IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 21-691 (MN)
	)	
AVADEL CNS PHARMACEUTICALS LLC,	)	
	)	
Defendants.	)	

JAZZ PHARMACEUTICALS, INC.'S FIRST AMENDED ANSWER TO AVADEL CNS PHARMACEUTICALS LLC'S COUNTERCLAIMS

Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals"), by its undersigned attorneys, hereby submits its First Amended Answer to the Counterclaims to its Complaint for Patent Infringement by Defendant Avadel CNS Pharmaceuticals LLC ("Avadel"), dated June 3, 2021 (the "Counterclaims"), as follows. Except as expressly admitted, all allegations are denied.

AVADEL'S COUNTERCLAIMS

1. Avadel's Counterclaims arise under the Patent Laws of the United States, 35 U.S.C. § 1 et seq., and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: Paragraph 1 states legal conclusions for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that this Court has subject matter jurisdiction over Avadel's counterclaims as to US. Patent Nos. 8,731,963 (the "'963 patent"), 10,758,488 (the "'488 patent"), 10,813,885 (the "'885 patent"), 10,959,956 (the "'956 patent"), and 10,966,931 (the "'931 patent") (collectively, the "patents-in-suit"), denies that Avadel is entitled to any of the relief that it seeks, and, except as so admitted, denies the allegations of paragraph 1.

2. The Court has subject matter jurisdiction over these Counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338.

ANSWER: Paragraph 2 states legal conclusions for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that this Court has subject matter jurisdiction over Avadel's counterclaims as to the patents-in-suit, denies that Avadel is entitled to any of the relief that it seeks, and, except as so admitted, denies the allegations of paragraph 2.

3. Venue in this District is proper pursuant to 28 U.S.C. §§ 1391(b), (c), and 1400(b).

ANSWER: Paragraph 3 states legal conclusions for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that venue is proper to adjudicate this action and, except as so admitted, denies the allegations of paragraph 3.

4. Counterclaim-Plaintiff Avadel CNS Pharmaceuticals, LLC ("Avadel") is a limited liability company organized and existing under the laws of the State of Delaware and has its principal place of business at 16640 Chesterfield Grove Road, Suite 200, Chesterfield, Missouri 63005.

ANSWER: Jazz Pharmaceuticals admits on information and belief the allegations of paragraph 4.

5. Upon information and belief, Counterclaim-Defendant Jazz Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at 3170 Porter Drive, Palo Alto, California 94304.

ANSWER: Jazz Pharmaceuticals admits the allegations of paragraph 5.

AVADEL'S PRELIMINARY STATEMENT

6. Avadel Ireland owns six United States patents that cover Avadel's innovative product FT218, a once-nightly formulation of sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy. One of those patents, U.S. Patent No. 10,272,062 (the "'062 patent"), entitled "Modified Release Gamma-Hydroxybutyrate Formulations Having Improved Pharmacokinetics," was filed on July 21, 2017 and issued on April 30, 2019.

ANSWER: Jazz Pharmaceuticals admits that U.S. Patent No. 10,272,062 (the "'062 patent") is titled, "Modified release gamma-hydroxybutyrate formulations having improved pharmacokinetics," lists July 21, 2017 as the filing date, and lists April 30, 2019 as the issue

date. Jazz Pharmaceuticals further admits on information and belief that the '062 patent covers Avadel's proposed sodium oxybate product, code named FT218. Jazz Pharmaceuticals lacks knowledge or information sufficient to form a belief as to the truth of the remaining allegations of paragraph 6 and, therefore, denies those allegations.

7. On information and belief, Jazz was aware of the disclosures in the '062 patent since at least January 25, 2018, when the application that ultimately issued as the '062 patent (the "'062 application") was first published.

ANSWER: Jazz Pharmaceuticals admits that the '062 patent lists January 25, 2018 as the publication date of the underlying patent application, and, except as so admitted, denies the allegations of paragraph 7.

8. On information and belief, Jazz presumed that at least Example 1 and Example 1bis of the '062 application disclose the formulation of FT218, Avadel's once-nightly sodium oxybate formulation for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy. Indeed, Jazz's complaint in the instant action makes such an assumption.

ANSWER: Jazz Pharmaceuticals admits on information and belief that Avadel's published data concerning the pharmacokinetic properties of Avadel's proposed sodium oxybate product, FT218, correspond to the Examples of Avadel's '062 patent, that at least Example 1 and Example 1bis of Avadel's '062 patent are covered by Jazz Pharmaceuticals' '488, '885, '956, and '931 patents, and, except as so admitted, denies the allegations of paragraph 8.

9. The '062 application disclosed modified release formulations of gammahydroxybutyrate ("GHB" with sodium oxybate being its sodium salt) containing methacrylic acid-methyl methacrylate co-polymers, with certain dissolution profiles when tested in deionized water using USP apparatus 2 and where the dissolution medium was maintained at 37°C ± 0.5° C with the rotating paddle speed fixed at 50 rpm.

ANSWER: Jazz Pharmaceuticals admits that the '062 patent discloses formulations of sodium oxybate containing methacrylic acid-methyl methacrylate co-polymers, that the '062 patent further discloses dissolution properties of sodium oxybate formulations, refers to the text

and claims of the '062 patent for the contents thereof, and otherwise denies the allegations of paragraph 9.

10. At the time that the '062 application was published on January 25, 2018, Jazz had not filed any of the patent applications that ultimately issued as Jazz's asserted '488, '885, '956, and '931 patents, and was instead prosecuting the parent application to those patents, U.S. Application No. 13/071369 (the "Jazz '369 application"). The then-pending claims of the Jazz '369 application were directed to a "controlled release dosage form for oral administration" including a "compressed tablet controlled release core," comprising at least one polymer comprising ethylcellulose, at least one polymeric "pore former," and also recited "providing a time dependent release" measuring release of the drug from time of administration. See, e.g., Jazz '369 application File History, October 4, 2017 Response to Final Office Action at claim 1. One dependent claim recited that the "at least one polymeric pore-former is at least one of a polyethylene glycol, poloxamer, polyvinyl alcohol, copovidone, povidone, a water soluble sugar, a water soluble organic acid, such as carboxylic acids and their salts, and a hydroxyalkyl cellulose selected from hydroxyethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose." See Jazz '369 application File History, October 4, 2017 Response to Final Office Action at claim 16. The Jazz '369 application claims therefore corresponded to the substance of the specification, which disclosed controlled release dosage forms containing a compressed tablet controlled release core, ethylcellulose, and hydroxypropyl cellulose or poloxamer. See, e.g., Jazz '369 application at Examples 1-13.

ANSWER: Jazz Pharmaceuticals admits that it filed U.S. Patent Application No. 13/071,369 (the "'369 application") on March 24, 2011, refers to the text, claims, and file history of the '369 application for the contents thereof, and otherwise denies the allegations of paragraph 10.

11. Claim 1 of the Jazz '369 application was originally directed to "a controlled release dosage form for oral administration," but the applicant narrowed claim 1 first to a "compressed tablet" and later to include a "compressed tablet controlled release core," in response to rejections finding that claim 1 was obvious over a prior art patent application to Liang et al. See Jazz '369 application File History, May 28, 2013 Response to Office Action at claim 1; January 27, 2014 response to Office Action at claim 1. These narrowing amendments conformed the claims to the disclosure of the Jazz '369 application, which was limited to a compressed tablet dosage form. Further, the Jazz '369 application had no claims or teachings of dissolution testing or the release profiles resulting from such testing of formulations containing methacrylic acid-methyl methacrylate co-polymers in deionized water using apparatus 2 at a temperature of 37°C and a paddle speed of 50 rpm, as described in the '062 application. After the '062 application was published, Jazz let its '369 application become abandoned on November 2, 2018.

ANSWER: Jazz Pharmaceuticals refers to the text, claims, and file history of the '369 application for the contents thereof, and otherwise denies the allegations of paragraph 11.

12. Jazz did not file the application that ultimately led to the issuance of the '488 patent until July 2, 2018 – after the '062 application was published. The '488 patent was filed and characterized as a continuation of the Jazz '369 application. Notably, Jazz canceled all 108 original claims that generally recited the four components described supra – namely a "compressed tablet" controlled release dosage form, comprising at least one polymer comprising ethylcellulose, at least one polymeric "pore former," and reciting "providing a time dependent release" measuring release of the drug from time of administration. In stark contrast to its prior set of claims, Jazz deleted each of those four attributes, and replaced them with claims directed to a generic formulation (rather than a compressed tablet) comprising specifically methacrylic acid-methyl methacrylate co-polymers (rather than one polymer comprising ethylcellulose and at least one polymeric "pore former"), and recited a specific dissolution profile defined by tests performed "in a dissolution apparatus 2 in deionized water at a temperature of 37°C and a paddle speed of 50 rpm" (rather than reciting attributes following administration).

ANSWER: Jazz Pharmaceuticals admits that it filed U.S. Patent Application No. 16/025,487 (the "'487 application") on July 2, 2018 as a continuation of the '369 application, that the '487 application issued as the '488 patent on September 1, 2020, refers to the text, claims, and file history of the '488 patent for the contents thereof, and otherwise denies the allegations of paragraph 12.

13. On information and belief, Jazz drafted the claims that ultimately issued as the '488 patent based not on any commensurate disclosure of its underlying application, but solely in view of the disclosures set forth in the '062 application. The '488 patent specification does not disclose dissolution testing or the release profile resulting from such testing of formulations containing methacrylic acid-methyl methacrylate co-polymers in deionized water using apparatus 2 at a temperature of 37°C and a paddle speed of 50 rpm. As such, the '488 patent claims as filed and issued are neither described nor supported by its specification as, on information and belief, the claims were instead solely based on Avadel Ireland's inventive work disclosed in at least the '062 Application.

ANSWER: Jazz Pharmaceuticals refers to the text, claims, and file history of the '488 patent for the contents thereof, and otherwise denies the allegations of paragraph 13.

14. Jazz filed the application that ultimately issued as the '885 patent on June 30, 2020 as a continuation of at least the '488 patent. Like with the '488 patent, on information and belief, the claims of the '885 patent were written based on the disclosures in the '062 application. The '885 patent was filed and has issued with claims to formulations comprising methacrylic acidmethyl methacrylate co-polymers and a specific dissolution profile defined by tests

performed "in a dissolution apparatus 2 in deionized water at a temperature of 37°C and a paddle speed of 50 rpm." For the same reasons as above, the '885 patent claims are neither described nor supported by its patent specification, as the claims were written based solely on Avadel Ireland's inventive work disclosed in at least the '062 application.

ANSWER: Jazz Pharmaceuticals admits that it filed U.S. Patent Application No. 16/916,677 (the "'677 application") on June 30, 2020 as a continuation of U.S. Patent Application No. 16/712,260, which was a continuation of the '487 application, that the '677 application issued as the '885 patent on October 27, 2020, refers to the text, claims, and file history of the '885 patent for the contents thereof, and otherwise denies the allegations of paragraph 14.

15. Jazz filed the application that ultimately issued as the '956 patent on September 4, 2020 as a continuation of at least the '885 patent. As with the '885 patent, the '956 patent was filed and has issued with claims to formulations comprising methacrylic acid-methyl methacrylate co-polymers and a specific dissolution profile defined by tests performed "in a dissolution apparatus 2 in deionized water at a temperature of 37°C and a paddle speed of 50 rpm." For the same reasons as above, the '956 patent claims are neither described nor supported by its patent specification, as the claims were written solely based on Avadel Ireland's inventive work disclosed in at least the '062 application.

ANSWER: Jazz Pharmaceuticals admits that it filed U.S. Patent Application No. 17/012,823 (the "'823 application") on September 4, 2020 as a continuation of the '677 application, that the '823 application issued as the '956 patent on March 30, 2021, refers to the text, claims, and file history of the '956 patent for the contents thereof, and otherwise denies the allegations of paragraph 15.

16. Jazz filed the application that ultimately issued as the '931 patent on September 4, 2020 as a continuation of at least the '885 patent. As with the '885 patent, the '931 patent was filed and has issued with claims to formulations comprising methacrylic acid-methyl methacrylate co-polymers and a specific dissolution profile defined by tests performed "in a dissolution apparatus 2 in deionized water at a temperature of 37°C and a paddle speed of 50 rpm." For the same reasons as above, the '931 patent claims are neither described nor supported by its patent specification, as the claims were written solely based on Avadel Ireland's inventive work disclosed in at least the '062 application.

ANSWER: Jazz Pharmaceuticals admits that it filed U.S. Patent Application No. 17/012,831 (the "'831 application") on September 4, 2020 as a continuation of the '677 application, that the '831 application issued as the '931 patent on April 6, 2021, refers to the text, claims, and file history of the '931 patent for the contents thereof, and otherwise denies the allegations of paragraph 16.

Count I: Declaratory Judgment of Alleged Non-Infringement of the '963 Patent

17. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

18. An actual controversy exists between Avadel and Jazz over the alleged infringement of at least one claim of the '963 patent. Jazz holds itself out as the owner of the '963 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '963 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '963 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 18 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '963 patent, that Jazz Pharmaceuticals owns the '963 patent, that Avadel's filing of a New Drug Application ("NDA") to commercially market Avadel's proposed sodium oxybate drug product before the '963 patent expires infringes at least claim 1 of the '963 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '963 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 18.

19. The submission of Avadel's NDA does not infringe the '963 patent in violation of 35 U.S.C. § 271(e), either literally or under the doctrine of equivalents. The making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States would not infringe any valid claim of the '963 patent in violation of 35 U.S.C. §§ 271(a), 271(b),

and/or 271(c), either literally or under the doctrine of equivalents. Avadel hereby seeks a declaration that the submission of Avadel's NDA, and the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States does not infringe and/or will not infringe any valid claim of the '963 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 19.

20. Avadel has not infringed, is not infringing, and will not infringe any valid claim of the '963 patent, directly, indirectly, by inducement, contributorily, literally, under the doctrine of equivalents, or in any other manner. A judicial declaration is necessary and appropriate so that Avadel may ascertain its rights regarding the '963 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 20.

Count II: Declaratory Judgment of Alleged Invalidity of the '963 Patent

21. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

22. An actual controversy exists between Avadel and Jazz over the invalidity of the '963 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '963 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '963 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 22 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '963 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '963 patent expires infringes at least claim 1 of the '963 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '963 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 22.

23. All claims of the '963 patent are invalid because they fail to comply with one or more requirements of the United States Code Title 35, including, without limitation, one or more

requirements of 35 U.S.C. §§ 102, 103, and/or 112. Avadel expressly reserves all rights to identify and assert additional invalidity positions in this case.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 23.

24. Avadel hereby seeks a declaration that the claims of the '963 patent are invalid.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek a declaration that the claims of the '963 patent are invalid, denies that Avadel is entitled to the relief that it seeks and, except as so admitted, denies the allegations of paragraph 24.

Count III: Declaratory Judgment Alleging Required Delisting of the '963 Patent

25. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

26. An actual controversy exists between Avadel and Jazz over the listing of the '963 patent in the Orange Book.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek an order requiring Jazz Pharmaceuticals to remove the '963 patent from the United States Food and Drug Administration ("FDA") publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") listing with respect to XYREM®, denies that Avadel is entitled to the relief that it seeks, and denies all other allegations of paragraph 26.

27. Under 21 C.F.R. § 314.53(c), only patents claiming a drug product, drug substance, or method of using the drug may be listed in the Orange Book.

ANSWER: Jazz Pharmaceuticals admits that 21 C.F.R. § 314.53(c) contains regulations relating to the submission of patent information to the FDA, refers to the regulations for the terms thereof and, except as so admitted, denies the allegations of paragraph 27.

28. The '963 patent only includes claims to a "computer-implemented system for treatment of a narcoleptic patient with a prescription drug . . . ," which are neither method claims nor claims to a drug product or drug substance.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 28.

29. The FDA requires patent holders who list patents in the Orange Book to submit a Use Code, which is a code to designate a method patent that covers the approved indication or use of a drug product. Jazz characterized the "computer system" claimed in the '963 Patent according to the use code "U-1110: METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION."

ANSWER: Jazz Pharmaceuticals admits that it submitted the use code U-1110, method of treating a patient with a prescription drug using a computer database in a computer system for distribution, to the FDA with respect to the Orange Book listing for the '963 patent for XYREM®, and, except as so admitted, denies the allegations of paragraph 29.

30. The '963 patent does not claim a method of using the approved drug product as required by 21 C.F.R. § 314.53(c) and thus should be removed from the Orange Book.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 30.

31. Avadel hereby seeks a declaration pursuant to 21 U.S.C. § 355(c)(3)(D)(ii)(I) ordering Jazz to remove the '963 patent from the Orange Book.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek a declaration ordering Jazz Pharmaceuticals to remove the '963 patent from the Orange Book, denies that Avadel is entitled the relief that it seeks and, except as so admitted, denies the allegations of paragraph 31.

Count IV: Declaratory Judgment of Alleged Non-Infringement of the '488 Patent

32. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

33. An actual controversy exists between Avadel and Jazz over the alleged infringement of at least one claim of the '488 patent. Jazz holds itself out as the owner of the '488 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '488 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '488 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 33 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '488 patent, that Jazz Pharmaceuticals owns the '488 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '488 patent expires infringes at least claim 1 of the '488 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '488 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 33.

34. The submission of Avadel's NDA does not infringe the '488 patent in violation of 35 U.S.C. § 271(e), either literally or under the doctrine of equivalents. The making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States would not infringe any valid claim of the '488 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), either literally or under the doctrine of equivalents. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '488 patent. Avadel hereby seeks a declaration that the submission of Avadel's NDA, and the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States does not infringe and/or will not infringe any valid claim of the '488 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 34.

35. Avadel has not infringed, is not infringing, and will not infringe any valid claim of the '488 patent, directly, indirectly, by inducement, contributorily, literally, under the doctrine of equivalents, or in any other manner. A judicial declaration is necessary and appropriate so that Avadel may ascertain its rights regarding the '488 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 35.

Count V: Declaratory Judgment of Alleged Invalidity of the '488 Patent

36. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

37. An actual controversy exists between Avadel and Jazz over the invalidity of the '488 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA

infringes at least claim 1 of the '488 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '488 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 37 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '488 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '488 patent expires infringes at least claim 1 of the '488 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '488 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 37.

38. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '488 patent. To the extent otherwise, all of the claims of the '488 patent are invalid because they fail to comply with one or more requirements of the United States Code Title 35, including, without limitation, one or more requirements of 35 U.S.C. §§ 102, 103, and/or 112. For example, as set forth in Paragraphs 6 through 13 of the Counterclaims, the claims of the '488 patent are invalid for at least derivation pursuant to pre-AIA 35 U.S.C. § 102(f) and/or lack of written description under 35 U.S.C. § 112 because the claims as filed are neither described nor supported by the specification.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 38.

39. Alternatively, because the claims of the '488 patent are unsupported by the written description, they are not entitled to claim priority to the Jazz '369 application and are subject to the provisions of the AIA. Under post-AIA law, the claims of the '488 patent are invalid under 35 U.S.C. § 102 over the '062 application, because Avadel Ireland effectively filed a patent application with the pertinent subject matter before the earliest date to which the '488 patent can claim priority. Avadel expressly reserves all rights to identify and assert additional invalidity positions in this case.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 39.

40. Avadel hereby seeks a declaration that the claims of the '488 patent are invalid.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek a declaration that the claims of the '488 patent are invalid, denies that Avadel is entitled to the relief that it seeks, and, except as so admitted, denies the allegations of paragraph 40.

