripentol was granted an Orphan Designation for the treatment of Dravet syndrome in 2008; however, the drug is not FDA approved.

Potent sodium channel blockers used to treat epilepsy actually increase seizure frequency in patients with Dravet Syndrome. The most common are phenytoin, carbamazepine, lamotrigine and rufinamide.

Management may also include a ketogenic diet, and physical and vagus nerve stimulation. In addition to anticonvulsive drugs, many patients with Dravet syndrome are treated with anti-psychotic drugs, stimulants, and drugs to treat insomnia.

Common AED defined by their mechanisms of action are described in the following tables:

Examples of narrow spectrum AED

Narrow-spectrum AED	Mechanism
Phenytoin	Sodium channel
Phenobarbital	GABA/Calcium channel
Carbamazepine	Sodium channel
Oxcarbazepine	Sodium channel
Gabapentin	Calcium channel
Pregabalin	Calcium channel
Lacosamide	Sodium channel
Vigabatrin	GABA

Examples of broad spectrum AED

Broad-spectrum AED	Mechanism
Valproic acid	GABA/Sodium channel
Lamotrigine	Sodium channel
Topiramate	GABA/Sodium channel
Zonisamide	GABA/Calcium/Sodium channel
Levetiracetam	Calcium channel
Clonazepam	GABA
Rufinamide	Sodium channel

Examples of AED used specifically in childhood epilepsy

AED	Mechanism
Clobazam	GABA
Stiripentol	GABA

Over the past forty years there have been a number of animal studies on the use of the non-psychoactive cannabinoid cannabidiol (CBD) to treat seizures. For example, Consroe et al., (1982) determined that CBD was able to prevent seizures in mice after administration of pro-convulsant drugs or an electric current.

Studies in epileptic adults have also occurred in the past forty years with CBD. Cunha et al, reported that administration of CBD to eight adult patients with generalized epilepsy resulted in a marked reduction of seizures in 4 of the patients (Cunha et al., 1980).

A study in 1978 provided 200 mg/day of pure CBD to four adult patients, two of the four patients became seizure free, whereas in the remainder seizure frequency was unchanged (Mechoulam and Carlini, 1978).

In contrast to the studies described above, an open label study reported that 200 mg/day of pure CBD was ineffective in controlling seizures in twelve institutionalized adult patients (Ames and Cridland, 1986).

Based on the fact that chronologically the last study to look at the effectiveness of CBD in patients with epilepsy proved that CBD was unable to control seizures, there would be no expectation that CBD might be useful as an anti-convulsant agent.

In the past forty years of research there have been over thirty drugs approved for the treatment of epilepsy none of which are cannabinoids. Indeed, there appears to have been a prejudice against cannabinoids, possible due to the scheduled nature of these compounds and/or the fact that THC, which is a known psychoactive, has been ascribed as a pro-convulsant (Consroe et al., 1977).

A paper published recently suggested that cannabidiol-enriched *cannabis* may be efficacious in the treatment of

epilepsy. Porter and Jacobson (2013) report on a parent survey conducted via a Facebook group which explored the use of *cannabis* which was enriched with CBD in children with treatment-resistant epilepsy. It was found that sixteen of the 19 parents surveyed reported an improvement in their child's epilepsy. The children surveyed for this paper were all taking *cannabis* that was purported to contain CBD in a high concentration although the amount of CBD present and the other constituents including THC were not known. Indeed, whilst CBD levels ranged from 0.5 to 28.6 mg/kg/day (in those extracts tested), THC levels as high as 0.8 mg/kg/day were reported.

Providing children with TRE with a *cannabis* extract that comprises THC, which has been described as a pro-convulsant (Consroe et al., 1977), in even small amounts, let alone at a potentially psychoactive dose of 0.8 mg/kg/day, is extremely dangerous and as such there is a real need to determine whether CBD is in fact efficacious.

To date there have been no controlled trials of CBD in children and young adults with TRE.

BRIEF SUMMARY OF THE DISCLOSURE

In accordance with a first aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of treatment-resistant epilepsy (TRE), wherein the epilepsy is febrile infection related epilepsy syndrome (FIRES).

In accordance with a second aspect of the present invention there is provided cannabidiol (CBD) for use in the treatment of epilepsy, wherein the epilepsy is a treatment-resistant epilepsy (TRE), and wherein the CBD is present in an amount that reduces total convulsive seizure frequency by greater than 50% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED).