Count VI: Declaratory Judgment of Alleged Non-Infringement of the '885 Patent

41. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

42. An actual controversy exists between Avadel and Jazz over the alleged infringement of at least one claim of the '885 patent. Jazz holds itself out as the owner of the '885 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '885 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '885 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 42 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '885 patent, that Jazz Pharmaceuticals owns the '885 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '885 patent expires infringes at least claim 1 of the '885 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '885 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 42.

43. The submission of Avadel's NDA does not infringe the '885 patent in violation of 35 U.S.C. § 271(e), either literally or under the doctrine of equivalents. The making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States would not infringe any valid claim of the '885 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), either literally or under the doctrine of equivalents. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '885 patent. Avadel hereby seeks a declaration that the submission of Avadel's NDA, and the making, using, offering to sell, selling,

and/or importation of Avadel's Proposed Product in the United States does not infringe and/or will not infringe any valid claim of the '885 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 43.

44. Avadel has not infringed, is not infringing, and will not infringe any valid claim of the '885 patent, directly, indirectly, by inducement, contributorily, literally, under the doctrine of equivalents, or in any other manner. A judicial declaration is necessary and appropriate so that Avadel may ascertain its rights regarding the '885 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 44.

Count VII: Declaratory Judgment of Alleged Invalidity of the '885 Patent

45. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

46. An actual controversy exists between Avadel and Jazz over the invalidity of the '885 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '885 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '885 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 46 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '885 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '885 patent expires infringes at least claim 1 of the '885 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '885 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 46.

47. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '885 patent. To the extent otherwise, all of the claims of the '885 patent are invalid because they fail to comply with one or more requirements of the United States Code Title 35, including, without limitation, one or more requirements of 35 U.S.C. §§ 102, 103, and/or 112. For example,

as set forth in Paragraphs 6 through 12 and 14 of the Counterclaims, the claims of the '885 patent are invalid for at least derivation pursuant to pre-AIA 35 U.S.C. § 102(f) and/or lack of written description under 35 U.S.C. § 112 because the claims as filed are neither described nor supported by the specification.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 47.

48. Alternatively, because the claims of the '885 patent are unsupported by the written description, they are not entitled to claim priority to the Jazz '369 application and are subject to the provisions of the AIA. Under post-AIA law, the claims of the '885 patent are invalid under 35 U.S.C. § 102 over the '062 application, because Avadel Ireland effectively filed a patent application with the pertinent subject matter before the earliest date to which the '885 patent can claim priority. Avadel expressly reserves all rights to identify and assert additional invalidity positions in this case.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 48.

49. Avadel hereby seeks a declaration that the claims of the '885 patent are invalid.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek a declaration that the claims of the '885 patent are invalid, denies that Avadel is entitled to the relief that it seeks and, except as so admitted, denies the allegations of paragraph 49.

Count VIII: Declaratory Judgment of Alleged Non-Infringement of the '956 Patent

50. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

51. An actual controversy exists between Avadel and Jazz over the alleged infringement of at least one claim of the '956 patent. Jazz holds itself out as the owner of the '956 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '956 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '956 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 51 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '956 patent, that Jazz Pharmaceuticals owns the '956 patent, that Avadel's filing of an NDA to commercially market

Avadel's proposed sodium oxybate drug product before the '956 patent expires infringes at least claim 1 of the '956 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '956 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 51.

52. The submission of Avadel's NDA does not infringe the '956 patent in violation of 35 U.S.C. § 271(e), either literally or under the doctrine of equivalents. The making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States would not infringe any valid claim of the '956 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), either literally or under the doctrine of equivalents. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '956 patent. Avadel hereby seeks a declaration that the submission of Avadel's NDA, and the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States does not infringe and/or will not infringe any valid claim of the '956 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 52.

53. Avadel has not infringed, is not infringing, and will not infringe any valid claim of the '956 patent, directly, indirectly, by inducement, contributorily, literally, under the doctrine of equivalents, or in any other manner. A judicial declaration is necessary and appropriate so that Avadel may ascertain its rights regarding the '956 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 53.

Count IX: Declaratory Judgment of Alleged Invalidity of the '956 Patent

54. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

55. An actual controversy exists between Avadel and Jazz over the invalidity of the '956 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '956 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '956 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 55 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy

exists between Avadel and Jazz Pharmaceuticals regarding the '956 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '956 patent expires infringes at least claim 1 of the '956 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '956 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 55.

56. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '956 patent. To the extent otherwise, all of the claims of the '956 patent are invalid because they fail to comply with one or more requirements of the United States Code Title 35, including, without limitation, one or more requirements of 35 U.S.C. §§ 102, 103, and/or 112. For example, as set forth in Paragraphs 6 through 12 and 15 of the Counterclaims, the claims of the '956 patent are invalid for at least derivation pursuant to pre-AIA 35 U.S.C. § 102(f) and/or lack of written description under 35 U.S.C. § 112 because the claims as filed are neither described nor supported by the specification.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 56.

57. Alternatively, because the claims of the '956 patent are unsupported by the written description, they are not entitled to claim priority to the Jazz '369 application and are subject to the provisions of the AIA. Under post-AIA law, the claims of the '956 patent are invalid under 35 U.S.C. § 102 over the '062 application, because Avadel Ireland effectively filed a patent application with the pertinent subject matter before the earliest date to which the '956 patent can claim priority. Avadel expressly reserves all rights to identify and assert additional invalidity positions in this case.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 57.

58. Avadel hereby seeks a declaration that the claims of the '956 patent are invalid.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek a declaration that the claims of the '956 patent are invalid, denies that Avadel is entitled to the relief that it seeks, and, except as so admitted, denies the allegations of paragraph 58.

Count X: Declaratory Judgment of Alleged Non-Infringement of the '931 Patent

59. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

60. An actual controversy exists between Avadel and Jazz over the alleged infringement of at least one claim of the '931 patent. Jazz holds itself out as the owner of the '931 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '931 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '931 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 60 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '931 patent, that Jazz Pharmaceuticals owns the '931 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '931 patent expires infringes at least claim 1 of the '931 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '931 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 60.

61. The submission of Avadel's NDA does not infringe the '931 patent in violation of 35 U.S.C. § 271(e), either literally or under the doctrine of equivalents. The making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States would not infringe any valid claim of the '931 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), either literally or under the doctrine of equivalents. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '931 patent. Avadel hereby seeks a declaration that the submission of Avadel's NDA, and the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States does not infringe and/or will not infringe any valid claim of the '931 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 61.

62. Avadel has not infringed, is not infringing, and will not infringe any valid claim of the '931 patent, directly, indirectly, by inducement, contributorily, literally, under the doctrine of equivalents, or in any other manner. A judicial declaration is necessary and appropriate so that Avadel may ascertain its rights regarding the '931 patent.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 62.

Count XI: Declaratory Judgment of Alleged Invalidity of the '931 Patent

63. Avadel incorporates by reference the allegations made in Avadel's Defenses and in the preceding paragraphs of the Counterclaims above.

ANSWER: Jazz Pharmaceuticals incorporates its responses to the preceding paragraphs.

64. An actual controversy exists between Avadel and Jazz over the invalidity of the '931 patent. Jazz has filed suit against Avadel alleging that the submission of Avadel's NDA infringes at least claim 1 of the '931 patent in violation of 35 U.S.C. § 271(e). Jazz has also alleged that the making, using, offering to sell, selling, and/or importation of Avadel's Proposed Product in the United States infringes at least claim 1 of the '931 patent in violation of 35 U.S.C. §§ 271(a), 271(b), and/or 271(c).

ANSWER: Paragraph 64 states a legal conclusion for which no answer is required. To the extent that an answer is required, Jazz Pharmaceuticals admits that a justiciable controversy exists between Avadel and Jazz Pharmaceuticals regarding the '931 patent, that Avadel's filing of an NDA to commercially market Avadel's proposed sodium oxybate drug product before the '931 patent expires infringes at least claim 1 of the '931 patent under 35 U.S.C. § 271(e), that the making, using, offering to sell, selling, and/or importation of Avadel's proposed sodium oxybate drug product will infringe at least claim 1 of the '931 patent under 35 U.S.C. §§ 271(a), 271(b), and/or 271(c), and, except as so admitted, denies the allegations of paragraph 64.

65. In light of various statements made by the Jazz applicants during the course of prosecution, the Avadel FT218 product does not infringe and cannot infringe any valid claim of the '931 patent. To the extent otherwise, all of the claims of the '931 patent are invalid because they fail to comply with one or more requirements of the United States Code Title 35, including, without limitation, one or more requirements of 35 U.S.C. §§ 102, 103, and/or 112. For example, as set forth in Paragraphs 6 through 12 and 16 of the Counterclaims, the claims of the '931 patent are invalid for at least derivation pursuant to pre-AIA 35 U.S.C. § 102(f) and/or lack of written description under 35 U.S.C. § 112 because the claims as filed are neither described nor supported by the specification.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 65.

66. Alternatively, because the claims of the '931 patent are unsupported by the written description, they are not entitled to claim priority to the Jazz '369 application and are subject to the provisions of the AIA. Under post-AIA law, the claims of the '931 patent are invalid under 35 U.S.C. § 102 over the '062 application, because Avadel Ireland effectively filed a patent application with the pertinent subject matter before the earliest date to which the '931

patent can claim priority. Avadel expressly reserves all rights to identify and assert additional invalidity positions in this case.

ANSWER: Jazz Pharmaceuticals denies the allegations of paragraph 66.

67. Avadel hereby seeks a declaration that the claims of the '931 patent are invalid.

ANSWER: Jazz Pharmaceuticals admits that Avadel purports to seek a declaration that the claims of the '931 patent are invalid, denies that Avadel is entitled to the relief that it seeks and, except as so admitted, denies the allegations of paragraph 67.

AVADEL'S PRAYER FOR RELIEF

Jazz Pharmaceuticals denies that Avadel is entitled to any relief on its Counterclaims, either as prayed for in its pleading or otherwise.

JAZZ PHARMACEUTICALS' AFFIRMATIVE DEFENSES

1. Without prejudice to the denials set forth in this Answer and to the ability to amend this Answer to seek and allege any and all defenses not presently known or that are revealed during the course of discovery or otherwise, Jazz Pharmaceuticals asserts the following affirmative defenses in response to Avadel's Counterclaims:

I. Failure to State a Claim

2. The Counterclaims fail to state any claim for which relief may be granted.

II. Judicial Estoppel and Unclean Hands

3. In Civil Action Nos. Nos. 21-691, 21-1138, and 21-1594, Avadel's counterclaims seeking declaratory judgments of invalidity against Patent Nos. 10,758,488 ("the '488 Patent"), 10,813,885 ("the '885 Patent"), 10,959,956 ("the '956 Patent"), 10,966,931 ("the '931 Patent"), 11,077,079 ("the '079 Patent"), and 11,147,782 ("the '782 Patent") are barred, in whole or in part, under the equitable principles of estoppel and/or unclean hands.

A. Avadel's Inconsistent Positions Regarding the Jazz Sustained Release Patents

4. In this litigation, Avadel collectively refers to the '488 Patent, the '885 Patent, the '956 Patent, and the '931 Patent as the "Jazz Sustained Release Patents."

5. Avadel owns U.S. Patent No. 10,272,062 ("the '062 Patent"), which it prosecuted from July 2017 to April 2019. *See* Case No. 21-691, D.I. 11 at Counterclaim ¶ 6. Avadel refers to the patent application that led to the issuance of '062 Patent as the "'062 Application". *See id.* at ¶ 7.

6. Avadel has taken the position in this litigation that Jazz drafted the claims of each of the Jazz Sustained Release Patents "***solely based*** on Avadel Ireland's inventive work disclosed in at least the '062 Application." *See id.* at ¶ 13 (emphasis added); *see also id.* at ¶¶ 14-16.[1]

7. Avadel has also asserted in this litigation that fourteen alleged prior art references "anticipate and/or render obvious, either alone or in combination, the asserted claims of the . . . Jazz Sustained Release Patents." Ex. A, Avadel 10-13-21 Contentions at 4-5.

8. One of the references that Avadel contends "anticipate[s] and/or render[s] obvious" the asserted claims of the Jazz Sustained Release Patents is U.S. Patent No. 5,594,030, which issued to Ubaldo Conte et al. in 1997 (hereafter, "Conte 1997").

9. During prosecution of the '062 Patent—which Avadel contends is the sole basis for the claims of the Jazz Sustained Release Patents—Avadel argued to the United States Patent and Trademark Office ("USPTO") that Conte 1997 ***would not*** have taught or suggested the use of methacrylic acid-methyl methacrylate co-polymers in a sustained release GHB formulation, as is claimed in each asserted claim of the Jazz Sustained Release Patents. Instead, Avadel represented to the USPTO that "the coating of Conte [1997]'s compositions comprises

[1] Jazz Pharmaceuticals denies this claim.

copolymers that do not carry free carboxylic groups," and that "Conte [1997] provides no suggestion or rationale that would lead a person of ordinary skill in the art to modify the film coatings disclosed therein and include a polymer having free carboxylic groups," such as the claimed methacrylic acid-methyl methacrylate co-polymers. *See, e.g.*, Ex. B, App. No. 15/655,924, September 4, 2018 Response to Office Action at 12.

10. During prosecution of the '062 Patent, Avadel further represented to the USPTO that instead of rendering obvious a once-nightly GHB formulation, Conte 1997 would have affirmatively taught away from such an invention. Avadel represented to the USPTO that "Conte [1997] does ***not*** disclose or suggest a gamma-hydroxybutyrate composition in a unit dose suitable for administration only once-nightly," and that "[b]y requiring multiple doses (2 or more) during the day, and at substantially lower dosages to alleviate addiction symptoms in an awake state, Conte [1997] clearly teaches away." *Id.* at 12-13 (emphasis in original).

11. Avadel also relies on U.S. Patent Publication No. 2006/0210630 to Liang et al. (hereafter, "Liang 2006") in support of its assertion in this litigation that the Jazz Sustained Release Patents are invalid. More specifically, Avadel has taken the position in this litigation that the asserted claims of the Jazz Sustained Release Patents are obvious over Liang 2006, purportedly because the reference "discloses [GHB] formulations made up of an immediate release portion and a delayed/controlled release portion," and "[a]s in the Jazz Sustained Release Patent claims, Liang 2006's delayed/controlled release formulations are made up of a functional coating deposited over a core, with the core comprising gamma-hydroxybutyric acid salts and the functional coating comprising a pH sensitive enteric release coat such as a methacrylic acid-methyl methacrylate co-polymer." Ex. A, Avadel 10-13-21 Contentions at 20.

12. But Avadel advanced the exact opposite position during prosecution of the '062 Patent, arguing that Liang 2006 would ***not*** have rendered obvious a sustained release GHB formulation comprised of a functional coating containing 20-50 percent by weight methacrylic acid-methyl methacrylate co-polymers, as claimed in the Jazz Sustained Release Patents. Specifically, Avadel has represented to the USPTO that "Liang [2006] teaches that the compositions disclosed therein provide 'a convenient once nightly or once daily dose regiment for the oral delivery of one or more gamma-hydroxybutyric salts.' Thus, Liang [2006] provides no teaching or suggestion that would prompt a person of ordinary skill in the art to modify the coating of the delayed/controlled release component disclosed therein." *See* Ex. B, App. No. 15/655,924, September 4, 2018 Response to Office Action at 15.

13. Avadel's position in this litigation and its position before the USPTO are diametrically opposed. Avadel has taken the position in this litigation that Liang 2006—standing alone—renders the formulations claimed in the Jazz Sustained Release Patents obvious, but Avadel has taken the position before the USPTO that Liang 2006 would provide zero motivation to modify its disclosures to cover a formulation with the characteristics claimed in the Jazz Sustained Release Patents.

14. Avadel further advocated before the USPTO during prosecution of the '062 Patent that the data presented in Liang 2006 would not have given rise to any reasonable expectation that formulations that differ from those expressly disclosed in Laing 2006 would work for their intended purpose or exhibit any desired pharmacokinetic profile. Specifically, Avadel advocated that pharmacokinetic targets "could not be predicted" based upon the disclosures of Liang 2006. Ex. B, App. No. 15/655,924, September 4, 2018 Response to Office Action at 18.

15. Avadel also prosecuted U.S. Patent Nos. 10,736,866 ("the '866 Patent"), 10,952,986 ("the '986 Patent") and 10,973,795 ("the '795 Patent") prior to the initiation of this litigation. The '866 Patent is a continuation of the '062 Patent, and both the '986 and '795 Patents are continuations of the '866 Patent. All of these patents therefore contain substantively similar (if not identical) disclosures in their specifications.

16. Avadel continued to remark upon the Liang 2006 reference during prosecution of the '866 Patent, the '986 Patent, and the '795 Patent. Specifically, during prosecution of the '795 Patent, Avadel argued that, rather than give rise to any reasonable expectation regarding the properties of GHB formulations that differ from those expressly disclosed in Laing 2006, "**[u]sing Liang [2006] to guess the in vivo pharmacokinetic profile of [another] claimed invention would be pure speculation**." *See* Ex. C, Application No. 16/419,616, September 17, 2020 Response to Office Action at 10 (emphasis in original). During prosecution of the '866 Patent, Avadel represented to the USPTO that "because the dosage forms of Liang [2006] differ from the claimed formulation[s], a person of ordinary skill in the art would expect that pharmacokinetic properties would also differ." *See* Ex. D, Application No. 16/281,235, March 18, 2020 Response to Office Action at 21; *see also id.* at 19 (Avadel further arguing to the USPTO that "a person of ordinary skill in the art would not be prompted by the disclosure of Liang [2006] to modify the dosage forms disclosed therein"). And during prosecution of the '986 Patent, Avadel took the position that "[t]he unpredictability of GHB formulations is not merely academic . . . there is no reasonable predictability with respect to GHB formulations, even if a skilled artisan were trying to copy a formulation exactly. It's simply too unpredictable." Ex. E, App. No. 16/420,321, October 1, 2020 Response to Office Action at 9.

17. In sum, according to Avadel's own sworn statements to the USPTO, a POSA would not have been: (1) motivated to modify the disclosures of Liang 2006 or (2) able to reasonably expect that ***any*** sustained release formulation of GHB (let alone the claimed formulations of the Jazz Sustained Release Patents, with a functional coating comprised of 20-50 percent by weight methyl methacrylate, methacrylic acid copolymers) would demonstrate the claimed pharmacokinetic profiles based upon the disclosures of Liang 2006. Avadel has taken the opposite position in this litigation. *See* Ex. A, Avadel 10-13-21 Contentions at 20-25.

18. As set forth above, Avadel represented to the USPTO that Conte 1997 and Liang 2006 would not have rendered its GHB formulations obvious during prosecution of Avadel's Patent Application Nos. 15/655,924, 16/281,235, 16/419,616, and/or 16/420,321. Each of these Patent Applications issued as U.S. Patents (the '062 Patent, the '866 Patent, the '986 Patent, and the '795 Patent, respectively). Therefore, Avadel derived a benefit from the arguments it made to the USPTO in support of its patent applications.

B. Avadel's Inconsistent Positions Regarding the Jazz Resinate Patents

19. In this litigation, Avadel refers to the '079 Patent and the '782 Patent collectively as "the Jazz Resinate Patents."

(i). Avadel's Inconsistent Positions Regarding the '079 Patent

20. Avadel has taken the position in this litigation that the asserted claims of the '079 Patent "are generally directed to a method of treating narcolepsy with a single-dose oxybate formulation comprising opening a sachet containing a solid oxybate formulation comprising a mixture of immediate release and controlled release components and mixing the formulation with water for oral administration to a patient." Ex. F, Avadel 1-14-22 Contentions at 9-10.

21. Avadel has taken the position in this litigation that Liang 2006 anticipates the asserted claims of the '079 Patent. *See id.* at 10-11.

22. Avadel has also asserted in this litigation that eighteen alleged prior art references "anticipate and/or render obvious, either alone or in combination, the asserted claims of the '079 patent." *Id.* at 4-6.

23. As set forth below, these arguments are directly contradictory to arguments that Avadel has made before the USPTO.

24. Avadel asserts in the instant litigation that "Jazz, through its prosecution counsel, copied the claimed invention" of the '079 Patent from Avadel's then-pending Application No. 16/420,321 ("the '321 Application"). *See id.* at 65-69.[2] The '321 Application subsequently issued as the '986 Patent.

25. Avadel further asserts that the pending method claim that Jazz allegedly "copied" from the '321 Application into the '079 Patent was comprised of the following elements:

> A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:
>
> > administering a single daily dose to said human, the single daily dose comprising an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises
> >
> > > opening a sachet containing a gamma-hydroxybutyrate formulation,
> > >
> > > mixing the formulation with water, and
> > >
> > > orally administering the mixture.

See id. at 68; *see also* Ex. E, App. No. 16/420,321, October 1, 2020 Response to Office Action at 2.

[2] Jazz Pharmaceuticals denies this claim.

26. In 2020, the USPTO rejected this pending claim of the '321 Application as unpatentable over Liang 2006 in view of U.S. Patent App. Pub. No. 2002/0077334 to Cook et al. ("Cook 2002"). In response to that rejection, Avadel represented to the USPTO that Liang 2006 does "not expressly disclose opening a sachet containing a gamma hydroxybutyrate formulation, mixing the formulation with water and orally administering the mixture." *See* Ex. E, App. No. 16/420,321, October 1, 2020 Response to Office Action at 8.

27. Avadel has taken the opposite position in this litigation, arguing that Liang 2006 "discloses that the solid dosage form could be a sachet," and that "Liang 2006 discloses that the formulation could be stirred into a drink, and water is the most common form of drink." Ex. F, Avadel 1-14-22 Contentions at 10-11.

28. Avadel has also taken the position in this litigation that, to the extent that Liang 2006 is not found to anticipate claim 1 of the '079 Patent, that claim would "have been obvious to a POSA as of the earliest asserted priority date of the '079 patent [i.e., February 2015]," purportedly because "a POSA would have been motivated to develop a method for treating narcolepsy by administering a single daily dosage of GHB containing an immediate release component and a controlled release component in a sachet form." Ex. F, Avadel 1-14-22 Contentions at 11-12.

29. Avadel took the opposite position before the USPTO in October 2020 during prosecution of the '321 Application. More specifically, Avadel stated to the Patent Office that, at the time of alleged invention for the methods claimed in the '321 Application (2016), the prior art "***teaches away*** from a sachet as currently claimed." Ex. E, App. No. 16/420,321, October 1, 2020 Response to Office Action at 8 (emphasis in original). Avadel represented to the USPTO that the prior art disclosed "inherent problems" with sachet formulations and thus would have

taught a POSA to abandon the "problematic" sachet formulation "in favor of a purely liquid formulation." *Id.* Avadel further stated that there would be no reasonable expectation of success of formulating GHB into a sachet because "there are known problems of instability, microbial growth, and/or degradation of the GHB active ingredient into GBL," which Avadel stated would have taught away from a sachet formulation. *Id.* at 8-9. Thus, contrary to Avadel's position in this litigation that a POSA "***would have been motivated*** to develop a method for treating narcolepsy by administering a single daily dosage of GHB containing an immediate release component and a controlled release component in a sachet form" in 2015, Avadel expressly argued to the USPTO that, in 2016, "given the ***teachings away***" in the prior art, the prior art would "fail to provide an apparent reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed invention does with a reasonable expectation of success, as required by the law." *Id.* at 9.

30. The '321 Application issued as a U.S. Patent after Avadel overcame the obviousness rejection based upon Liang 2006 and Cook 2002. Therefore, Avadel derived a benefit from the arguments that it made to the USPTO.

(ii). Avadel's Inconsistent Positions Regarding the '782 Patent

31. Avadel has taken the position in this litigation that the asserted claims of the '782 Patent are "generally directed to a formulation or a unit dose of GHB with specific viscosity enhancing agents, acid, lubricants, amounts of GHB, or blood concentrations of GHB following administration of the claimed formulation." Ex. F, Avadel 1-14-22 Contentions at 27.

32. In this litigation, Avadel also contends that the claims of the '782 Patent were written after Jazz Pharmaceuticals allegedly "copied the claims from Avadel's application that led to the issuance of the '866 patent." *Id.* at 71.[3]

33. Avadel further argues in the present litigation that the asserted claims of the '782 Patent are obvious in view of Liang 2006. Specifically, Avadel asserts in this case that "Liang 2006 discloses all of the limitations of claim 1 other than a viscosity enhancing agent and acid that are separate from the immediate release and modified release particles." *Id.* at 28. Avadel further argues that "the addition of an acid and/or a viscosity enhancing agent separate from the immediate and modified release particles was well-known in the art as part of a multi-particulate drug form," and that "a POSA would have been motivated to modify the formulations in Liang 2006 . . . to include an acid and/or viscosity enhancing agent separate from the immediate and modified release particles of GHB with a reasonable expectation of arriving at the claimed formulation." *Id.* at 30.

34. As set forth below, this argument stands in direct contradiction to representations that Avadel made to the USPTO in March 2020, during the prosecution of Avadel's Patent Application No. 16/281,235 ("the '235 Application"), which led to the '866 Patent. In March 2020, then-pending claim 1 of the '235 Application was as follows:

A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent . . .

an acidifying agent . . .

[3] Jazz Pharmaceuticals denies this claim.

> wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion; and
>
> wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

See Ex. D, App. No. 16/281,235, March 18, 2020 Response to Office Action at 2.

35. Avadel contends in the instant litigation that Jazz "copied" this claim into the '782 Patent. Ex. F, Avadel 1-14-22 Contentions at 70-71.

36. The USPTO rejected claim 1 of the '235 Application as unpatentable over Liang 2006. In response to that rejection, Avadel stated to the USPTO that Liang 2006 would not render obvious the claimed formulation, because "Liang [2006]'s only teaching regarding excipients is that they have to be actually part of Liang [2006]'s immediate release and delayed/controlled release components. As such, nowhere does Liang [2006] disclose or suggest a formulation having a suspending / viscosifying agent and an acidifying agent that are separate and distinct from the immediate release component and the delayed/controlled release component of the formulation." Ex. D, App. No. 16/281,235, March 18, 2020 Response to Office Action at 18. Avadel further represented to the USPTO that "a person of ordinary skill in the art would not be prompted by the disclosure of Liang [2006] to modify the dosage forms discussed therein and arrive at the claimed formulation with a reasonable expectation of success." *Id.* at 19. This directly contradicts the obviousness arguments Avadel has made in this litigation with respect to the '782 Patent.

37. The '235 Application issued as a U.S. Patent after Avadel overcame the obviousness rejection based upon Liang 2006. Therefore, Avadel derived a benefit from the arguments made to the USPTO and set forth above.

C. Avadel is Estopped, Under Principles of Judicial Estoppel and/or the Doctrine of Unclean Hands, from Seeking Declaratory Judgments that the Asserted Claims of the Jazz Sustained Release Patents and Jazz Resinate Patents Are Invalid As Anticipated or Obvious In View of Its Inconsistent Arguments to the USPTO

38. As set forth above, Avadel has made invalidity arguments in this litigation that are inconsistent with—and in many cases the exact opposite of—validity arguments that Avadel made under the penalty of perjury to the USPTO.

39. Based upon: (1) Avadel's derivation and validity contentions, (2) the fact that the patent applications to which the inventions claimed in the Jazz Sustained Release Patents and the Jazz Resinate Patents claim priority were filed before Avadel's alleged inventions, and (3) Avadel's positions before the USPTO, Avadel is estopped from raising any arguments pursuant to 35 U.S.C. §§ 102 or 103 against the Jazz Sustained Release Patents and the Jazz Resinate Patents in this case.

40. Avadel gained an advantage by making the aforementioned validity arguments to the USPTO, having overcome the USPTO's obviousness rejections in view of those arguments and obtaining issued U.S. patents as a result.

41. It would be unconscionable to allow Avadel to maintain positions in this litigation that are inconsistent with positions Avadel has taken before the USPTO and from which Avadel derived a clear benefit; namely, the issuance of U.S. Patents from its Patent Application Nos. 15/655,924, 16/281,235, 16/419,616, and/or 16/420,321.

42. Avadel's derived benefits from the grant of the '062, '986, '886, and '795 Patents relate to the subject matter of this litigation because Avadel argues that Jazz copied the novel inventions of the Jazz Sustained Release Patents and Jazz Resinate Patents from the Avadel '062, '986, '886, and '795 Patents, but at the same time argues that Jazz Pharmaceuticals' inventions in the Jazz Sustained Releases Patents and Jazz Resinate Patents are invalid over references that

Avadel overcame during prosecution of the Avadel '062, '986, '886, and '795 Patents by making contradictory arguments earlier in time.

43. Avadel's inconsistent positions constitute unconscionable and bad-faith actions that directly relate to this litigation, are intended to injure Jazz Pharmaceuticals (and its rights in the Jazz Sustained Release Patents and Jazz Resinate Patents), and affect the balance of equities between Avadel and Jazz Pharmaceuticals.

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February 25, 2022

CERTIFICATE OF SERVICE

I hereby certify that on February 25, 2022, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on February 25, 2022, upon the following in the manner indicated:

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL PHARMACEUTICALS PLC, AVADEL US HOLDINGS, INC., AVADEL SPECIALTY PHARMACEUTICALS, LLC, AVADEL LEGACY PHARMACEUTICALS, LLC, AVADEL MANAGEMENT CORPORATION and AVADEL CNS PHARMACEUTICALS, LLC, Defendants.	)	C.A. No. 21-cv-691-MN

DEFENDANTS' INITIAL INVALIDITY CONTENTIONS

Pursuant to Paragraph 4(d) of the Default Standard for Discovery and the Scheduling Order entered in the above-captioned action on August 6, 2021 (*see* D.I. 31), Defendants Avadel Pharmaceuticals PLC, Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation and Avadel CNS Pharmaceuticals, LLC. (collectively, "Defendants" or "Avadel"), hereby provide Plaintiff Jazz Pharmaceuticals, Inc. ("Plaintiff") their initial invalidity contentions regarding the asserted claims of U.S. Patent Nos. 8,731,963 (the "'963 patent"); 10,758,488 (the "'488 patent"); 10,813,885 (the "'885 patent"); 10,959,956 (the "'956 patent"); and 10,966,931 (the "'931 patent") (collectively the "Patents-in-Suit"). Under separate cover, Defendants provide their document production accompanying these contentions.

I. GENERAL STATEMENTS

Defendants submit these initial invalidity contentions based upon information presently available. Discovery is ongoing and the terms of the asserted claims have not yet been construed by the Court. Therefore, Defendants reserve the right to supplement, alter, amend and/or modify

these contentions based on further investigation, fact or expert discovery, evaluation of the scope and content of the prior art, any claim construction by the Court, or as a result of Plaintiff's asserted claims and contentions.

To the extent that Plaintiff is permitted to assert additional claims not presently identified in its infringement contentions, Defendants reserve the right to address the invalidity of such claims. Defendants' invalidity positions in these contentions may be in the alternative and do not constitute any concession by Defendants for purposes of claim construction or infringement. *See, e.g.*, *Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000). Furthermore, these contentions are provided without prejudice to Defendants' right to introduce at trial any subsequently-discovered evidence or expert opinions relating to currently-known facts and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently-discovered facts. Moreover, facts, documents, and things now known may be imperfectly understood and, accordingly, such facts, documents, and things may not be included in the following contentions. Defendants reserve the right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, expert opinion testimony, documents, and things notwithstanding the written statements herein. Defendants further reserve their right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, documents, and things that are not currently recalled but might be recalled at some time in the future.

Defendants object to the disclosure of information that is protected by the attorney-client privilege, the attorney work-product immunity, the common interest privilege, or any other applicable privilege or immunity. To the extent that Defendants inadvertently disclose information that may be protected from discovery under the attorney-client privilege, the attorney work-

product immunity, the common interest privilege, or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

The information set forth below is provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other action, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time. Defendants further reserve the right to amend and/or supplement these contentions in accordance with the Federal Rules of Civil Procedure and/or the Rules of this Court. Defendants reserve the right to allege the invalidity of the asserted claims on bases other than those disclosed herein.

II. BACKGROUND

On September 7, 2021, Plaintiff provided Defendants with its Initial Infringement Chart pursuant to Paragraph 4(c) of the Delaware Default Standard. In this Initial Infringement Chart, Plaintiff asserted that the product described in Defendants' NDA infringes Claims 1-23, 25, and 28 of the '963 patent; claims 1-12 of the '488 patent; claims 1-15 of the '885 patent; claims 1-20 and 23-25 of the '956 patent; and claims 1-15 of the '931 patent.

In view of Plaintiff's Initial Infringement Chart, the following invalidity contentions address the asserted claims of the Patents-in-Suit.

III. PRIOR ART

At this time, Avadel contends that at least the following prior art references anticipate and/or render obvious, either alone or in combination, the asserted claims of the '963 patent:

1. The Advisory Committee Art:

    a. FDA Center for Drug Evaluation and Research, Peripheral and Central Nervous System Drugs Advisory Committee, Transcript and Slides (June 6, 2001);

b. Ranjit B. Mani, FDA Peripheral and Central Nervous System Drugs Advisory Committee, Division of Neuropharmacological Drug Products, Preliminary Clinical Safety Review of NDA 21-196 (May 3, 2001);

c. Xyrem® (sodium oxybate) oral solution NDA #21-196: Briefing Booklet for the FDA Peripheral and Central Nervous System Drugs Advisory Committee (May 3, 2001);

d. FDA Peripheral and Central Nervous System Drugs Advisory Committee, Briefing Information, Xyrem Prescription and Distribution Process Video and Transcript (Feb. 2, 2001) ("Xyrem Video and Transcript");

2. Robert R. Korfhage, Information Storage and Retrieval (John Wiley & Sons, Inc. 1997);

3. Fred M. Eckel and Clifton J. Latiolais, *An Effective Narcotic Control System Using Electronic Data Processing*, American J. of Hospital Pharmacy 22(9) (1965);

4. John T. Nazzaro, *A System for automatic data processing of controlled substance disposition*, Hospital Pharmacy 13(1) (1978);

5. Robert W. Case, et al., *Automated Narcotic Control System Saves Time for Pharmacy and Nursing*, Hospitals 41:97, May 16, 1967 at 97;

6. William N. Elwood, *Sticky Business: Patterns of Procurement and Misuse of Prescription Cough Syrup in Houston*, Journal of Psychoactive Drugs, 33(22), (2001);

7. Ted Parran, Jr., *Prescription Drug Abuse*, Medical Clinics of North America 81(4), (1997);

8. Gabay, *The Federal Controlled Substances Act*, HOSPITAL PHARMACY, June 2013;

9. O'Keefe, *Compliance With Drug Abuse Control Amendments of 1965*, FOOD DRUG COSMETIC LAW J., July 1966, 360.

At this time, Avadel contends that at least the following prior art references anticipate and/or render obvious, either alone or in combination, the asserted claims of the '488, '885, '956, and '931 patents (collectively, the "Jazz Sustained Release Patents").

1. U.S. Patent No. 6,514,531, issued February 4, 2003 ("Alaux 2003");

2. U.S. Patent No. 5,594,030, issued January 14, 1997 ("Conte 1997");

3. U.S. Patent No. 6,913,768, issued July 5, 2005 ("Couch 2005");

4. HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, Fifth Edition, 2006 ("HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 2006");

5. Hu, et al., *Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets*, European Journal of Pharmaceutics and Biopharmaceutics, 64 (2006) 185–192 ("Hu 2006");

6. Jones, *Pharmaceutical Applications of Polymers for Drug Delivery*, Rapra Review Reports, Volume 15, Number 6, (2004) ("Jones 2004");

7. Lecomte, et al., *Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns*, Journal of Controlled Release, 89 (2003) 457-471 ("Lecomte 2003");

8. U.S. Patent Publication No. 2006/0210630 ("Liang 2006");

9. Majeed, *Formulation, Drug Release and Animal Bioavailability for an Oral Controlled-Release Dosage Form of Propranolol Hydrochloride*, St. John's University, Ph.D. 1986 ("Majeed 1986");

10. Miller, et al., *Aqueous Polymeric Film Coating*, College of Pharmacy, University of Texas at Austin, Austin, Texas, U.S.A. (2008) ("Miller 2008");

11. European Patent No. 2 034 970, issued March 18, 2009 ("Monteith 2009");

12. Savaşer, et al., *Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium*, Il Farmaco 60 (2005) 171–177 ("Savaşer 2005");

13. Tabandeh, et al., *Preparation of Sustained-Release Matrix Tablets of Aspirin with Ethylcellulose, Eudragit RS100 and Eudragit S100 and Studying the Release Profiles and their Sensitivity to Tablet Hardness*, Iranian Journal of Pharmaceutical Research (2003) 201-206 ("Tabandeh 2003");

14. U.S. Patent No. 6,623,730, issued September 23, 2003 ("Williams 2003").

IV. PRIORITY DATES

The '963 patent issued on May 20, 2014 and was filed on August 22, 2012. The '963 patent claims priority to an application filed on December 17, 2002.

The '488 patent issued on September 1, 2020 and was filed on July 2, 2018. The '488 patent is a continuation of U.S. Appl. No. 13/071,369 ("'369 application"), now abandoned, which claims priority to Provisional Application No. 61/317,212, filed on March 24, 2010. For the

reasons discussed in Section X, the asserted claims of the '488 patent are not entitled to claim priority to the '369 application, and should be entitled to a priority date no earlier than July 2, 2018.

The '885 patent issued on October 27, 2020 and was filed on June 30, 2020. The '885 patent is a continuation of U.S. Appl. No. 16/712,260, now U.S. Patent No. 10,987,310, which is a continuation of U.S. Appl. No. 16/025,487, now the '488 patent. For the reasons discussed in Section X, the asserted claims of the '885 patent are not entitled to claim priority to the '369 application, and should be entitled to a priority date no earlier than June 30, 2020.

The '956 patent issued on March 30, 2021 and was filed on December 24, 2020. The '956 patent is a continuation of U.S. Appl. No. 16/916/677, now the '885 patent. For the reasons discussed in Section X, the asserted claims of the '956 patent are not entitled to claim priority to the '369 application, and should be entitled to a priority date no earlier than December 24, 2020.

The '931 patent issued on April 6, 2021 and was filed on December 24, 2020. The '931 patent is a continuation of U.S. Appl. No. 16/916,677, now the '885 patent. For the reasons discussed in Section X, the asserted claims of the '931 patent are not entitled to claim priority to the '369 application, and should be entitled to a priority date no earlier than December 24, 2020.

V. THE ASSERTED CLAIMS OF THE '963 PATENT ARE INVALID UNDER 35 U.S.C. § 101

The asserted claims of the '963 patent are invalid because they fail to satisfy the patent-eligibility requirements of 35 U.S.C. § 101. These grounds are identified based on knowledge in Defendants' possession at this time. Further investigation may uncover additional grounds for invalidity under § 101 and Defendants reserve the right to supplement these disclosures to include all such additional grounds as appropriate.