Preferably the CBD is used in combination with two or more concomitant anti-epileptic drugs (AED). The CBD may be formulated for administration separately, sequentially or simultaneously with one or more AED or the combination may be provided in a single dosage form.

Preferably the seizure type to be treated is a complex partial seizure (focal seizure with impairment).

Preferably the CBD is present in an amount that reduces total convulsive seizure frequency by greater than 70% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED). More preferably the CBD is present in an amount that reduces total convulsive seizure frequency by greater than 90% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED). More preferably still the CBD is present in an amount that reduces total convulsive seizure frequency by 100% with respect to the seizure frequency achieved on concomitant anti-epileptic drugs (AED).

In one embodiment the CBD is present as a highly purified extract of *cannabis* which comprises at least 98% (w/w) CBD.

The one or more AED is preferably selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

Preferably the CBD is used in combination with clobazam.

Preferably the number of different anti-epileptic drugs or the dose of AED that are used in combination with the CBD is reduced. More preferably the dose of AED which is reduced is of clobazam.

Preferably the dose of CBD is greater than 5 mg/kg/day. Thus for a 15 kg patient a dose of greater than 75 mg of CBD per day would be provided. Doses greater than 5 mg/kg/day such as greater than 10/mg/kg/day, greater than 15 mg/kg/day, greater than 20 mg/kg/day and greater than 25 mg/kg/day are also envisaged to be effective.

In accordance with a third aspect of the present invention there is provided a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a subject, wherein the epilepsy is febrile infection related epilepsy syndrome (ARES).

In accordance with a fourth aspect of the present invention there is provided a method of treating treatment-resistant epilepsy comprising administering cannabidiol (CBD) to a subject in an amount sufficient to reduce total convulsive seizure frequency by greater than 50% with respect to the seizure frequency achieved on one or more concomitant anti-epileptic drugs (AED).

Definitions

Definitions of some of the terms used to describe the invention are detailed below:

The cannabinoids described in the present application are listed below along with their standard abbreviations.

The table above is not exhaustive and merely details the cannabinoids which are identified in the present application for reference. So far over 60 different cannabinoids have been identified and these cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).

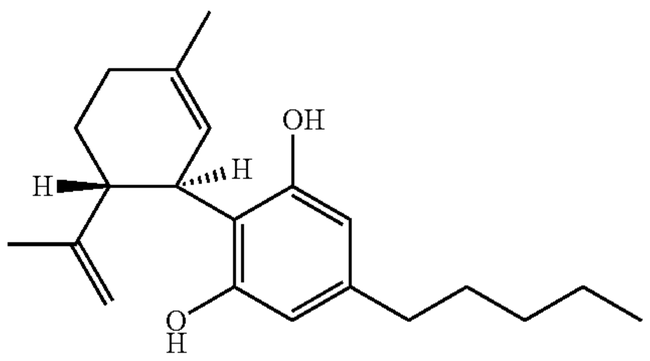
"Phytocannabinoids" are cannabinoids that originate from nature and can be found in the *cannabis* plant. The phytocannabinoids can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.

"Highly purified cannabinoids" are defined as cannabinoids that have been extracted from the *cannabis* plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been removed, such that the highly purified cannabinoid is greater than or equal to 98% (w/w) pure.

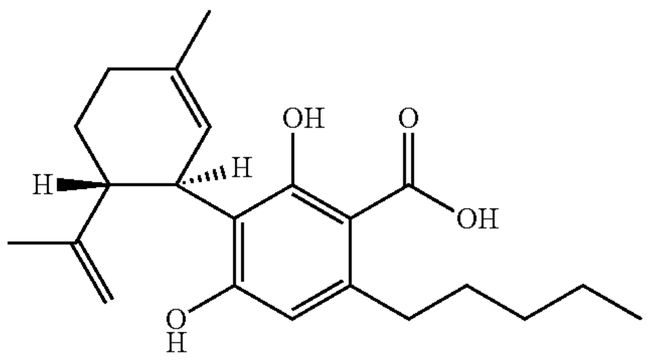
"Synthetic cannabinoids" are compounds that have a cannabinoid or cannabinoid-like structure and are manufactured using chemical means rather than by the plant.

Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For

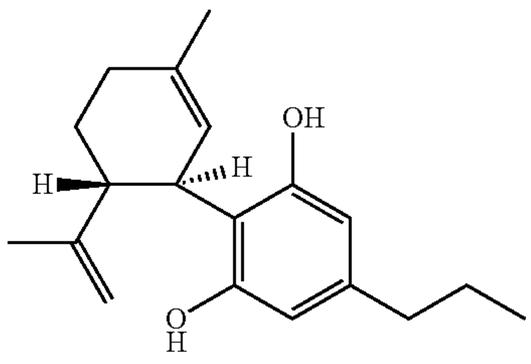
CBD Cannabidiol



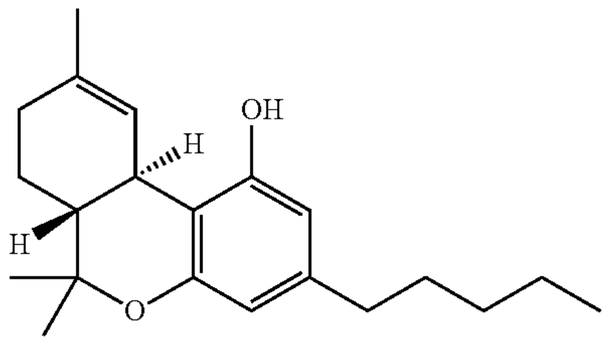
CBDA Cannabidiolic acid



CBDV Cannabidivarin



THC Tetrahydrocannabinol



example it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.

"Treatment-resistant epilepsy" (TRE) is defined as per the ILAE guidance of 2009 as epilepsy that is not adequately controlled by trials of one or more AED.

"Childhood epilepsy" refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of some of these are as follows: Dravet Syndrome; Myoclonic-Absence Epilepsy; Lennox-Gastaut syndrome; Generalized Epilepsy of unknown origin; CDKL5 mutation; Aicardi syndrome; bilateral polymicrogyria; Dup15q; SNAP25; and febrile infection related epilepsy syndrome (FIRES); benign rolandic epilepsy; juvenile myoclonic epilepsy; infantile spasm (West syndrome); and Landau-Kleffner syndrome. The list above is non-exhaustive as many different childhood epilepsies exist.

DETAILED DESCRIPTION

Preparation of Highly Purified Cbd Extract

The following describes the production of the highly-purified (>98% w/w) cannabidiol extract which has a known and constant composition which was used for the expanded access trials described in Examples below.

In summary the drug substance used in the trials is a liquid carbon dioxide extract of high-CBD containing chemotypes of *Cannabis sativa* L. which had been further purified by a solvent crystallization method to yield CBD. The crystallisation process specifically removes other cannabinoids and plant components to yield greater than 98% CBD.

The *Cannabis sativa* L. plants are grown, harvested, and processed to produce a botanical extract (intermediate) and then purified by crystallization to yield the CBD (drug substance).

The plant starting material is referred to as Botanical Raw Material (BRM); the botanical extract is the intermediate; and the active pharmaceutical ingredient (API) is CBD, the drug substance.

Both the botanical starting material and the botanical extract are controlled by specifications. The drug substance specification is described in Table 1 below.

TABLE 1

CBD Specification		
Test	Test Method	Limits
Appearance	Visual	Off-white/pale yellow crystals
Identification A	HPLC-UV	Retention time of major peak corresponds to certified CBD Reference Standard
Identification B	GC-FID/MS	Retention time and mass spectrum of major peak corresponds to certified CBD Reference Standard
Identification C	FT-IR	Conforms to reference spectrum for certified CBD Reference Standard
Identification D	Melting Point	65-67° C.
Identification E	Specific Optical Rotation	Conforms with certified CBD Reference Standard; −110° to −140° (in 95% ethanol)
Total Purity	Calculation	≥98.0%
Chromatographic Purity 1	HPLC-UV	≥98.0%
Chromatographic Purity 2	GC-FID/MS	≥98.0%
Impurities (Other Cannabinoids):	HPLC-UV	NMT 0.15% w/w
CBDA		NMT 1.0% w/w
CBDV		NMT 0.15% w/w
Δ^9 THC		NMT 0.5% w/w
CBD-C4		NMT 0.5% w/w
Residual Solvents:	GC	NMT 0.5% w/w
Alkane		NMT 0.5% w/w
Ethanol		
Residual Water	Karl Fischer	NMT 1.0% w/w

NMT—Not more than

TABLE 1-continued

CBD Specification		
Test	Test Method	Limits
CBDV		NMT 0.5% w/w
Δ^9 THC		
CBD-C4		
Residual Solvents:	GC	NMT 0.5% w/w
Alkane		NMT 0.5% w/w
Ethanol		
Residual Water	Karl Fischer	NMT 1.0% w/w

NMT—Not more than

The purity of the CBD drug substance achieved is greater than 98%. The possible impurities are related cannabinoids: CBDA, CBDV, CBD-C4 and THC.