Whether claims are directed to patent-eligible subject matter is determined under a two-step framework: (1) "determin[ing] whether the claims at issue are directed to" an abstract idea; and, if directed to an abstract idea (2) whether "additional features" of the claim reflect an "'inventive concept'…that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" *Alice Corp. Pty. V. CLS Bank Int'l*, 573 U.S. 298, 216 (2014) (quoting *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 77 (2012)). With respect to claims directed to computer systems capable of performing a series of steps, the recitation of computers, alone, does not satisfy the requirements for section 101: claims that "merely require generic computer implementation" and lack any "additional features" or "inventive concept" sufficient to transform the abstract idea into a patent-eligible application, "amount to 'nothing significantly more' than an instruction to apply the [abstract idea] using some unspecified, generic computer" are not patentable. *Alice Corp.*, 573 U.S. at 225-26.

A. The Asserted Claims of the '963 Patent are Directed to an Abstract Idea

The asserted claims of the '963 patent are directed to nothing more than the abstract idea of computer systems capable of collecting and analyzing information about tightly-controlled prescription drugs to detect misuse. *See FairWarning IP, LLC v. Iatric Systems, Inc.*, 839 F.3d 1089, 1094 (Fed. Cir. 2016). Pharmacists can, and long have, performed exactly the type of steps recited in the claim to guard against this type of misuse of prescription drugs. Indeed, pharmacists have specifically been conducting inventory reconciliation (using pen and paper or computers) since long before the priority date of the '963 patent. *See* Fred M. Eckel and Clifton J. Latiolais, *An Effective Narcotic Control System Using Electronic Data Processing*, American J. of Hospital Pharmacy 22(9), 519 (1965) ("Eckel") ("For the nurse to maintain control off her narcotics, she

performs an inventory audit at each change of shift. In addition, nurses must prepare a requisition, sign the receipt for narcotics, place them into inventory and properly file the certificate of disposition."). As addressed in Section VI, pharmacies and others in the medical field also were utilizing the human mind, pen and paper, and/or computer systems to track cash payment as an indicator of potential misuse or diversion. Both were conventional. And the claims at issue, at best, merely computerize such conventional activity.

The asserted claims of the '963 patent recite nothing more than computer systems that collect, analyze, and present data—"essentially mental processes within the abstract-idea category." *Id.* (quoting *Elec. Power Grp., LLC v. Alstom S.A.*, 830 F.3d 1350, 1353 (Fed. Cir. 2016)). And "'merely selecting information, by content or source, for collection, analysis, and [announcement] does nothing significant to differentiate a process from ordinary mental processes.'" *Id.* Indeed, the claims are very similar to other claims for computers capable of storing information and detecting misuse that the Federal Circuit has found ineligible. *See, e.g.*, *FairWarning*, 839 F.3d at 1094 (claims "are directed to collecting and analyzing [patient health] information to detect misuse and notifying a user when misuse is detected"); *Bozeman Financial LLC v. Federal Reserve Bank of Atlanta*, 955 F.3d 971 (Fed. Cir. 2020) ("claims are directed to the abstract idea of collecting and analyzing information for financial transaction fraud or error detection"). Thus, the claims are directed to nothing more than computer systems capable of performing the same steps that pharmacists and other healthcare professionals have been taking for decades to prevent prescription drug misuse. Because the claims are directed to abstract ideas and lack any "inventive features" that would remove the claimed subject matter from the realm of unpatentable subject matter, the remaining claims of the '963 patent are invalid for failing to satisfy the requirements of section 101.

B. The Asserted Claims of the '963 Patent Do Not Recite an Inventive Concept

The asserted claims of the '963 patent do not recite any sort of inventive concept that would render the claimed abstract idea eligible for patent protection. The patent itself does not purport to improve computer technology; instead, it merely recites using the most generic types of components (*e.g.*, a "personal computer" and database) capable of performing routine functions (storing and querying data). *See* '963 patent at 7:40-67, Fig. 1 (basic computer components), Fig. 7 (basic database fields), Fig. 8 (basic database queries). Indeed, the problem identified is a human problem (misuse of tightly-controlled drugs) and, as discussed, the solution is using a generic computer capable of aiding human functions (storing and analyzing data to identify potential misuse based on indicia such as whether the patient is paying with cash). *See id.* at 1:22-44. Plaintiff does not contend otherwise: the Complaint says not one word about anything related to § 101—nothing suggesting, let alone plausibly alleging, that the claims require any unconventional computer technology or improvement. *See* Compl. ¶¶ 46-58.

Furthermore, computers capable of storing and querying data in particular fields (*e.g.*, "prescription fields," "patient fields," and "prescriber fields") are not remotely non-abstract or inventive—that is conventional database functionality and, again, simply mirrors what humans could do using pen and paper. Claims with far more specific data storage fields have nonetheless been found patent ineligible by the Federal Circuit. *See, e.g.*, *Universal Secure Registry LLC v. Apple Inc.*, 10 F.4th 1342, 1354 (Fed. Cir. 2021) (access-control claims ineligible despite using "multiple fields, including a digital signature field (e.g., biometric data), further identifying information (e.g., name, height, weight, eye color), and a one-time varying code field (e.g., a PKI encrypted one-time DES key)"); *Intellectual Ventures I LLC v. Capital One Fin. Corp.*, 850 F.3d 1332, 1340 (Fed. Cir. 2017) (data management claims' use of "specific data structures and objects (PRTs and MRTs) also does not change our analysis").

VI. THE ASSERTED CLAIMS OF THE '963 PATENT ARE INVALID UNDER 35 U.S.C. § 103

For the reasons set forth below, as well as set forth in the claim chart attached as Appendix A, the asserted claims of the '963 patent are invalid as obvious over the prior art.

Under 35 U.S.C. § 103(a), an applicant is not entitled to a patent "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious" to a POSA at the time the invention was made. The relevant factual inquiries include:

(a) determining the scope and content of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966). The Supreme Court reiterated the applicability of the *Graham* factors in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

The '963 patent is directed to a computer-implemented system for controlling access to an abuse-prone prescription drug by using a central pharmacy and database to track all prescriptions, patients, and prescribers. Information regarding all physicians authorized to prescribe the drug and all patients receiving the drug is maintained in the database. Abuses are identified by monitoring the database for prescription patterns by physicians and prescriptions obtained by patients.

The United States Patent Trial and Appeal Board ("PTAB") previously instituted *inter partes* review of claims 24, 26, and 27 of the '963 patent (as well as all claims of Jazz's related U.S. Patent Nos. 7,668,730; 7,765,106; 7,765,107; 7,895,059; 8,589,182; and 8,457,988). The

PTAB thereafter issued six final written decisions finding all instituted claims invalid, largely based on Jazz's public disclosure of its alleged invention. The Federal Circuit affirmed those decisions, including the PTAB's ruling that certain Advisory Committee Art: (1) the FDA advisory committee meeting transcript and slides; (2) an FDA preliminary clinical safety review of Xyrem®; (3) a Xyrem® briefing booklet; and (4) a video and transcript regarding a proposed distribution system for Xyrem® (collectively the "ACA materials") qualify as printed publications under §102(b). *Jazz Pharms., Inc. v. Amneal Pharm., LLC*, 895 F.3d 1347, 1355-60 (Fed. Cir. 2018).[1]

With regard to claims 24, 26, and 27 of the '963 patent, the Federal Circuit affirmed the PTAB's decision of obviousness based on the ACA materials in view of Robert R. Korfhage, Information Storage and Retrieval ("Korfhage"). *Id*. at 1362-63. The Board relied on Korfhage in finding that the POSA "would have been motivated to distribute the ACA's single, centralized computer database over multiple computers, for reasons of cost, efficiency, and the anticipated volume of prescription-related information to be received, entered, and queried." *Id*. at 1353-54.

In denying institution of the remaining claims of the '963 patent, the PTAB relied on the following limitations:

- Element 1.6: "a data processor configured to: . . . reconcile inventory of the prescription drug before the shipments for a day or other time period are sent by using said database query to identify information in the prescription fields and patient fields";

- Element 1.7: "wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database";

[1] Avadel incorporates the final written decisions of the PTAB and any associated prior art references to the extent that the final written decisions reflect that a reference discloses any claim limitation of the '963 patent or any substantially similar claim limitation in any related patent.

- Element 1.8: "said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database."

See IPR2015-01903, Institution Decision at 12-20.

The backdrop for the claimed subject matter is the fact that the asserted claims involve GHB or sodium oxybate drug products, which were scheduled as controlled substances. *See, e.g.*, '963 patent at 1:20-33. "The Federal Comprehensive Drug Abuse Prevention and Control Act of 1970, more commonly known as the Controlled Substances Act, became effective on May 1, 1971." Gabay, *The Federal Controlled Substances Act*, HOSPITAL PHARMACY, June 2013. Since the early 1970s:

> dispensers of controlled substances must be registered with the Drug Enforcement Administration (DEA), the agency charged with enforcement of the Act on the federal level. Registration of these entities with the DEA results in the formation of a "closed system" for controlled substances distribution. This closed system allows for controlled substances to be traced from initial manufacture to final dispensing to the patient.

Id. *See also* O'Keefe, *Compliance With Drug Abuse Control Amendments of 1965*, FOOD DRUG COSMETIC LAW J., July 1966, 360, 362 ("[e]very person engaged in manufacturing, compounding, processing, selling, delivering, or otherwise disposing of psychotoxic drugs must prepare an initial inventory of stocks on hand as of the effective date, February 1, 1966, and thereafter keep accurate and complete records showing quantities manufactured or received and their disposition" in order to "be able to detect points of diversion of the drugs to illicit channels"). And since that time, pharmacists could lose their DEA license – or pharmacy license generally – for failing to appropriately facilitate the tracing of such substances through final dispensing to the patient. *See, e.g*., Gabay. Thus, those of skill in the art were motivated to optimize the "closed system" and to implement measures that would facilitate tracking in order to adhere to applicable law, maintain

DEA and state licensure, and/or to maintain community standing and reputation. *See, e.g.*, O'Keefe at 367 (encouraging those in the field to be mindful of "any suspicious circumstances which you believe bear looking into, whether it be with respect to counterfeit drugs, illegal distribution of psychotoxic drugs, or any other violation pertaining to drugs which may endanger the public health").

With regard to Element 1.6, the PTAB found that the FDA Briefing Booklet (part of the ACA materials), "does not disclose the use of database queries to 'reconcile' inventory prior to shipment for a given time period, e.g., daily or weekly." IPR2015-01903, Institution Decision at 14-15. The PTAB noted that although the Petitioner's expert stated that "it was well-known in the art for pharmacies to utilize inventory auditing controls for prescriptions that are prone to abuse by making sure that the current on-hand inventory aligns with the inventory identified as being present on the database," he did not cite to any supporting evidence. Furthermore, although the Petitioner's expert "testifie[d] that a person of ordinary skill would have understood to query the database 'to ensure that there was sufficient Xyrem on hand to fulfill upcoming prescriptions or refills that were likely within the forthcoming period,' [n]either the Petition nor Dr. Valuck's Declaration, … assert that the FDA Briefing Booklet or other ACA documents disclose, teach, or suggest the use of database queries to reconcile inventory 'before the shipments for a day or other time period are sent," as recited in Element 1.6.'" *Id*. at 15-16.

However, numerous prior art references that were not considered by the PTAB—going back decades before the priority date of the '963 patent—show that it was well-known in the art for pharmacies to utilize inventory auditing controls for prescriptions of drugs that are prone to abuse by making sure that the current on-hand inventory aligns with the inventory identified as being present on the database. For example, Eckel discloses a computer system that would "print

out a theoretical bulk inventory" of narcotics every 24 hours. *Id*. at 523. "This inventory will be compared daily to the actual inventory by a pharmacist." *Id*. Similarly, John T. Nazzaro, *A System for automatic data processing of controlled substance disposition*, Hospital Pharmacy 13(1) 16-29 (1978) ("Nazzaro"), discloses a hospital computer system that performs inventory reconciliation and only provided new supply of drugs if the amount of drugs matched the expected inventory in the computer system. *Id*. at 18-19. Robert W. Case, et al., further discloses a computer system whereby "[w]hen a nursing unit needs a new container of drug" the system compares "a narcotic requisition card" to a "dose disposition" sheet. Robert W. Case, et al., *Automated Narcotic Control System Saves Time for Pharmacy and Nursing*, Hospitals 41:97, May 16, 1967 at 97 ("Case"). "[T]he system adds up the total amount of drug that was distributed by the pharmacy and checks this amount against the amount used in the nursing unit." *Id.* A discrepancy of greater than 10 percent requires "further investigation" from pharmacy personnel. *Id.*

The POSA would have been motivated to and had a reasonable expectation of success in combining the inventory reconciliation disclosed in any of Eckel, Nazzaro, or Case with the computer system disclosed in the ACA documents such that the system would use database queries to reconcile inventory before the shipments for a day or other time period are sent as claimed in the asserted claims of the '963 patent. A POSA would have been so motivated at least because inventory reconciliation provides an additional safeguard against abuse and because inventory reconciliation can assist with managing pharmacy stocks. Eckel, Nazzaro, and Case acknowledge such benefits. *See, e.g.*, Eckel at 519, 522-23; Nazzaro at 16, 28-29; and Case at 97-98. A POSA further would have been so motivated to optimize the "closed system" described *supra*, to facilitate

compliance with applicable laws, maintain DEA and state licensure, and/or to maintain reputation and standing in the community.

With regard to Elements 1.7 and 1.8, the PTAB found that these elements were not inherently met by the ACA documents, because although the ACA disclosed "tracking all GHB prescriptions, even cash-paying patients," that "did not necessarily disclose a database query directed to identifying cash-paying patients as an indicator of potential misuse, abuse, or diversion of the prescription drug." Moreover, the PTAB found that "[t]he additional ACA disclosures cited by Petitioner, moreover, also do not necessarily provide a link between cash payers and the potential for abuse." IPR2015-01903, Institution Decision at 20.

However, the link between cash payers and the potential for abuse was well known long before the priority date of the '963 patent and was explicitly disclosed in prior art not considered by the PTAB. For example, William N. Elwood, *Sticky Business: Patterns of Procurement and Misuse of Prescription Cough Syrup in Houston*, Journal of Psychoactive Drugs, 33(22), 121-133 (2001) ("Elwood") addresses the use of cash payments to improperly obtain prescriptions for codeine cough syrup. The article notes that "some participants reported paying cash for visits to medical doctors rumored to unquestioningly provide prescriptions at patients' requests." *Id*. at 128. The article further discloses that certain patients used cash payments other than health insurance "because they never wanted to imperil their medical insurance coverage for essential health needs." *Id*. at 129. Ted Parran, Jr., Prescription Drug Abuse, Medical Clinics of North America 81(4), 967-78 (1997) ("Parran") discloses that payment in cash was an indicator of misuse or diversion, stating that "dishonest physicians" or "script docs" traditionally ask their patients "to pay in cash." *Id*. at 974. Indeed, the '963 patent Background explicitly admits that "an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients,

who use cash to pay for the drugs." *Id*. at 1:37-39. Such admissions are relevant to the content of the prior art. *Papyrus Tech. Corp. v. New York Stock Exch., LLC*, 653 F. Supp. 2d 402, 418 (S.D.N.Y. 2009), aff'd, 396 F. App'x 702 (Fed. Cir. 2010) ("The prior art also includes those devices referred to in the background section of the patents, which details the problems with which the inventors were involved and the technology utilized in the field of the inventor's endeavor."); *see also Cabinet Vision v. Cabnetware*, 230 F.3d 1382 (Fed. Cir. 2000) ("[T]he background section of the '207 patent sheds light on the state of the prior art.")

Given that it was well known in the art that cash payments for prescription drugs were a potential sign of abuse, the POSA would have been motivated to track cash payments in the "single computer database" so that a query could be run to identify a cash payer and their physician and notify the physician of the cash payments. The ACA materials already disclosed a computer system to track patients and their prescribing physicians in the database and to run queries to check for abuse. Adding in additional fields such as cash payments, which were known to be indicators of potential abuse, would have been a routine addition recognized in the prior art. The POSA would have been motivated to combine the cash payment tracking to address the known abuse disclosed in Elwood and/or Parran in order to improve the effectiveness of a REMS database at detecting abuse, facilitate compliance with applicable laws, to optimize the "closed system" described *supra*, to maintain DEA and state licensure, and/or to maintain reputation and standing in the community. Moreover, as it was a routine, well-understood addition to an already-known database system, a POSA would have had a reasonable expectation of success in adding this capability to the computer system disclosed in the ACA materials.

VII. UNDER PLAINTIFF'S THEORY OF THE CASE, THE ASSERTED CLAIMS OF THE '963 PATENT ARE INVALID UNDER 35 U.S.C. § 112

For the reasons set forth below, under Plaintiff's theory of the case, the asserted claims of the '963 patent are invalid under 35 U.S.C. § 112 as indefinite.

As set forth in 35 U.S.C. § 112, an applicant must "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." Under *IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377 (Fed. Cir. 2005), a claim that attempts to claim both a system and a method for using that system is invalid as indefinite, as such a claim does not make clear when infringement occurs.

The asserted claims of the '963 patent claim systems, and not methods. *E.g.*, claim 1 of the '963 claims "A computer-implement system . . . ." Plaintiff, however, has taken the untenable position that the asserted claims of the '963 patent also claim methods. *See, e.g.*, 9/7/21 Plaintiff's Initial Infringement Chart at 3 (alleging that "Avadel's NDA Product and REMS Program are specifically adapted for use in connection with the ***claimed method***" (emphasis added). Plaintiff is wrong, but for purposes of these contentions, Defendants note that Plaintiff's theory would render the claims invalid as indefinite under *IPXL Holdings*.

VIII. THE SUSTAINED RELEASE PATENTS ARE INVALID UNDER 35 U.S.C. § 103

For the reasons set forth below, as well as set forth in the claim charts attached as Appendices B-E, the asserted claims of the Jazz Sustained Release Patents are invalid as obvious over the prior art.

Under 35 U.S.C. § 103(a), an applicant is not entitled to a patent "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious" to a POSA at the time the invention was made. The relevant factual inquiries include:

(a) determining the scope and content of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966). The Supreme Court reiterated the applicability of the *Graham* factors in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

Claim 1 of the '488 patent recites:

> A formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein:
> a. the sustained release portion comprises a functional coating and a core, wherein the functional coating is deposited over the core, wherein the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate copolymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gammahydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;
> b. the immediate release portion comprises about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

> c. the formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;
> d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

The other claims of the Jazz Sustained Release Patents similarly recite dosage forms comprising a sustained release formulation made up of a functional coating deposited over a core, with the core comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate ("GHB") and pharmaceutically acceptable salts of GHB, and the functional coating comprising one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating. The sustained release formulation has a dissolution profile wherein greater than about 40% of the GHB is released by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm.

Some of the claims of the Jazz Sustained Release Patents impose additional limitations, such as an immediate release portion wherein the combined immediate and sustained release portions release "at least about 30% of the gamma-hydroxybutyrate by one hour" and "greater than about 90% of gamma-hydroxybutyrate" by 6, 7, or 8 hours when tested in dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm. *See, e.g.*, '488 patent claims 1, 2, 3; '885 patent claims 1, 13, 14, 15; '956 patent claims 1, 2, 3, 13, 14; '931 patent claims 1, 14, 15. Other claims of the Jazz Sustained Release Patents impose limitations such as the sustained release portion releasing about 10% or less of its GHB by about 1 hour and about 60% to about 90% of its GHB by about 6 hours when tested in dissolution apparatus 2 in deionized

water at a temperature of 37 °C and a paddle speed of 50 rpm. *See, e.g.*, '488 patent claims 4, 11; '885 patent claims 2, 3; '956 patent claims 4, 10, 15; '931 patent claims 2, 3.

Jazz appears to assert that the "sustained release" and "functional coating" limitations are satisfied so long as a dosage form satisfies the *in vitro* release characteristics recited in the asserted claims. *See, e.g.*, 9/7/21 Plaintiff's Initial Infringement Chart at 27-37. Utilizing that view of the subject limitations, the asserted claims of the Jazz Sustained Release Patents are obvious over Liang et al., U.S. Patent Publication No. 2006/0210630 ("Liang 2006"). Specifically, Liang 2006 discloses gamma hydroxybutyric acid ("GHB") formulations made up of an immediate release portion and a delayed/controlled release portion. As in the Jazz Sustained Release Patent claims, Liang 2006's delayed/controlled release formulations are made up of a functional coating deposited over a core, with the core comprising gamma-hydroxybutyric acid salts and the functional coating comprising a pH sensitive enteric release coat such as a methacrylic acid-methyl methacrylate co-polymer.

A POSA would have been motivated to formulate a once-nightly dose of sodium oxybate composition at the time. A POSA would have arrived at the claimed amounts of GHB and the percentage of methacrylic acid-methyl methacrylate co-polymer in the coating through routine experimentation, with an expectation to succeed in achieving the claimed dissolution profile.

A. Liang 2006

Liang 2006 discloses immediate release and delayed/controlled release components of GHB. Liang 2006 states that GHB is "highly soluble, hygroscopic, and strongly alkaline, and the therapeutic dose is normally very high." Liang 2006 at ¶ 5. Liang 2006 discloses that "the immediate release dose can be equivalent of, higher than, or lower than, the one or more delayed release doses." *Id.* at ¶ 39. "It is contemplated that the delayed release dose amount, which is used to replace the second nightly dose (currently as a solution) in the current treatment of narcolepsy

patients, can be the same as the immediate release dose amount, although the bioavailability is lower further along the GI tract, or even at a reduced dose amount, since the patients do not need to wake up and take a separate second nightly dose to go back to sleep." *Id*. at ¶ 40.

Liang 2006 describes that the delayed/controlled release components in the form of particles (e.g., beads, granules, minitabs, or pellets) containing GHB as the core that provide for delayed/controlled release lease of the drug. For these delayed/controlled release components, Liang 2006 discloses that the GHB core is surrounded by a barrier coat to control the migration of GHB from the core. The barrier coat is in turn surrounded by an enteric release coat that will allow release of the GHB at a predetermined pH after ingestion.

1. Barrier Coat

In describing the delayed/controlled release portion of the formulations, Liang 2006 explains that the barrier coat can be applied to a GHB core. Liang teaches that suitable coating materials for the barrier coat include, but are not limited to, cellulosic polymers such as ethylcellulose. Liang 2006 at ¶ 74. In addition, a pore former may also be used, but importantly, whether one is used at all and the amount will determine the function of the barrier coat: "For example, if the pH sensitive delayed/controlled release particles are intended for immediate release after entering the targeted site in the GI tract, high amounts of pore formers (e.g., as high as about 50% by weight of the barrier coat) can be used. If the pH sensitive delayed/controlled release particles are for controlled release after entering the targeted site in the GI tract, little or ***no*** pore formers are used (e.g., no more than about 25% by weight of the barrier coat)." Liang 2006 at ¶ 76. Example 4 discloses the barrier coat of the immediate release core, containing the following unevaporated solids: 73.9 g of ethylcellulose, 1.72 g of PV7 [sic] K90, and 8.1 g triethyl citrate. Example 4 also discloses that "[f]or a slower release core, PVP K90 is used at lower levels or ***can***

be omitted." Liang 2006 at ¶ 101 (emphasis added). Thus, the barrier coat in Example 4 discloses about 2.1% by weight of the pore former.

2. pH Sensitive Enteric Coat

Liang 2006 also describes a pH sensitive enteric coat that is applied to the barrier coat. Suitable materials for the pH sensitive enteric coat "include, but are not limited to, methacrylate-based coating materials such as polymers of methacrylic acid and methacrylates." Liang 2006 at ¶ 82. And suitable materials for targeting drug release to each region of the gastrointestinal tract were "known in the art, such as Eudragit E 100 or Eudragit E PO (stomach), Eudragit L 30 D-55 and Eudragit L 100-55 (duodenum), Eudragit L 12.5 and Eudragit L 100 (jejunum), Eudragit S 100 (ileum), and Eudragit FS 30 D (colon)." Liang 2006 at ¶ 86. Of the Eudragits disclosed by Liang 2006, Eudragit L 12.5, Eudragit L 100, Eudragit S 100, and Eudragit FS 30D are "methacrylic acid-methyl methacrylate copolymers."[2] According to Liang 2006, there was a preference for pH sensitive enteric release coats that release or dissolve in the upper GI tract, such as the duodenum or the jejunum, because it would allow for better absorption of the drug. *Id.* at ¶ 87.

Liang 2006 discloses four examples (Examples 6a-6d) of the pH sensitive enteric coat, which is sprayed onto a barrier coat covering the GHB core. All four examples have around 90% Eudragit in the enteric coating, and target different portions of the intestine by virtue of the type of Eudragit used—each of which dissolves at different pHs and therefore would dissolve at

[2] Eudragit L 12.5 and L 100 (both targeting jejunum) are methacrylic acid-methyl methacrylate copolymers (1:1), Eudragit S 100 (targeting colon) is a methacrylic acid-methyl methacrylate copolymer (1:2), and Eudragit FS 30 D targeting colon) is a methyl acrylate, methyl methacrylate, methacrylic acid copolymer (7:3:1). *See* Rowe et al., HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (5th ed.) at 554, 557 ("HPE"); Eudragit at a Glance. Eudragit L 30 D-55 and L 100-55 (both targeting duodenum) are methacrylic acid, ethyl acrylate copolymers (1:1).

different portions of the intestine. Examples 6a and 6b target the upper intestine (duodenum and jejunum, respectively), and Examples 6c and 6d target the lower intestine, *i.e.*, colon. The examples also use different barrier coats: Examples 6a and 6b are sprayed onto the barrier coat from Example 4 (described above), while Examples 6c and 6d are sprayed onto the barrier coat from Examples 3 and 5, respectively.

3. Dissolution Testing

Liang 2006 reports the dissolution profiles of Examples 6a, 6c, and 6d, but not Example 6b. As discussed above, these examples contained the pH sensitive enteric coat, barrier coat, and GHB core. The Examples were tested using USP Apparatus 2 at a paddle speed of 75 rpm in media at time points that approximated the time in the digestive system (*i.e.*, two hours in an acidic stomach environment followed by four hours in a neutral intestinal environment). Example 6a, which corresponds to Figure 3, reproduced below, uses a pH 1.1 media from 0-2 hours followed by a pH 6.8 buffer from 2-6 hours.[3]

[3] According to Jazz's Declaration of Clark Allphin submitted on April 20, 2020 in U.S. Patent Appl. No. 16/025,487, "the release profile in DI water would be substantially similar" to the release profile in physiological media. *See, e.g.*, Declaration at 1 n.1.

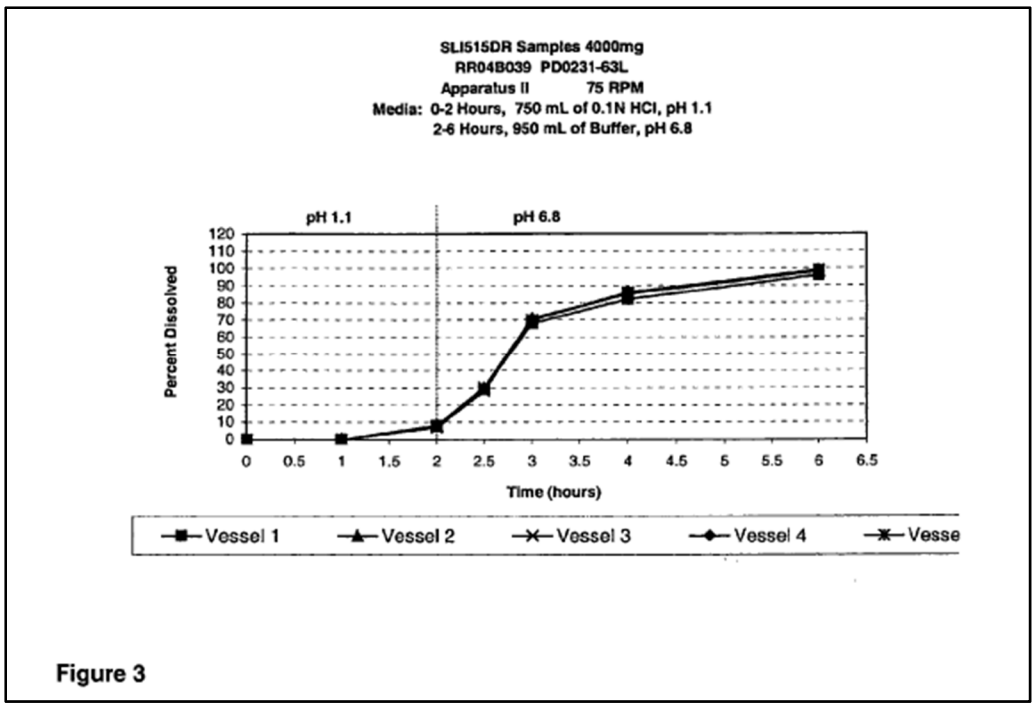
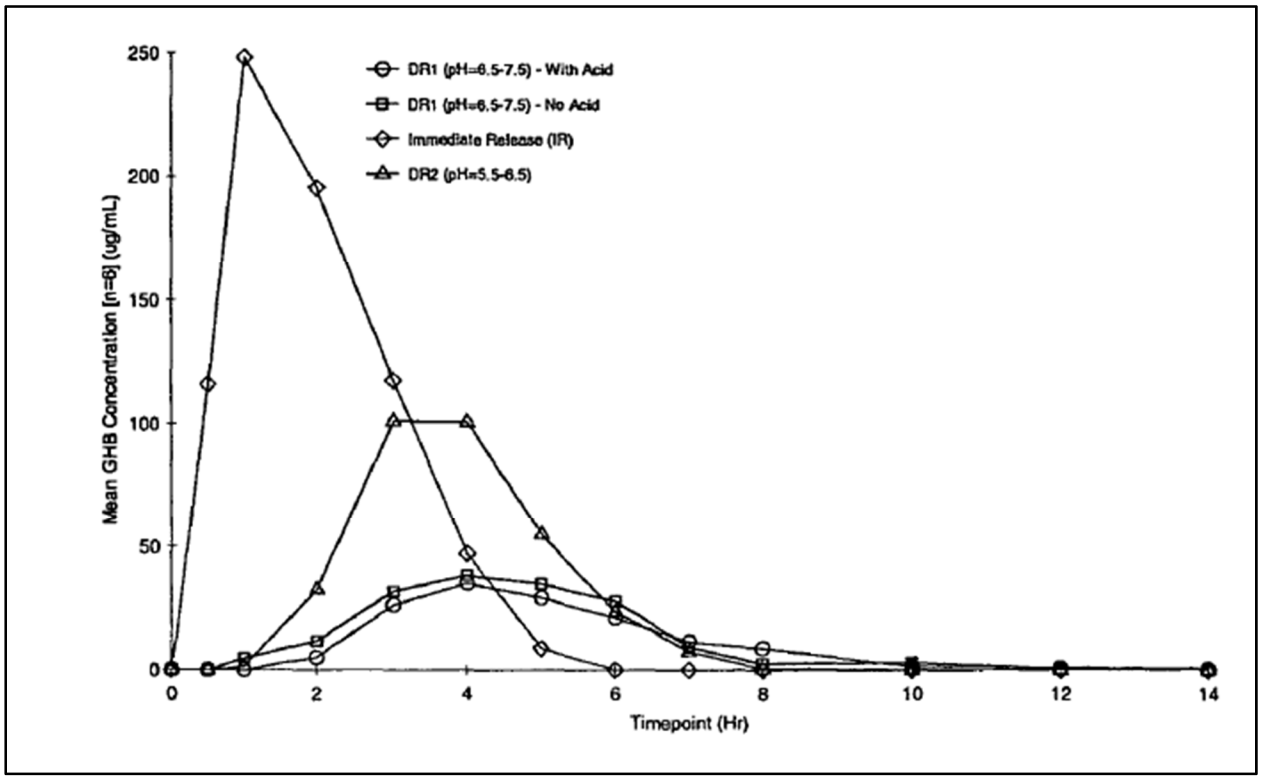


Figure 3

4. Pharmacokinetic Study

Liang 2006 also reports the results of a pharmacokinetic ("PK") study in which Examples 6a, 6c, and 6d, and an immediate release control formulation were administered to dogs. Liang 2006 reports better relative bioavailability was achieved for the controlled release formulation of Example 6a (around 50% of the immediate release control) compared to the formulation tested in Examples 6c and 6d (around 25%).

Figure 7, reproduced below, shows the mean GHB concentration over time for each of the tested formulations compared to the immediate release control. Figure 7 shows that each of Examples 6a, 6c, and 6d released most of the GHB by 8 hours, while the immediate release control released all the GHB by 6 hours. Based on the PK study, Liang 2006 concluded that "[t]he results show that the lower in the GI, the lower the bioavailability (BA); i.e., absorption is higher at upper GI." Liang 2006 at ¶ 115. Liang 2006 therefore concluded that "[p]referably, the pH sensitive enteric release coat releases/dissolves in the upper GI tract of an animal, which will allow for better absorption of the drug," and more preferably, in the "duodenum or the jejunum." *Id.* at ¶ 86.



The table below summarizes Examples 6a-6d from Liang:

Exs.	Barrier Coat	Enteric Coat	Target Area	Target pH	Related Figure	Relative BA*
6a	Example 4	Eudragit L30-55	Duodenum	> 5.5	3	53%
6b	Example 4	Eudragit L 100	Jejunum	> 6–7	N/A	N/A
6c	Example 3	Eudragit FS 30 D	Colon	> 7	2	27%
6d	Example 5	Eudragit FS 30 D	Colon	> 7	1	22%

* Relative bioavailability is compared to an immediate release control

B. A POSA Would Have Been Motivated to Formulate a Once-Nightly Dose of Sodium Oxybate Composition

The Background of the Jazz Sustained Release Patents notes a shortcoming with regard to the prior art Xyrem formulation: "Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice

during the night." '488 Patent at 2:59-64. A POSA would have been motivated, as of the priority date of the Jazz Sustained Release Patents, to replace Xyrem®'s twice-nightly dosage with an oral pharmaceutical dosage form of GHB that could be taken once a night. Thus, Liang 2006 notes that "in the treatment of narcolepsy, a twice-nightly dosage regimen can be reduced to a single dose with the compositions of the present invention." Liang 2006 at ¶ 1. Such a dosage form would be more convenient than Xyrem®, which requires patients to take an initial dose at bedtime and wake up four hours later to take a second dose. *See* '488 Patent at 2:51-67. A once-nightly formulation of GHB would allow patients to sleep through the night. *See, e.g.*, Alaux 2003 (describing a controlled release formulation for a sleep aid drug in order to "sustain release over a period compatible with the desired time of sleep").

Motivation for a POSA to develop "longer acting" formulations of GHB to "reduc[e] the need for more frequent administration" for narcoleptic patients would have come from at least Williams 2003. Williams 2003 states that "in the treatment of narcoleptic patients, patients were found to benefit from two, or even three, doses of GHB during the night instead of a single dose which left patients wide awake before their planned awaking time." Williams 2003 at 3:45-49. Although increasing the dosage prolonged sleep duration from two to four hours, Williams 2003 taught that it would still "be desirable to develop new compositions and methods to deliver therapeutic amounts of GHB in vivo that were longer acting, reducing the need for more frequent administration. Such formulations would have many advantages, including increased compliance, reduced medical care, and less intrusion, for example, allowing patients under treatment with narcolepsy and alcoholism to sleep uninterrupted." *Id.* at 3:53-60.

A POSA would also have been motivated to formulate a sodium oxybate composition in which the sustained release portion comprises about 500 mg to 12 g of at least one

pharmaceutically active ingredient selected from GHB and pharmaceutically acceptable salts of GHB. *See, e.g.*, Liang 2006 at ¶¶ 14, 39, 40. For example, Conte 1997 disclosed "examples of delayed release compositions of the present invention," which included tablets of 1000 mg of GHBNa. Conte 1997 at Exs. 1, 2.

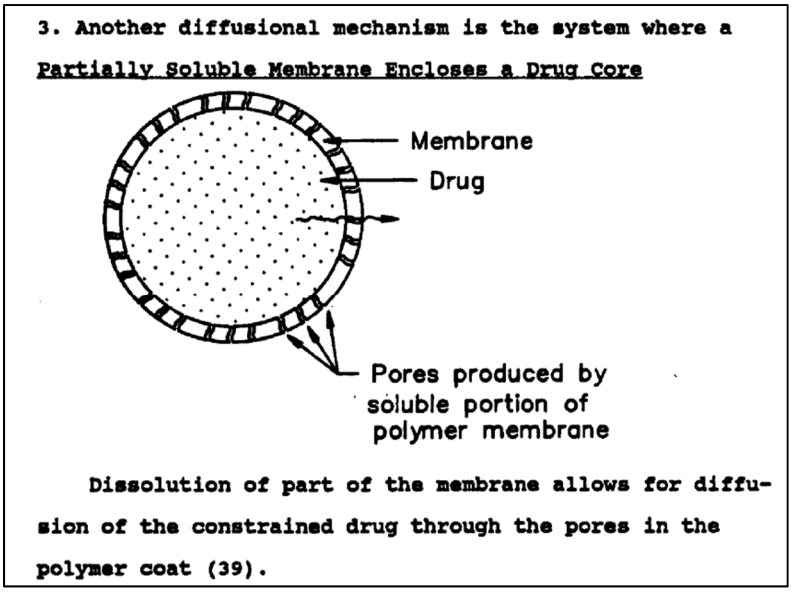
C. A POSA Would Have Arrived at the Claimed Percentage of Methacrylic Acid-Methyl Methacrylate in the Coating Through Routine Experimentation

It would have been obvious for a POSA to arrive at a "functional coating compris[ing] one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating." *See, e.g.*, *Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc.*, 642 F. Supp. 2d 329, 372 (D. Del. 2009) (finding obviousness when a prior art reference "discloses the active ingredient at issue, in an even smaller list, without so much as a hint that its use is uncommon" and describes "controlled release coatings comprising either hydrophobic water-insoluble, acrylic polymers or polymethacrylates such as Eudragit, just as claimed in the [asserted claims].")

1. The Prior Art Taught the Use of Methacrylic Acid-Methyl Methacrylate Co-Polymer in the Functional Coating

The prior art taught that the use of methacrylic acid-methyl methacrylate co-polymer in a functional coating was a commonplace method for achieving a desired dissolution profile for controlled release formulations.

- Majeed 1986 explains that a common type of controlled release coating includes a blend of water soluble (*e.g.*, pH-responsive Eudragits) and water insoluble polymers. Majeed 1986 shows that the mechanism by which such coatings release drugs is the creation of "pores produced by soluble portion of polymer membrane," *i.e.*, the pH-responsive Eudragits.



Majeed 1986 states that a common type of controlled release coating includes a blend of water soluble (*e.g.*, pH responsive Eudragits) and water insoluble polymers. Majeed 1986 lists examples of polymers that can be used as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, carboxymethyl ethylcellulose, ***Eudragit L, and Eudragit S***. Majeed 1986 specifically discloses that Eudragit L 12.5 and L100 are poly(methacrylic acid, methylmethacrylate) and soluble at a pH >6.0.