Distinct chemotypes of *Cannabis sativa* L. plant have been produced to maximize the output of the specific chemical constituents, the cannabinoids. One type of plant produces predominantly CBD. Only the (−)-trans isomer occurs naturally, furthermore during purification the stereochemistry of CBD is not affected.

Production of the Intermediate

An overview of the steps to produce a botanical extract, the intermediate, are as follows:

1.	Growing
2.	Decarboxylation
3.	Extraction No. 1 - using liquid CO_2
4.	Extraction No. 2 - 'winterization' using ethanol
5.	Filtration
6.	Evaporation

High CBD chemovars were grown, harvested and dried and stored in a dry room until required. The botanical raw material (BRM) was finely chopped using an Apex mill fitted with a 1 mm screen. The milled BRM was stored in a freezer for up to 3 months prior to extraction.

Decarboxylation of CBDA to CBD was carried out using a large Heraeus tray oven. The decarboxylation batch size in the Heraeus is approximately 15 Kg. Trays were placed in the oven and heated to 105° C.; the BRM took 96.25 minutes to reach 105° C. Held at 105° C. for 15 Minutes. Oven then set to 150° C.; the BRM took 75.7 minutes to reach 150° C.; BRM held at 150° C. for 130 Minutes. Total time in the oven was 380 Minutes, including 45 minutes cooling and 15 Minutes venting.

Extraction No 1 was performed using liquid CO2 at 60 bar/10° C. to produce botanical drug substance (BDS) which was used for crystallisation to produce the test material.

The crude CBD BDS was winterised in Extraction No 2 under standard conditions (2 volumes of ethanol at minus 20° C. for around 50 hours). The precipitated waxes were removed by filtration and the solvent evaporated using the rotary evaporator (water bath up to 60° C.) to yield the BDS.

Production of the Drug Substance

The manufacturing steps to produce the drug substance from the intermediate botanical extract are as follows:

1. Crystallization using C5-C12 straight chain or branched alkane
2. Filtration
3. Optional recrystallization from C5-C12 straight chain or branched alkane
4. Vacuum drying

Intermediate botanical extract (12 kg) produced using the methodology above was dispersed in C5-C12 straight chain or branched alkane (9000 ml, 0.75 vols) in a 30 litre stainless steel vessel.

The mixture was manually agitated to break up any lumps and the sealed container then placed in a freezer for approximately 48 hours.

The crystals were isolated by vacuum filtration, washed with aliquots of cold C5-C12 straight chain or branched alkane (total 12000 ml), and dried under a vacuum of <10 mb at a temperature of 60° C. until dry before submitting the drug substance for analysis.

The dried product was stored in a freezer at minus 20° C. in a pharmaceutical grade stainless steel container, with FDA food grade approved silicone seal and clamps.

Examples 1 to 3 below describe the use of a highly purified *cannabis* extract comprising cannabidiol (CBD). Cannabidiol is the most abundant non-psychoactive cannabinoid in the *cannabis* plant. Previous studies in animals have demonstrated that CBD has anticonvulsant efficacy in multiple species and models.

Example 1 describes data produced in an expanded access treatment program in children with TRE.

Examples 2 to 4 demonstrates the efficacy of CBD in children with Dravet syndrome, myoclonic absence seizures and FIRES respectively.

Example 1: Efficacy of Cannabidiol in Children and Young Adults with Treatment-Resistant Epilepsy

Materials and Methods

Twenty-seven children and young adults with severe, childhood onset treatment-resistant epilepsy (TRE) were tested with a highly purified extract of cannabidiol (CBD) obtained from a *cannabis* plant. The participants in the study were part of an expanded access compassionate use program for CBD.

All patients entered a baseline period of 4 weeks when parents/caregivers kept prospective seizure diaries, noting all countable motor seizure types.

The patients then received a highly purified CBD extract (greater than 98% CBD w/w) in sesame oil, of known and constant composition, at a dose of 5 mg/kg/day in addition to their baseline anti-epileptic drug (AED) regimen.

The daily dose was gradually increased by 2 to 5 mg/kg increments until intolerance occurred or a maximum dose of 25 mg/kg/day was achieved.

Patients were seen at regular intervals of 2-4 weeks. Laboratory testing for hematologic, liver, kidney function, and concomitant AED levels was performed at baseline, and after 4, 8 and 12 weeks of CBD therapy.

Results

There were 27 children and young adult patients who received at least 3 months of treatment all of whom suffered from treatment-resistant epilepsy.

All patients were taking at least two concomitant anti-epileptic drugs. These included clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide. The average number of concomitant anti-epileptic drugs being taken was 2.7. The majority took either clobazam and/or valproic acid.

Co-treatment of CBD with clobazam was a significant predictor of a positive treatment response of greater than 50% responder rate. There was an odds ratio (OR) of 3.3 for total seizure reduction and of 1.9 for convulsive seizures. The OR evaluates whether the odds of a certain event or outcome is the same for two groups. Specifically, the OR measures the ratio of the odds that an event or result will occur to the odds of the event not happening. An OR greater than 1 signifies that patients treated with a combination of CBD with clobazam will have a better odds of having a positive reduction in seizures than if they were not taking this combination of medications.

The median number of seizures that these patients suffered from before starting treatment was 30 seizures per month, with a range of 4 to 2,800 seizures per month being recorded.

Efficacy results for the 27 patients are summarized in Table 2 below.

TABLE 2

Changes in Seizure Frequency with CBD Therapy

All patients	Month 3 (n = 27)
Responder rate (>50% reduction) [%]	13 [48%]
Responder rate (>70% reduction) [%]	11 [41%]
Responder rate (>90% reduction) [%]	6 [22%]
Seizure free [%]	2 [7%]

Table 2 shows that after 3 months of therapy, 48% of patients had an equal to or greater than >50% reduction in seizures.

Remarkably, two of the patients, equating to 7%, were entirely free from seizures at the three month stage.

None of the 27 subjects withdrew during the 3-month treatment period and adverse events were mild and well tolerated. Common adverse events included somnolence, fatigue, decreased appetite, increased appetite and diarrhoea.

In five subjects their dose of clobazam was reduced due to its sedative effect.

Conclusions

These preliminary results indicate that CBD significantly reduces the number of seizures in a high proportion of patients that do not respond well to existing AED. The cannabidiol was generally well-tolerated in doses up to 25 mg/kg/day.

It was surprising that in this group of patients which are treatment-resistant such a high number were able to gain an effect. The fact that nearly half of the patients (48%) benefitted from at least a fifty percent reduction in the number of seizures that they suffered from was remarkable.

Furthermore, nearly a quarter (22%) of patients whose seizures were not controlled with at least two anti-epileptic drugs, experienced a reduction of 90% of the number of seizures they were experiencing and 7% were completely seizure free at the end of the 3 month trial period.

Even more remarkable were the results for some defined sub-sets of this generic group and these are set out on Examples 2 to 4 below.

Example 2: Efficacy of Cannabidiol in Children and Young Adults with Treatment Resistant Dravet Syndrome

Materials and Methods

Nine children and young adults with treatment-resistant Dravet syndrome were part of an expanded access compassionate use program for highly purified CBD extract as described in Example 1.

Results

All nine patients with Dravet syndrome were taking at least two concomitant anti-epileptic drugs. These were largely AED operating via GABA and included clobazam;

levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; and zonisamide. The average number of concomitant antiepileptic drugs being taken was 2.7.

The mean number of seizures that these patients suffered from before starting treatment was 35 seizures per month, with a range of 6 to 112 seizures per month recorded.

Efficacy results for the 9 patients are summarized in Table 3 below.

TABLE 3

Changes in Seizure Frequency with CBD Therapy in Dravet Syndrome patients

	Dravet patients (n = 9)	All patients (n = 27)	All patients excluding Dravet patients (n = 18)
Responder rate (>50% reduction) [%]	5 [56%]	13 [48%]	8 [44%]
Responder rate (>70% reduction) [%]	4 [44%]	11 [41%]	7 [39%]
Responder rate (>90% reduction) [%]	3 [33%]	6 [22%]	3 [17%]
Seizure free [%]	2 [22%]	2 [7%]	0

Table 3 shows that after 3 months of therapy, 56% of patients had an equal to or greater than 50% reduction in seizures, a third had a 90% reduction and remarkably 22%, were entirely free from seizures at the three month stage.