- Monteith 2009 tests formulations of phenylephrine decongestants and states that: "An example of such enteric coating comprises hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate or ***methacrylic acid copolymers***. Commercially available preparations include ***Eudragit® L-100***, which dissolves at pH 6.0, and ***S-100***, which dissolves at pH 7.0, used as a mixture."
- THE HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 2006 explains that the primary use for polymethacrylates are for oral capsules and tablet formulations. They may act as enteric coating agents and/or for sustained release, and a POSA would

understand that these coatings could be mixed to different extents in order to achieve different release profiles. It also teaches how to select the right type of Eudragit, including the claimed methacrylic acid-methyl methacrylate co-polymer. "***Eudragit L, S and FS types*** are used as ***enteric coating agents because they are resistant to gastric fluid***… Eudragit RL, RS, RD 100, NE 30 D and NE 40 D are used to form water insoluble film coats for sustained-release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together."

- Jones 2004 similarly has a helpful guide for selection of the different Eudragits, including the claimed methacrylic acid-methyl methacrylate co-polymers (Eudragit L and Eudragit S).

Table 1 Chemical Structure and Properties of Commercial Polymethacrylates

Chemical Name	Trade Name	Properties	Applications
Poly (butyl methacrylate, (2-dimethyl aminoethyl) methylacrylate) 1:2:1 R^1, $R^3 = CH_3$ $R^2 = CH_2CH_2N(CH_3)_2$ $R^4 = CH_3$, C_4H_9	Eudragit E	Cationic polymer. Soluble in gastric juices and weakly acidic buffer solutions pH~5.	Film coatings.
Poly(methacrylic acid, methacrylate) 1:1 1:2 R^1, $R^3 = CH_3$ $R^2 = H$ $R^4 = CH_3$	Eudragit L Eudragit S	Anionic copolymers. Soluble in neutral to weakly alkaline solutions (pH~6-7) and form salts with alkali. Soluble in intestinal pH.	Enteric coatings; resistant to gastric juices.
Poly(ethyl acrylate, methylmethacrylate, trimethylaminoethyl methacrylate chloride) 1:2:0.1 1:2:0.2 $R^1 = H$, CH_3 $R^2 = CH_3$, C_2H_5 $R^3 = CH_3$ $R^4 = CH_2CH_2N(CH_3)_3^+Cl^-$	Eudragit RS Eudragit RL	Water insoluble copolymer. Water permeable films. Water impermeable films.	Water insoluble, used as film coats for sustained release.

- Miller 2008 is a review that includes distinct sections for "enteric release," or coatings that "dissolve rapidly in the intestinal tract" and "sustained release" or coatings that aim to provide "a constant rate of drug release (and absorption)." The Eudragit polymers that were developed by the 1960s are now "widely used for

enteric coating applications." The most common polymers for sustained release coatings are "insoluble cellulose derivatives, insoluble polymethacrylates, as well as polyvinylacetate." Miller 2008 also states that there are four types of Eudragit polymers with enteric release capabilities, three of which are the claimed methacrylic acid-methyl methacrylate co-polymers: "There are four types of Eudragit polymers with enteric release capabilities: Eudragit L 100-55 (also marketed by BASF as Kollicoat MAE 100P), ***Eudragit L 100, Eudragit S 100***, and ***Eudragit FS 30 D***."

2. The Prior Art Taught the Use of Methacrylic Acid-Methyl Methacrylate Co-Polymer That Are from About 20% to about 50% by Weight of the Functional Coating

It would further have been obvious to use methacrylic acid-methyl methacrylate co-polymers that comprise from about 20% to about 50% by weight of the functional coating. Formulators frequently use these polymers in amounts that fall within the claimed range, and the selection of the recited percentage would have been a matter of routine optimization.

- Couch 2005 discloses sustained release delivery of amphetamine salts in which Eudragit L100, a methacrylic acid-methyl methacrylate co-polymer, is around 45.5% by weight of the functional coating. *See, e.g.*, Couch 2005 at Ex. 6.
- Monteith 2009 discloses formulations with sustained release over 12 hours in order to reduce administration frequency for a nasal decongestant drug. One method to achieve this sustained release may be with a pH sensitive "erodible" layer comprising methacrylic acid-methyl methacrylate co-polymers. Table 6 discloses a methacrylic acid-methyl methacrylate co-polymer forming 1-50%.

- Tabandeh 2003 discloses in Figure 3 a Eudragit S100 formulation of aspirin with 10, 20, and 30% polymer content.

D. A POSA Would Have a Reasonable Expectation of Success to Achieve the Claimed Dissolution Profile

1. The Claimed Dissolution Profile Was Known in the Art

The claimed dissolution profile of "the sustained release portion releas[ing] greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37 ℃ and a paddle speed of 50 rpm" was described as desirable and disclosed in a number of prior art references. In addition, the sustained release portion releasing 10% or less of its GHB by about 1 hour and about 60% to about 90% of its GHB by about 6 hours when tested in dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm was also disclosed in a number of prior art references. Further, the claimed dissolution profile of "wherein the formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour [and greater than about 90% of its GHB by 6, 7, or 8 hours] when tested in dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm" was described as desirable and disclosed in a number of prior art references.

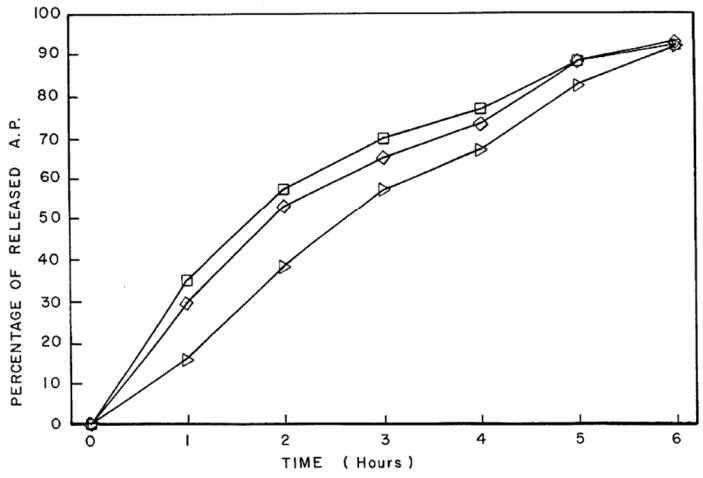
- Conte 1997 teaches controlled release compositions of GHB for treating alcoholism. Conte 1997 found that pharmaceutical compositions of GHB having a controlled release component with a nucleus in the form of granules or tablets comprising an active principle dispersed in a cellulosic matrix consisting of, for example, ethylcellulose, and optionally a film coating consisting of copolymers of acrylic and methacrylic acid esters exhibited controlled release characteristics. The formulations were tested using USP apparatus 2 at a speed of 110 rpm at a

temperature of 37 °C in distilled water (pH adjusted with 1 N HCl). Table 3 and Figure 3 of Conte 1997 shows a dissolution profile with near-constant release over an 8-hour period.

TABLE 3

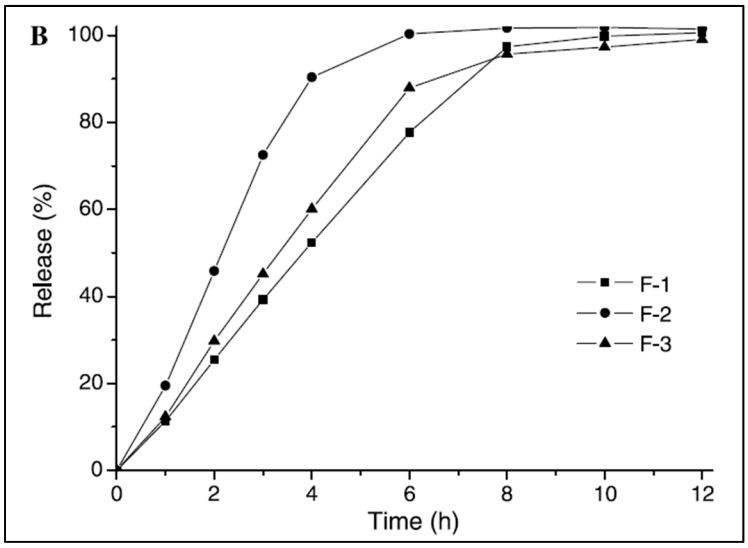
	3.7%	4.5%	8.2%
1st hour	35.1	29.7	16.0
2nd hour	57.4	52.9	38.3
3rd hour	70.1	65.1	57.1
4th hour	77.1	73.6	67.1
6th hour	88.2	88.2	82.6
8th hour	92.2	93.1	91.8

FIG.3



Conte 1997 found "that the right coupling between a tablet or a granule realized as described and the filming matrix based on Eudragit® can substantially reduce the GHBNa in vitro release. In this way, we pass from 100% active principle release with the presently available formulations on the market, to formulations having an active principle release reduced to about ¼ after the first hour and reaching a 90% release of the same not before 8 hours."

- Hu 2006 shows sustained formulations of metformin with "excellent" dissolution release profiles. The formulations were tested using USP apparatus 2 at 50 rpm at a temperature of 37 °C in different media including distilled water (*see* image below; no pH given). Formulations F-2 and F-3 released around 40-60% of the metformin at 4 to 6 hours, in a near-constant release with around 10% released within the first hour and 100% within 8 hours.



- Similarly, Savaser 2005 describes sustained release formulations of diclofenac sodium approximating a "target profile" of: after 2 h: % 35 ± 15; after 4 h: % 60 ± 15; after 8 h: % 90 ± 15. The formulation best fitting the "target profile" also "exhibited the best-fitted formulation into the zero order kinetics." The formulations were tested using a USP apparatus 2 device at 50 rpm with a temperature of 37 °C in phosophate buffered water (0.1 N HCl for first hour and then 7.5 pH).

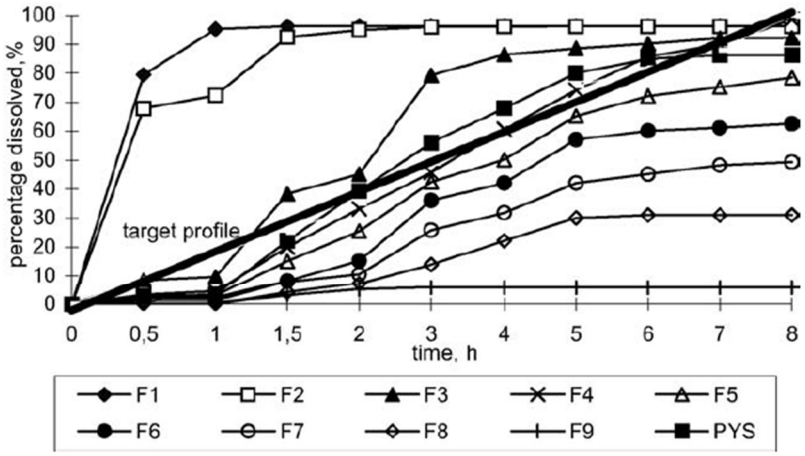


Fig. 1. The dissolution profiles of DS from commercial tablets and HPMC—containing tablets prepared with dry method. F, code of formulation; PYS, commercial tablet.

- Lecomte 2003 states that "two different polymers can be blended to provide a large spectrum of physiochemical properties by varying the polymer blend ratio. In the present study, a gastrointestinal tract (GIT)-insoluble polymer (ethyl cellulose, EC) was dissolved together with an enteric polymer (methacrylic-acid-ethyl acrylate copolymer 1:1, Eudragit L [sic]), in ethanol to coat multiparticulate pharmaceutical dosage forms." The formulations in Lecomte 2003 were tested using a USP apparatus 2 at a speed of 100 rpm and temperature of 37 °C in a medium of 0.1 M HCl & phosphate buffered water (pH 7.4). 0:100 to 50:50 ethylcellulose:Eudragit L coating ratio provides dissolution profiles that meet the claimed dissolution limitations at 1 hour, 4-6 hours, 6 hours, and 8 hours.

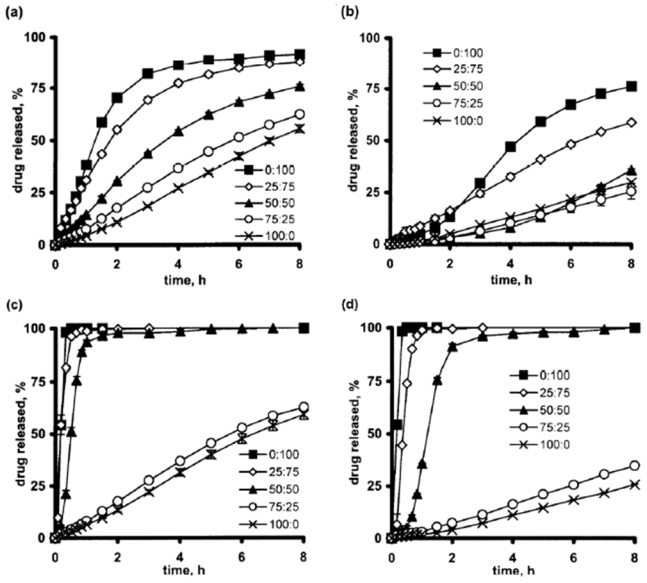


Fig. 1. Effect of the EC:Eudragit® L ratio (given in the figure) on propranolol HCl release from coated pellets in: (a) 0.1 M HCl, 10% coating level; (b) 0.1 M HCl, 20% coating level; (c) phosphate buffer pH 7.4, 10% coating level; and (d) phosphate buffer pH 7.4, 20% coating level.

- Monteith 2009 discloses dissolution profiles for various formulations using apparatus 2 at 50 rpm in simulated gastric fluid for 1 hour followed by pH 6.8 for the remainder of the study.

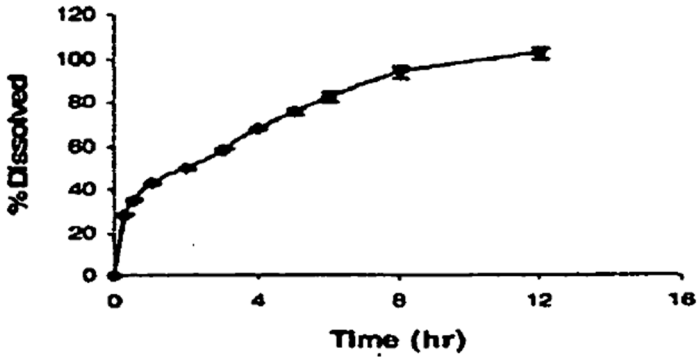


Figure 4

2. The Claimed Dissolution Profile Encompasses a Broad Range

The claimed in vitro dissolution profile of the sustained release formulation—having greater than about 40% of the GHB in the sustained release portion released by about 4 to about 6

hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm (and additionally, 10% or less of the GHB in the sustained release portion by about 1 hour and about 60% to about 90% of its GHB by about 6 hours)—broadly captures the dissolution profiles of immediate release and sustained release formulations. Similarly, the claimed in vitro dissolution profile of the formulation—having at least about 30% of the formulation's GHB released by one hour and/or greater than about 90% of the formulation's GHB by 6, 7, or 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm—broadly captures immediate release formulations in addition to formulations containing both an immediate and sustained release component. This case is similar to *Purdue Pharma*, 642 F. Supp. 2d at 372, in which the Court found that "[d]eveloping a controlled release formulation of tramadol that would fall within the claimed ranges and would be suitable for once-a day dosing would have been obvious to one of skill in the art" based on disclosures in the prior art of dissolution profiles that were necessary in order to achieve in vitro dissolution profiles that would be deemed suitable for purposes of seeking once-a-day dosing.

- All the tested formulations in Liang 2006 have greater than about 40% of the GHB in the sustained release portion released by about 4 to about 6 hours when tested in a dissolution apparatus 2. For Example 6a (which corresponds to Figure 3, reproduced below), a pH 1.1 media was used from 0-2 hours, and then a pH 6.8 buffer (correlating to the pH of the targeted upper intestine) was used from 2-6 hours[4]. For Examples 6c and 6d (which correspond to Figures 2 and 1 respectively, with Fig. 2 reproduced below), a pH 1.1 media was used from 0-2 hours, a pH 6.0

[4] According to Jazz's Declaration of Clark Allphin submitted on April 20, 2020 in U.S. Patent Appl. No. 16/025,487, "the release profile in DI water would be substantially similar" to the release profile in physiological media. *See, e.g.*, Declaration at 1 n.1.

buffer (correlating to the pH of the upper intestine) was used from 2-3 hours, and then a pH 7.5 buffer (correlating to the pH of the targeted colon) was used from 3-6 hours. The use of the buffers is used to approximate the dissolution of the delayed/controlled release portion in different portions of the intestine. The examples in Liang 2006 also meet the other claimed dissolution profiles of releasing 10% or less of the GHB in the sustained release portion by about 1 hour and about 60% to about 90% of the GHB in the sustained release portion by about 6 hours. The examples in Liang 2006 (including the immediate release formulations, which correspond to Figure 4, reproduced below) also meet the dissolution profiles of releasing at least about 30% of the formulation's GHB by one hour and greater than about 90% of the formulation's GHB by 6, 7, or 8 hours when tested in a dissolution apparatus 2.