None of the 9 subjects withdrew during the 3-month treatment period and adverse events were mild and well tolerated. Common adverse events included somnolence, fatigue, decreased appetite, increased appetite and diarrhoea.

Conclusions

These data demonstrate that in this sub-group of patients with treatment-resistant Dravet syndrome a surprisingly high number were able to gain a dramatic reduction in the number of seizures.

Nearly a quarter (22%) of patients were entirely seizure free at the end of the 3 month trial period. This would not be expected in this group of patients who were taking a large number of different anti-epileptic medications and yet were still suffering from a large number of seizures per day.

Example 3: Efficacy of Cannabidiol in Children and Young Adults with Treatment Resistant Myoclonic Absence Seizures

Materials and Methods

Four children and young adults with treatment-resistant myoclonic absence seizures were part of an expanded access compassionate use program for highly purified CBD extract as described in Example 1.

Results

All four patients with myoclonic absence seizures were taking at least two concomitant anti-epileptic drugs. These were largely AED operating via GABA and included clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; and zonisamide. The average number of concomitant antiepileptic drugs being taken was 27.

Efficacy results for the four patients are summarized in Table 4 below.

TABLE 4

Changes in Seizure Frequency with CBD Therapy in patients with myoclonic absence seizures (MAS)

	MAS patients (n = 4)	All patients (n = 27)	All patients excluding MAS patients (n = 23)
Responder rate (>50% reduction) [%]	2 [50%]	13 [48%]	11 [48%]
Responder rate (>70% reduction) [%]	2 [50%]	11 [41%]	9 [39%]
Responder rate (>90% reduction) [%]	1 [25%]	6 [22%]	5 [22%]
Seizure free [%]	0	2 [7%]	2 [9%]

Table 4 shows that after 3 months of therapy, half of the patients had an equal to or greater than 50% reduction in seizures, one patient (25%) had a 90% reduction at the three month stage.

None of the 4 subjects withdrew during the 3-month treatment period and adverse events were mild and well tolerated. Common adverse events included somnolence, fatigue, decreased appetite, increased appetite and diarrhoea.

Conclusions

These data demonstrate that in this sub-group of patients with treatment-resistant MAS a surprisingly high number were able to gain a reduction in the number of seizures.

Example 4: Efficacy of Cannabidiol in Children with Treatment Resistant Febrile Infection Related Epilepy Syndrome (Fires)

Febrile Infection Related Epilepsy Syndrome (FIRES) is a catastrophic epileptic encephalopathy with an unidentified aetiology that comprises a small minority of all patients with refractory status epilepticus.

This syndrome occurs in previously healthy children with 66-100% of survivors becoming developmentally disabled. The mortality rate is up to 30%. There is a critical need for new therapies to treat this condition.

Materials and Methods

Three patients with FIRES, with an age range of from 4 to 15 years, were treated with CBD under an expanded access program as described previously in Example 1.

Safety laboratory studies, physical/neurological exams, 24 hour video/EEG and seizure types and frequencies were assessed at baseline and one month after starting CBD.

A highly purified extract of CBD as an oral solution in sesame oil was used at a concentration of 25 mg/mL.

Treatment was initiated at a dose of 10 mg/kg/day given in two divided doses, increasing by 5 mg/kg/day every 3 days.

Following seizure improvement an average of 2 AEDs were weaned.

Results

Prior to initiation of treatment with highly purified CBD, the patients all suffered from refractory seizures or status epilepticus. These had been treated with anaesthetics including midazolam infusion, pentobarbital infusion, propofol infusion, and isofluorane infusion, additionally patients also were given steroids including lidocaine infusion, and methylprednisolone and other treatments including ketamine,

fosphenytoin, thiamine, rituximab, cyclophosphamide, intravenous immunoglobulin, and a hypothermia protocol.

At the time of initiation of CBD, the patients were taking between three and five anti-epileptic drugs including: levetiracetam, clobazam, perampanel, phenobarbital, phenytoin, carbamezapine, felbamate, ketogenic diet, lamotrigine, valproic acid and vagus nerve stimulation therapy.