Exs.	**Barrier Coat**	**Enteric Coat**	**Target Area**	**Target pH**	**Related Figure**	**Relative BA***
6a	Example 4	Eudragit L30-55	Duodenum	> 5.5	3	53%
6b	Example 4	Eudragit L 100	Jejunum	> 6–7	N/A	N/A
6c	Example 3	Eudragit FS 30 D	Colon	> 7	2	27%
6d	Example 5	Eudragit FS 30 D	Colon	> 7	1	22%

* Relative bioavailability is compared to an immediate release control

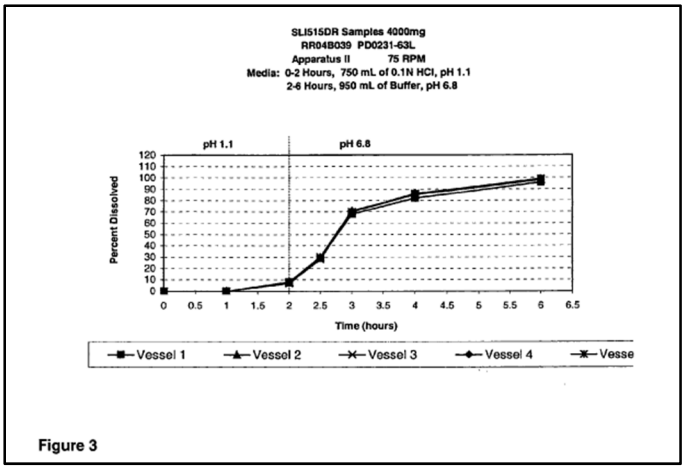


Figure 3

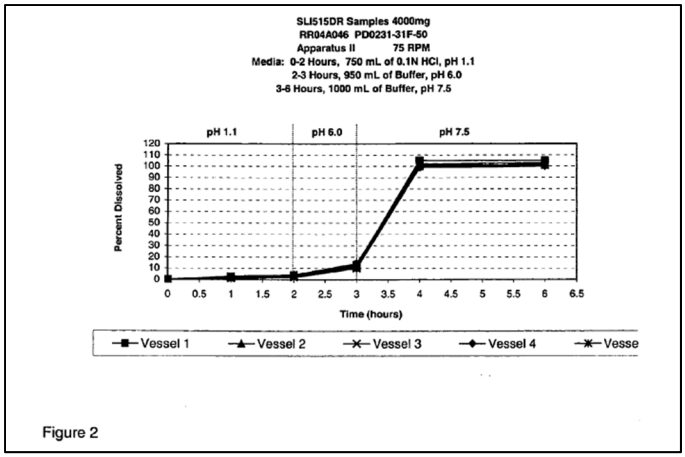


Figure 2

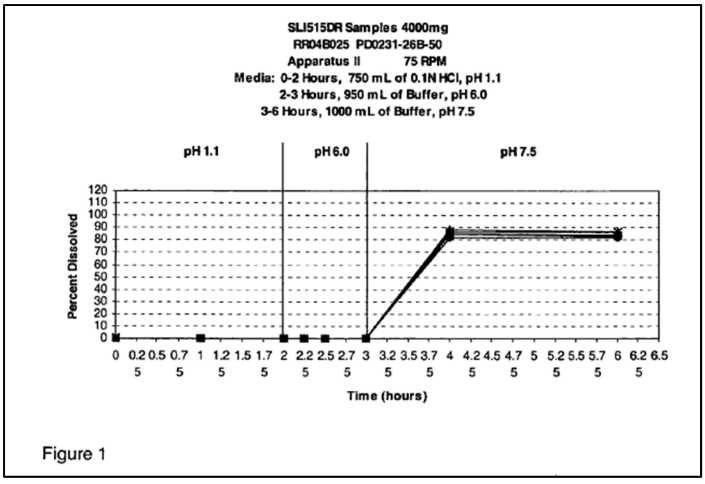
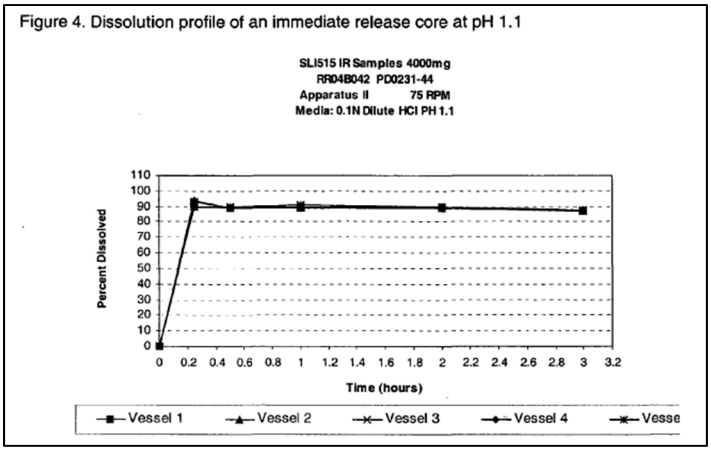


Figure 1

Figure 4. Dissolution profile of an immediate release core at pH 1.1



- All the formulations in Conte 1997 (with either no or varying amounts of a film coating) also had greater than about 40% of the GHB in the sustained release portion released by about 4 to about 6 hours when tested in a dissolution apparatus 2. *See* Table 3 and Figure 3 below. Conte 1997 also shows formulations that release at least about 30% of the formulation's GHB by one hour and greater than about 90% of the formulation's GHB by 6, 7, or 8 hours.

TABLE 3

	3.7%	4.5%	8.2%
1st hour	35.1	29.7	16.0
2nd hour	57.4	52.9	38.3
3rd hour	70.1	65.1	57.1
4th hour	77.1	73.6	67.1
6th hour	88.2	88.2	82.6
8th hour	92.2	93.1	91.8

FIG.3

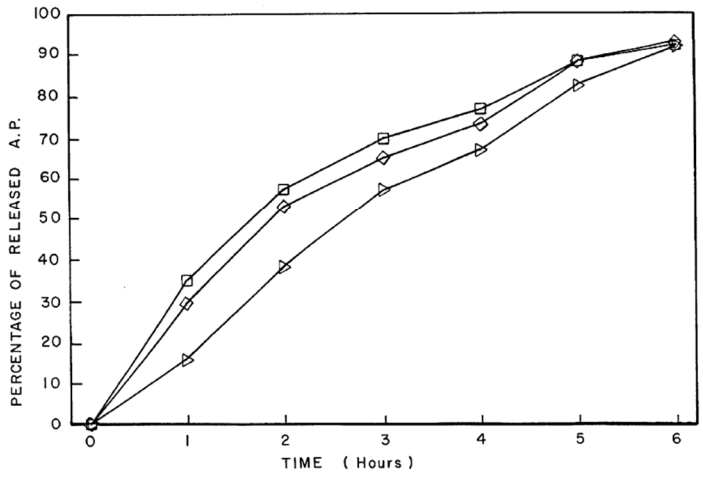
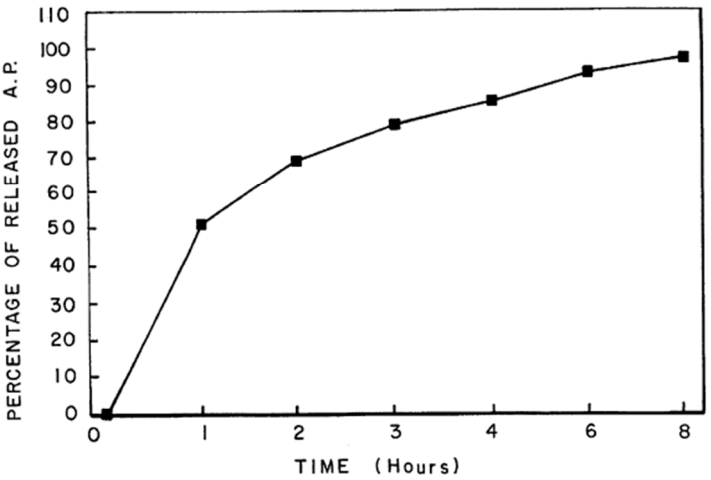


FIG.2



- All the formulations in Hu 2006 also met the claimed dissolution profile of greater than about 40% of the active ingredient in the sustained release portion released by about 4 to about 6 hours when tested in a dissolution apparatus 2, no matter what was in the coating, the amounts of Eudragit in the coating, the amount of talc in the coating, or the media that was used.

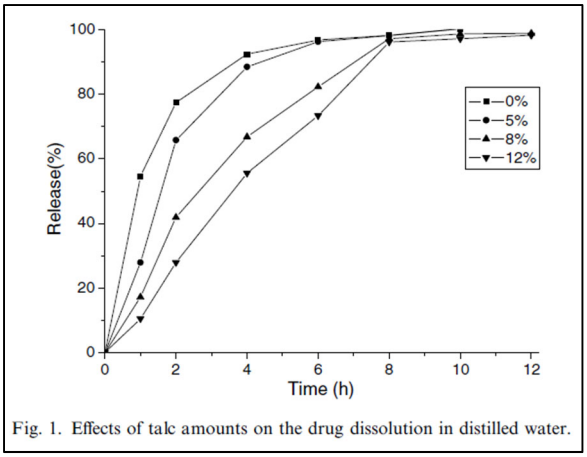


Fig. 1. Effects of talc amounts on the drug dissolution in distilled water.

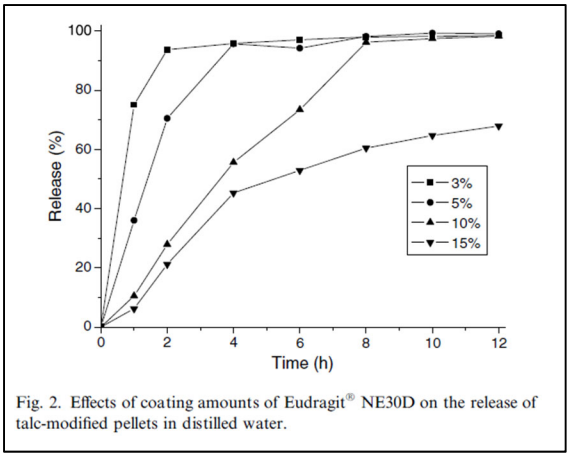


Fig. 2. Effects of coating amounts of Eudragit® NE30D on the release of talc-modified pellets in distilled water.

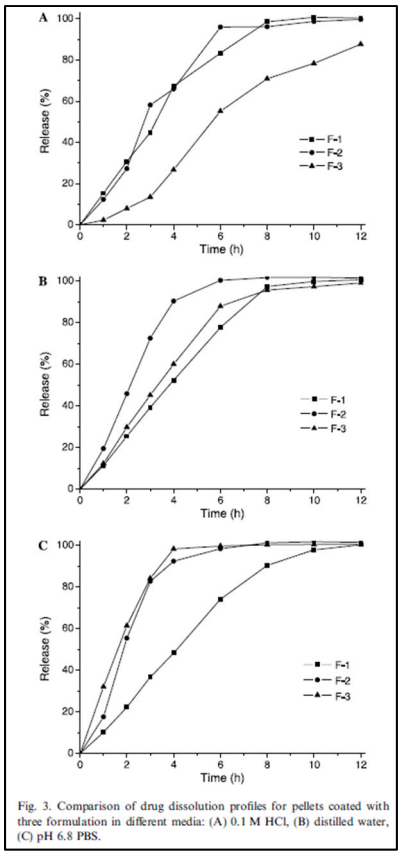


Fig. 3. Comparison of drug dissolution profiles for pellets coated with three formulation in different media: (A) 0.1 M HCl, (B) distilled water, (C) pH 6.8 PBS.

- The majority of the formulations in Savaser 2005 also depict that the majority of the tested formulations met the claimed dissolution profile of greater than about 40% of the active ingredient in the sustained release portion released by about 4 to about 6 hours when tested in dissolution apparatus 2. At least seven of the ten formulations tested met the claimed dissolution profile.

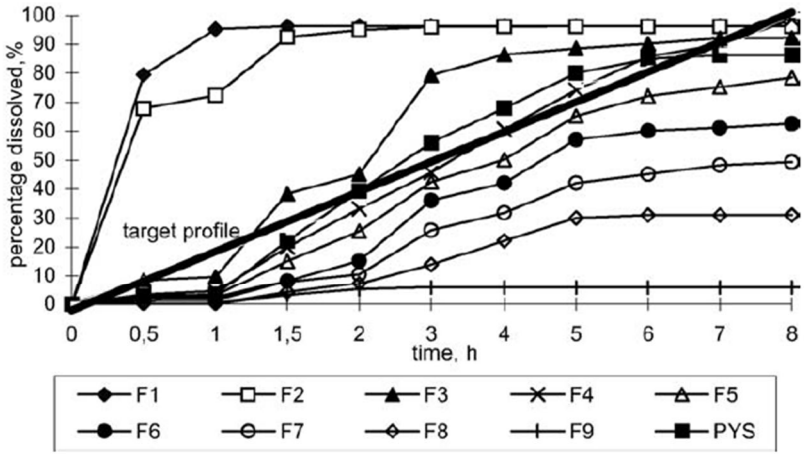


Fig. 1. The dissolution profiles of DS from commercial tablets and HPMC—containing tablets prepared with dry method. F, code of formulation; PYS, commercial tablet.

In conclusion, the claimed dissolution profile would encompass a broad range of release profiles, including immediate release.

Given the foregoing, the claimed subject matter would be obvious because a POSA would have been motivated to and had a reasonable expectation of success in formulating a once-nightly dose of sodium oxybate composition with an immediate release and sustained release component, the sustained release component made up of a functional coating deposited over a core, and the functional coating comprising one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating. It would be a matter of routine experimentation for a POSA to use the claimed co-polymer in the claimed amounts to achieve the claimed dissolution profile. The claimed dissolution profile, *i.e.*, wherein the sustained release portion releases greater than about 40% of the GHB by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37°C and a paddle speed of 50 rpm, and 10% or less of its GHB by about 1 hour, and about 60% to about 90% of its GHB by about 6 hours; and wherein the formulation releases at least about 30% of the GHB by one hour and greater than about 90% of the GHB by 6, 7, or 8 hours when tested in dissolution apparatus 2

in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm was known in the art and/or broadly encompasses immediate release formulations.

IX. THE SUSTAINED RELEASE PATENTS ARE INVALID FOR FAILING TO SATISFY THE REQUIREMENTS OF 35 U.S.C. § 112

For the reasons set forth below, the asserted claims of the Jazz Sustained Release Patents are invalid for failure to comply with the written description and enablement requirements of 35 U.S.C. § 112.

Pursuant to 35 U.S.C. § 112, ¶ 1, a patent specification "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make, and use the same[.]" *Id.* The Federal Circuit has held that this language creates two closely related, yet separate requirements for a specification: (i) a written description of the invention ("written description"), and (ii) a written description of the manner and process of making and using the invention ("enablement"). *See Ariad Pharm., Inc. v. Eli Lilly Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc).

"The test for sufficiency of a patent's written description requires an objective inquiry into the four corners of the specification from the person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan to show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351. A patent is invalid for inadequate written description unless "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id*.

The requirement of enablement mandates that the disclosure in the specification describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the [invention]." 35 U.S.C. § 112, ¶ 1. For a patent's specification to be enabling, it "must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010). In determining whether undue experimentation is required to practice the claimed invention, a court may assess some or all of the so-called *Wands* factors, which include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A patent specification must enable the full scope of the claimed invention. *See ALZA Corp.*, 603 F.3d at 939 (affirming invalidity of the claims based on lack of enabling disclosure because "developing non-osmotic oral dosage forms, such as tablets and capsules" requires undue experimentation).

A. The Jazz Sustained Release Patents neither describe nor enable the claimed formulation with the claimed dissolution profile

The claims of the Jazz Sustained Release Patents are directed to formulations containing "sustained release" components. *See, e.g.*, '488 patent at claim 1 ("A formulation comprising immediate release and sustained release portions . . ."); '885 patent at claim 1; '956 patent at claim 1; and '931 patent at claim 1. Jazz appears to contend that the claimed formulations are not restricted to particular dosage forms, but can include any dosage form, as indicated by its contention that Avadel's FT218 NDA infringes the Sustained Release Patents, even though FT218 is formulated as a sachet to deliver GHB by oral suspension. *See, e.g.*, 9/7/21 Plaintiff's Initial Infringement Chart at 27, 60, 84, 149-150.

The specification's disclosure of formulations containing both "immediate release" and "sustained release" components, however, is limited to two specific solid dosage forms: tablets and capsules. *See, e.g.*, '488 patent at col. 4:18-22 ("However, the IR component may also be formulated as part of a single dosage form that integrates both the IR and CR components. In such an embodiment, the pharmaceutical formulation may be provided in the form of the coated tablet or capsules); *id.* at col. 9:31-35 ("In certain embodiments, the controlled release formulations described herein are provided as a coated tablet composition having a controlled release core coated by a functional overcoat."); *see also* '885 patent at col. 4:26-30, 9:39-42 (same); '956 patent at col. 4:26-30, 9:39-42 (same); '931 patent at col. 4:26-30, 9:39-42.

The asserted claims of the Sustained Release Patents specifically require a "functional coating" in the "sustained release portion" of the claimed formulations. *See, e.g.*, '488 Patent at claim 1. The specification describes that the functional "coating composition works to preserve the integrity of the unit dosage form post administration and serves to facilitate controlled release of drug from the CR core." '488 Patent at 11:56-59.

Based on these disclosures, a POSA would not have understood the inventors to have been in possession of the full scope of GHB formulations containing "sustained release" components which would fall within the scope of the claims under Jazz's view of the claims. Specifically, a POSA would not have understood the inventors to have been in possession of solid formulations containing "sustained release" components other than tablets or capsules. Thus, to the extent Jazz asserts the asserted claims of the Jazz Sustained Release Patents encompass GHB formulations containing "sustained release" components other than tablets or capsules (such as FT218's sachet formulation), the claims are invalid for lack of written description support.

The claims of the Jazz Sustained Release Patents are also invalid for lack of written description because the specification fails to disclose that the inventors were in possession of sustained release formulations possessing a "functional coating" containing methacrylic acid-methyl methacrylate co-polymers, let alone in the percentages recited in the asserted claims. As described above, the claims of the Jazz Sustained Release Patents recite formulations in which the sustained release portion possesses a functional coating comprising "one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating," or substantially similar language. *See, e.g.* '488 patent at col. 27:35-38; '885 patent at col. 26:64-67; '956 patent at col. 27:13-15; and '931 patent at col. 28:1-4. The specification, however, lacks any disclosure of a sustained release formulation in which a functional coating contains methacrylic acid-methyl methacrylate co-polymers comprising "about 20% to about 50% by weight of the functional coating." The only disclosure of methacrylic acid-methyl methacrylate co-polymers is a passing mention in column 13, which identifies methacrylic acid-methyl methacrylate copolymers as potential materials for use as pore formers. *See, e.g.*, '488 patent at col. 13:30-31; '885 patent at col. 13:39-40; '956 patent at col. 13:39-40; and '931 patent col. 13:39-40. But this cursory disclosure of methacrylic acid-methyl methacrylate co-polymers as part of a broader description of possible polymer materials with no indication of the appropriate quantity for use in a sustained release formulation would not lead a POSA to believe that the inventors were in possession of the full scope of the recited sustained release formulations containing "about 20% to about 50% by weight" of methacrylic acid-methyl methacrylate co-polymers with a particular in vitro dissolution profile in very specific medium (de-ionized water) using a very specific dissolution method.

Nor do any of the examples describe dissolution experiments performed on sustained release formulations containing methacrylic acid-methyl methacrylate co-polymers, let alone at the recited amounts. The asserted claims of the Jazz Sustained Release Patents require that the recited release of GHB from the immediate and sustained release portions be determined when the claimed formulation is tested in a dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50 rpm. *See, e.g.*, '488 patent at col. 27:44-46; '885 patent at col. 27:1-5; '956 patent at col. 27:22-24; and '931 patent at col. 28:5-9. But the specification contains no test results or other data indicating to a POSA that the inventors were in possession of any formulation that contained a sustained release portion comprising a functional coating containing "about 20% to about 50% by weight" of methacrylic acid-methyl methacrylate co-polymers that results in a formulation exhibiting such *in vitro* characteristics. *See, e.g.*, '488 Patent at *passim*.

Other than Examples 2 and 3, none of the examples disclosed in the specification utilize USP Apparatus 2. Further, while Example 2 describes the use of USP Apparatus 2, the sustained release formulation tested contains, in addition to a sodium oxybate tablet core, hydroxypropyl cellulose, dibutyl sebacate, ethylcellulose, ethanol, and water, but no methacrylic acid-methyl methacrylate co-polymer, much less in the concentration range recited in the claims. *See* '488 patent, Table 2A; '885 patent, Table 2A; '956 patent, Table 2A; and '931 patent, Table 2A. In addition, the formulation tested in Example 2 only discloses a "functional coating" comprising polymers, and contains no disclosure of a functional coating incorporating, e.g., hydrogenated vegetable oil. In addition, the formulation tested in Example 2 does not demonstrate possession of the claimed dissolution profile, at least because it fails to demonstrate that the subject "formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37 °C and a paddle speed of 50

rpm." *See, e.g.*, '488 patent at col. 20:31-37; *see also* '885 patent at col. 20:43-49; '956 patent at col. 20:27-33; '931 patent at col. 20: 48-54. Thus, Example 2 fails to disclose a GHB formulation meeting the limitations of the Jazz Sustained Release Patent claims that displays the recited GHB release profile when measured using the recited dissolution apparatus.

Example 3 relies on the sustained release tablets from Example 2 but further adds an immediate release overcoat of GHB. Thus, like Example 2, Example 3 fails to disclose dissolution of a formulation in USP Apparatus 2 that contains a functional coating with methacrylic acid-methylmethacrylate co-polymer, much less in the concentration range recited in the claims, and describes only a functional coating made of polymers, with no disclosure of a functional coating incorporate hydrogenated vegetable oil.