Baseline 24 hour EEG of seizures were recorded. The total seizures at baseline and during the treatment period are shown in Table 5. Patient 1 was shown to be seizure free after starting treatment for almost all of the treatment period, with the number of seizures being reduced from 7 to 0.3 over a 24 week period. Patient 2 had a 50% reduction in seizures after 4 weeks however the seizure frequency increased after a further 4 weeks then started to decrease again after 16 weeks of treatment. The most remarkable response was seen in Patient 3, who suffered from 5600 seizures at baseline. The number of seizures were dramatically reduced after 4 weeks and at week 24 this patient was still demonstrating a greater than 90% reduction in the number of seizures.

The type of seizures that occurred in the three FIRES patients were all complex partial seizures (focal seizures with impairment). None of the FIRES patients suffered from focal seizures with secondary generalisation or convulsive seizures.

TABLE 5

Total Seizure Data

Visit	Frequency (per month)	Change from Baseline	% Change from Baseline	Responder (>=50% Reduction)	Responder (>=70% Reduction)	Responder (>=90% Reduction)	Seizure Free
Patient 1							
BL	4.0	n/a	n/a	n/a	n/a	n/a	n/a
Wk 4	0.0	~4.0	~100.0	Yes	Yes	Yes	Yes
Wk 8	1.0	~3.0	~75.0	Yes	Yes	No	No
Wk 12	0.0	~4.0	~100.0	Yes	Yes	Yes	Yes
Wk 16	0.0	~4.0	~100.0	Yes	Yes	Yes	Yes
Wk 24	0.3	~3.7	~92.0	Yes	Yes	Yes	No
Patient 2							
BL	7.0	n/a	n/a	n/a	n/a	n/a	n/a
Wk 2	0.8	~6.2	~88.6	Yes	Yes	No	No
Wk 4	3.0	~4.0	~57.1	Yes	No	No	No
Wk 8	10.0	3.0	42.9	No	No	No	No
Wk 12	8.0	1.0	14.3	No	No	No	No
Wk 16	4.0	~3.0	~42.9	No	No	No	No
Patient 3							
BL	5600.0	n/a	n/a	n/a	n/a	n/a	n/a
Wk 4	47.2	~5552.8	~99.2	Yes	Yes	Yes	No
Wk 8	9.2	~5590.8	~99.8	Yes	Yes	Yes	No
Wk 12	141.6	~5458.4	~97.5	Yes	Yes	Yes	No
Wk 24	542.0	~5058.0	~90.3	Yes	Yes	Yes	No

Follow up laboratory tests showed no changes in safety studies or concomitant AED levels. No treatment related adverse effects were observed.

Conclusions

CBD treatment was very well tolerated and associated with a dramatic and nearly immediate greater than 90% improvement in clinical and electrographic seizure burden in two of the three children with refractory seizures or status epilepticus due to FIRES.

After a reduction in seizures the patients were able to walk and verbalise once more.

SUMMARY TABLE AND CONCLUSIONS

Table 6 below summarises the data obtained in the three sub-sets: Dravet syndrome; myoclonic absence seizures (MAS) and febrile infection related epilepsy syndrome (FIRES) after 12 weeks of treatment which have been described in the Examples 2 to 4 above. In addition the data for the remainder of the patients with other epilepsy syndromes are detailed. These data which exclude the patients with Dravet, MAS and FIRES show a far lower responder rate than for the specified sub-sets of the above specified sub-sets of epilepsy.

In particular, the responder rate for patients obtaining a greater than 90% reduction in their seizures is reduced from 33% in Dravet patients to only 8% in the unspecified group. This suggests that patients suffering from a TRE of sub-type Dravet syndrome, myoclonic absence seizures or FIRES will respond better to treatment with highly purified CBD than patients with other epilepsy sub-types.

TABLE 6

Changes in Seizure Frequency with CBD Therapy in patients with sub-type TRE and all patients excluding the sub-types.

	All patients (excluding Dravet, MAS and FIRES) (n = 13)	Dravet patients (n = 9)	MAS patients (n = 4)	FIRES patients (n = 3)
Responder rate (>50% reduction) [%]	5 [38%]	5 [56%]	2 [50%]	2 [67%]
Responder rate (>70% reduction) [%]	4 [31%]	4 [44%]	2 [50%]	2 [67%]

TABLE 6-continued

Changes in Seizure Frequency with CBD Therapy in patients with sub-type TRE and all patients excluding the sub-types.

	All patients (excluding Dravet, MAS and FIRES) (n = 13)	Dravet patients (n = 9)	MAS patients (n = 4)	FIRES patients (n = 3)
Responder rate (>90% reduction) [%]	1 [8%]	3 [33%]	1 [25%]	2 [67%]
Seizure free [%]	0	2 [22%]	0	1 [33%]

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The invention claimed is:

1. A method of treating a type of treatment-resistant epilepsy, which is Dravet syndrome, in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a cannabidiol (CBD) drug substance and sesame oil, wherein the CBD drug substance comprises at least 98% w/w CBD; and

wherein the dose of CBD administered to the patient ranges from about 5 mg/kg/day to about 25 mg/kg/day.

2. The method of claim **1**, wherein the CBD is synthetic.

3. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD and not more than 0.15% w/w CBDA.

4. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD and not more than 1.0% w/w CBDV.

5. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD and not more than 0.15% w/w Δ^9THC.

6. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD and not more than 0.5% w/w CBD-C4.

7. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD, not more than 1.0% w/w CBDV, and not more than 0.15% w/w Δ^9THC.

8. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD, not more than 1.0% w/w CBDV, not more than 0.15% w/w Δ^9THC, and not more than 0.5% w/w CBD-C4.

9. The method of claim **1**, wherein the CBD drug substance comprises at least 98% w/w CBD, not more than 0.15% w/w CBDA, not more than 1.0% w/w CBDV, not more than 0.15% w/w Δ^9THC, and not more than 0.5% w/w CBD-C4.

10. The method of claim **1**, wherein the administering treats convulsive seizures.

11. The method of claim **1**, wherein the administering reduces seizure frequency.

12. The method of claim **1**, wherein the administering reduces seizure frequency by at least 50% compared to a seizure frequency experienced during a baseline period before CBD was administered.

13. The method of claim **9**, wherein the administering treats convulsive seizures.

14. The method of claim **9**, wherein the administering reduces seizure frequency.

15. The method of claim **9**, wherein the administering reduces total absence seizure frequency by at least 50% compared to a seizure frequency experienced during a baseline period before CBD was administered.

16. The method of claim **1**, wherein the dose of CBD is 10 mg/kg/day.

17. The method of claim **1**, wherein the dose of CBD is 20 mg/kg/day.

18. The method of claim **16**, wherein the administering treats convulsive seizures.

19. The method of claim **16**, wherein the administering reduces seizure frequency.

20. The method of claim **16**, wherein the administering reduces seizure frequency by at least 50% compared to a frequency experienced during a baseline period before CBD was administered.

21. The method of claim **17**, wherein the administering treats convulsive seizures.

22. The method of claim **17**, wherein the administering reduces seizure frequency.

23. The method of claim **17**, wherein the administering reduces seizure frequency by at least 50% compared to a seizure frequency experienced during a baseline period before CBD was administered.

24. A method of treating a type of treatment-resistant epilepsy, which is Lennox-Gastaut syndrome, in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising a cannabidiol (CBD) drug substance and sesame oil, wherein the CBD drug substance comprises at least 98% w/w CBD; and

wherein the dose of CBD administered to the patient ranges from about 5 mg/kg/day to about 25 mg/kg/day.

25. The method of claim **24**, wherein the administering treats convulsive seizures.

26. The method of claim **24**, wherein the administering reduces seizure frequency.

27. The method of claim **24**, wherein the administering reduces total absence seizure frequency by at least 50% compared to a seizure frequency experienced during a baseline period before CBD was administered.

28. The method of claim **24**, wherein the dose of CBD is 10 mg/kg/day.

29. The method of claim **24**, wherein the dose of CBD is 20 mg/kg/day.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,963,937 B2
APPLICATION NO. : 18/320906
DATED : April 23, 2024
INVENTOR(S) : Geoffrey Guy et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

At Column 16, Claim number 15, Line number 39:
“total absence seizure frequency”
Should read:
--seizure frequency--

At Column 17, Claim number 27, Line number 8:
“total absence seizure frequency”
Should read:
--seizure frequency--

Signed and Sealed this
Fourth Day of June, 2024

Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office