Based on the disclosures of formulations tested using USP Apparatus 2 in the Jazz Sustained Release Patents, a POSA would have concluded that the inventors did not demonstrate that they were in possession of the claimed GHB formulations for this additional reason.

Moreover, the asserted claims specifically recite that claimed formulations exhibit behavior whereby "the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours" when tested in the specified manner. *See, e.g.*, '488 Patent at claim 1(a); *see also* '885 patent at claim 1; '956 patent at claim 1(a); '931 patent at claim 1. But the specification contains no teaching as to how a POSA could even discern that the released gamma-hydroxybutyrate comes from the sustained release portion as opposed to any other source. Nor does the specification provide any discussion of how to measure the gamma-hydroxybutyrate from the sustained release portion using the recited equipment, method, and medium that would show the inventors' possession of the claimed subject matter, let alone data showing possession of such subject matter in a sustained release portion with a functional coating containing "about 20%

to about 50% by weight" of methacrylic acid-methyl methacrylate co-polymers. *See, e.g.*, '488 Patent at *passim*.

More generally, the asserted claims of the Jazz Sustained Release Patents are functional claims directed to formulations possessing a broad array of functional coatings that would result in the release profiles for GHB when tested using USP Apparatus 2 under the recited conditions. Further, those functional coatings are limited only by the requirement that the include a wide range of possible concentrations of methacrylic acid-methylmethacrylate. As discussed above, the specification provides no working examples of formulations with functional coatings containing methacrylic acid-methylmethacrylate, much less formulations meeting the recited drug release profile. Nor does the specification provide a POSA with any guidance how one would achieve the claimed GHB release profiles across the entire range of formulations claimed by the Jazz Sustained Release Patents. Further, a POSA would understand that dissolution testing is unpredictable. In view of the breadth of the functional claims of the Jazz Sustained Release Patents, the unpredictability in the art, and the limited disclosures in the specification, a POSA would not believe the inventors were in possession of the full range of possible formulations that met the recited drug release profile. *See Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 330, 1339 (Fed. Cir. 2021) (finding invalid claims covering all scFvs that bind to a target of clinical interest); *Indenix Pharm. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1164-65 (Fed. Cir. 2019) ("The written description requirement specifically defends against such attempts to 'cover any compound later actually invented and determined to fall within the claim's functional boundaries.'" (quoting *Ariad*, 598 F.3d at 1353)); *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) ("Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are

highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus."); *Ariad*, 598 F.3d at 1352 ("The written description requirement also ensures that when a patent claims a genus by its function or result, the specification recites sufficient materials to accomplish that function . . . ."). To the extent Jazz contends that the specification of the Jazz Sustained Release Patents and level of skill in the art would lead a POSA to believe the inventors were in possession of the claimed formulations, that only further underscores the obviousness of the claims.

During prosecution of the '488 patent, the Examiner rejected the pending claims for failing to disclose a formulation containing a functional coating comprising the recited range of methacrylic acid-methyl methacrylate co-polymers that displayed the GHB release profile recited in the claims. *See* '488 patent File History, May 2, 2019 Office Action at 3-7. In response, the Applicant submitted a declaration from Clark Allphin ("Allphin Declaration"), one of the inventors of the Jazz Sustained Release Patents, that purportedly described the claimed release of GHB using a formulation containing "28% (w/w) Eudragit L100 (methacrylic acid-methyl methacrylate copolymer), 55% (w/w) ethylcellulose, and 17% (w/w/) poloxamer 199." *See* '488 patent File History, March 5, 2020 Allphin Declaration at ¶ 13.

Jazz, however, cannot rely on its submissions to the patent office—such as the Allphin Declaration and the accompanying data—to compensate for the lack of written description support of its claims. It is well established that written description support must be found in the four corners of the patent. 35 U.S.C. § 112, para. 1 (pre-AIA); *see also Enzo Biochem., Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 969 (Fed. Cir. 2002) ("After all . . . one can show possession of an invention by means of an affidavit or declaration during prosecution . . . However, such a showing

of possession alone does not cure the lack of a written description in the specification, as required by statute."). Jazz's submission to the patent office is legally irrelevant for purposes of the written description analysis.

Further, even if the Allphin Declaration could be considered, it fails to provide the necessary written description support. The dissolution study described in the Allphin Declaration was performed using either USP Apparatus 3 or 7, in which the dissolution profile was tested using deionized water at a temperature of 37 ºC and a dip rate of 30/min, where samples were taken at intervals of 30 minutes until 2 hours, then hourly thereafter.[5] Allphin Decl. ¶ 13. In contrast, the claims of the Jazz Sustained Release Patent require the use of USP Apparatus 2, with a paddle speed at 50 rpm. Because these are distinct dissolution protocols, the disclosure of testing using USP Apparatus 3 or 7 cannot serve as a substitute for dissolution testing using USP Apparatus 2. As a result, the data provided in the Allphin Declaration would not rescue the lack of written description support in the Jazz Sustained Release Patents.

For similar reasons, the Jazz Sustained Release Patents are invalid for lack of enablement across the full scope of the claims. For example, the specification provides no guidance how a POSA would generate any type of formulation with the recited GHB release profiles other than tablets and capsules, that would provide the necessary GHB release characteristics. Nor does the specification provide working examples of any of the foregoing dosage forms. Given the level of skill in the art, the formulations known in the art, the unpredictability of dissolution testing, and the breadth of the claims, to the extent Jazz contends the asserted claims are not obvious to one of

[5] The dissolution study described in the Allphin Declaration must have been performed in either USP Apparatus 3 or 7 because it recites a dip rate, rather than a paddle speed, as would be required for Apparatus 2.

ordinary skill in the art, the Asserted Patents do not enable a POSA to practice the full scope of the claims without undue experimentation.

B. The Sustained Release patents neither describe nor enable a functional coating without a "base polymer"

To the extent Jazz contends that FT218 possesses a "functional coating" around its controlled release component, the asserted claims of the Jazz Sustained Release Patents are invalid for lack of written description and enablement for failing to disclose non-polymeric functional coatings. *See* '488 patent, claim 1 ("the sustained release portion comprises a functional coating and a core"); '885 patent, claim 1; '956 patent, claim 1; '931 patent, claim 1.

FT218's controlled release component includes an outer layer comprising three components: (1) hydrogenated vegetable oil type I; (2) Eudragit S100; and (3) Eudragit L100-55. AVDL_00044786 at AVDL_00044788. That outer coating comprises 60% vegetable oil, a non-polymeric material. *Id.* To the extent Jazz contends that the asserted claims of the Jazz Sustained Release Patents are broad enough to encompass an outer layer with a vegetable-oil base, the claims are invalid for lack of written description. The specification only describes "functional coatings" having a base polymer and contains no disclosure of functional coatings made using a non-polymeric base, e.g., vegetable oil. *See* '488 patent at col. 12:40-13:13; '885 patent at col. 12:48-13:22; '956 patent at col. 12:48-13:22; and '931 patent at col. 12:48-13:22. A POSA would therefore not believe, based on the disclosures in the specification, that the inventors were in possession of the claimed GHB formulation in which the functional coating was made of hydrogenated vegetable oil.

Similarly, to the extent Jazz contends the Jazz Sustained Release Claims cover functional coatings that include hydrogenated vegetable oil, the claims are also invalid for lack of enablement. The specification provides no guidance that would allow a POSA to make a functional coating

comprising a hydrogenated vegetable oil base that would result in the required GHB release profile without undue experimentation. The specification also fails to provide any working examples of such a formulation. Given the level of skill in the art, the formulations known in the art, the level of predictability in the art and the breadth of the claims, to the extent Jazz contends the asserted claims are not obvious to one of ordinary skill in the art, the Sustained Release Patents do not enable a POSA to practice the full scope of the asserted claims without undue experimentation.

X. THE SUSTAINED RELEASE PATENTS ARE INVALID FOR IMPROPER INVENTORSHIP AND/OR AS ANTICIPATED BY AVADEL PATENT PUBLICATIONS

The claims of the Jazz Sustained Release Patents are further invalid for derviation or improper inventorship under 35 U.S.C. § 102(f) (pre-AIA) and/or 35 U.S.C. § 101 (post-AIA) because they were derived from the inventive work of Avadel. The inventive work by Avadel alternatively renders the claims of the Jazz Sustained Release Patents invalid as anticipated.

A patent is invalid for derivation "if the inventors named in the patent did not actually invent the claimed invention." *Apotex v. Cephalon, Inc.*, 2011 WL 6090696, at *17 (E.D. Pa. Nov. 7, 2011). Put differently "[o]ne cannot claim or reproduce the invention of another and obtain a patent on that 'invention.'" *Id.* (citing *OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1401-02 (Fed. Cir. 1997)). Establishing derivation under section 102(f) requires (1) "establish[ing] prior conception of the invention by another"; and (2) "communication of that conception to the patentee" prior to the date of the patent application. *In re Bendamustine Consolidated Cases*, 2016 WL 3381219, at *14 (D. Del. June 10, 2016); *Apotex*, 2011 WL 6090696, at *17, 20. "Communication" in this context requires conveying "sufficient information to allow someone or [sic] ordinary skill in the art to construct and operate the invention." *Adaptix, Inc. v. Apple, Inc.*, 2015 WL 218932, at *2 (N.D. Cal. Jan. 15, 2015). The asserted claims are subject to the provisions

of pre-AIA 35 U.S.C. § 102 because they purport to claim priority to an application filed on March 24, 2010.

To be sure, Avadel contests that the asserted claims are entitled to such a priority date and contend that the asserted claims cannot claim priority before July 2, 2018. As such, the asserted claims would potentially be subject to post-AIA 35 U.S.C. § 101. But the pertinent requirement continues to exist under the America Invents Act ('AIA') in 35 U.S.C. § 101. *See, e.g., Intel Corp. v. Tela Innovations, Inc.*, Case No. 3:18-cv-02848-WHO, 2019 WL 2476620 at *7 n. 5 (N.D. Cal. Jun. 13, 2019) ("This case cited 35 U.S.C. section 102(f) as embodying this requirement. Although section 102(f) was later eliminated with the passage of the America Invents Act ("AIA"), the requirement stands.") (citing Joe Matal, A Guide to the Legislative History of the America Invents Act: Part I of II, 21 Fed. Circuit B.J. 435, 451 (2012) ("Matal")); *Board of Trustees of University of Illinois v. Micron Tech., Inc.*, 245 F. Supp. 3d 1036, 1041 n.1 (C.D. Ill. 2017) ("Section 102(f) has been eliminated from the statutory scheme, but the defense is presumably still available under § 101, which allows patents to only be provided to "'[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter ....'") (alterations in original); and Matal at 451-52 ("Some may think that, because § 102(f) has been repealed, there is no longer any legal requirement that a patent for an invention be obtained by the inventor. Not so. Both the Constitution and § 101 still specify that a patent may only be obtained by the person who engages in the act of inventing.") (citing U.S. Const. art. I, § 8, cl. 8; and 35 U.S.C. § 101).

Direct evidence is not required to establish derivation. Thus, courts have held, for example, that circumstantial evidence may be used to establish communication. *See, e.g.*, *Adaptix, Inc. v. Alcatel-Lucent USA, Inc.*, 2015 WL 12696205, at *2 (E.D. Tex. Aug. 7, 2015) (finding that "circumstantial evidence of 'communication' is sufficient to defeat a motion for summary

judgment of no derivation"); *Adaptix*, 2015 WL 218932, at *2-3 (denying a motion for summary judgment for infringement, finding that circumstantial evidence of communication with the patentee was enough to create a genuine issue of material fact as to whether the patents-in-suit were invalid for derivation); *see also Robert Bosch, LLC v. Pylon Mfg. Co.*, 700 F. Supp. 2d 625, 642-43 (D. Del. 2010) (noting that "the inference that [third party] conceived of the solutions depicted…and communicated them to [patentee]…is supported by circumstantial evidence…" and that this circumstantial evidence "permit[s] a finding of corroboration for [third party's] testimony regarding his prior conception," although ultimately concluding that not all limitations of the claim were communicated).

Avadel's conception, reduction to practice, and publication of its controlled release formulation prior to the filing of the sustained release claims in Jazz's patents establishes that the claims of the Jazz Sustained Release Patents are invalid for derivation. The Jazz Sustained Release Patents claim priority to U.S. provisional application No. 61,317,212, filed March 24, 2010. However, as of January 2018, Jazz had not obtained any issued claims from this family. Instead, at the time, Jazz was engaged in the prosecution of U.S. Application No. 13/071,369 ("the '369 Application"), a parent application to the applications that would eventually issue as the Jazz Sustained Release Patents. Unlike the claims of the Jazz Sustained Release Patents, the pending claims of the '369 Application were directed to a "controlled release dosage form for oral administration" including "a compressed tablet controlled release core" containing "at least one polymer comprising ethylcellulose," at least one "polymeric pore former," and also reciting "providing a time dependent release" based on the release of drug measured from the time of administration. *See* '369 Application File History, Oct. 4, 2017 Response to Final Office Action at Claim 1 (emphasis added). Further, one dependent claim recited that the "at least on polymeric

pore-form is at least one of a polyethylene glycol, poloxamer, polyvinyl alcohol, copovidone, povidone, a water soluble sugar, a water soluble organic acid, such as carboxylic acids and their salts, and a hydroxyalkyl cellulose selected from hydroxyethyl cellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose." *See id.* at Claim 16 (emphasis added). These pending claims of the '369 Application were consistent with the disclosures in the specification, and in particular the disclosure of exemplary controlled release dosage forms comprising a compressed tablet controlled release core with a functional coating made of ethylcellulose, and using hydroxypropyl cellulose or poloxamer as pore formers. *See, e.g.*, '369 Application at Examples 1-13.

Notably, the claims of the '369 Application pending as of January 2018 were not the originally-filed claims. Rather, they were the product of narrowing amendments made by Jazz earlier in the prosecution of the '369 Application in order to overcome obviousness rejections by the Examiner in light of the Liang prior art reference. For example, claim 1 of the '369 Application was originally directed broadly to "a controlled release dosage form for oral administration," but was subsequently narrowed by Jazz, first to a "compressed tablet," then to "a compressed tablet controlled release core" following rejections over Liang. *See* '369 Application File History, May 28, 2013 Response to Office Action at Claim 1; Jan. 27, 2014 Response to Office Action at Claim 1. The claims resulting from these narrowing amendments, however, continued to match the disclosures of the '369 Application, which exemplified a compressed tablet controlled release dosage form, but no other controlled release form. Also consistent with the specification's disclosures was the fact that the claims pending as of January 2018 contained no claims directed to dissolution testing or drug release profiles resulting from the dissolution testing of formulations containing methacrylic acid methyl methacrylate co-polymers, much less testing of such

formulations in deionized water using apparatus 2 at a temperature of 37 ºC and a paddle speed of 50 rpm, none of which was disclosed in the specification.

On January 25, 2018, the application that ultimately issued as Avadel's U.S. Patent No. 10,272,062 ("the '062 patent") was first published. This application demonstrates Avadel's conception—and reduction to practice—of its novel controlled release formulations. Unlike Jazz's pending '369 Application, Avadel's application for the '062 patent described modified release forms of GHB containing methacrylic acid-methyl methacrylate co-polymers that had specific dissolution release profiles when tested in deionized water using USP Apparatus 2, where the dissolution medium was maintained at 37 ºC ± 0.5 ºC with the rotating paddle speed fixed at 50 rpm.

Less than six months after the publication of Avadel's patent application, Jazz filed U.S. Application 16/025,487 (the "'487 Application") (which would eventually issue as the '488 patent) as a continuation of its pending '369 Application. Immediately after filing the original application, Jazz canceled all 108 original claims which, like the parent '369 Application, recited "compressed tablet" controlled release dosage forms comprising at least one polymer comprising ethylcellulose, at least one polymeric "pore former," and "providing time dependent release" as measured by the release of drug from the time of administration. In their place, Jazz introduced claims directed to a generic formulation (rather than a compressed tablet) comprising specifically methacrylic acid-methyl methacrylate co-polymers (rather than one polymer comprising ethylcellulose and at least one polymeric "pore former"), and reciting specific dissolution profiles defined by tests performed "in a dissolution apparatus 2 in deionized water at a temperature of 37 ºC and a paddle speed of 50 rpm" (rather than reciting attributes following administration). *See* '487 Application File History, July 2, 2018 Applicant Submission.

The new claims filed by Jazz in the prosecution of the '487 Application hewed closely to the disclosures in Avadel's application for the '062 patent that had published only several months earlier. Given the timing of the new claims following the publication of descriptions of Avadel's new controlled release formulation, the reasonable inference is that Jazz's new claims were the result of Avadel's communication of its controlled release formulations to Jazz via its published application for the '062 patent.

Further, evidence of Jazz's reliance on Avadel's disclosure in its application for the '062 patent is reflected by the fact that in contrast to the original claims filed with the '487 Application, the new claims are not described or supported by the application's specification. In particular, the specification of the '487 Application does not disclose dissolution testing of formulations containing methacrylic acid-methyl methacrylate co-polymers using apparatus 2 at a temperature of 37 ºC and a paddle speed of 50 rpm, much less the release profiles resulting from such testing. The only source of dissolution testing of that formulation is in Avadel's published application, providing further evidence that the new claims submitted by Jazz were taken directly from the Avadel's inventive work on controlled release formulations.

Much like the '488 patent, which issued from the '487 Application, the remaining Jazz Sustained Release Patents claim formulations comprising methacrylic acid-methyl methacrylate co-polymers and specific dissolution release profiles resulting from testing performed with apparatus 2 at a temperature of 37 ºC and a paddle speed of 50 rpm. *See, e.g.*, '885 patent at claim 1; '956 patent at claim 1; '931 patent at claim 1. And because the Jazz Sustained Release Patents share the same specification, the claims of the remaining Jazz Sustained Release Patents, like the claims of the '488 patent, lack support for those claim limitations in the specification's disclosures. Instead, those claims, like the claims of the '488 patent, reflect Jazz's attempt to claim what

Avadel invented and disclosed in its applications, including the application giving rise to the '062 patent.

Because the issued claims of the Jazz Sustained Release Patents lack written description support, they are not entitled to the priority date of the March 24, 2010 provisional application. Instead, they are only entitled to the date of the earliest disclosure of formulations comprising methacrylic acid-methyl methacrylate co-polymers and specific dissolution release profiles resulting from testing performed with apparatus 2 at a temperature of 37 ºC and a paddle speed of 50 rpm, i.e., Jazz's July 2, 2018 filing during the prosecution of the '488 patent. *See* '488 patent File History, July 2, 2018 Claim Amendment. Because Avadel's application for '062 patent published on January 25, 2018, it is prior art to the claims of the Jazz Sustained Release Patents, and those claims are therefore anticipated. Further, as demonstrated by the disclosures in the '062 patent, the inventors of the Avadel application had fully conceived of (and reduced to practice) the subject matter claimed in the Jazz Sustained Release Patents prior to communicating their invention to Jazz by way of the published application for the '062 patent. The claims of the Jazz Sustained Release Patents are therefore invalid for derivation and lack of inventorship.

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EXHIBIT B

REMARKS:

I. Status of the Claims

Claims 75-106 are pending, and claims 1-74 are canceled.

II. Amendments to the Claims

By this amendment, claim 2, 4, 8, 22, 26, 28, 33, 35-37, 39-44, 47, 49, 56, 60, 61, 64-68, 73, and 74 are canceled, and new claims 75-106 are added. The new claims are supported by the specification and do not add new matter. Support for the new claims is detailed in the table below.

New Claim	Support
75	Originally filed claims and specification, including Claim 35, published paragraphs [0026], [0040], [0041], [0048], [0179], [0180], [0187], [0411], [0413], and [0433]
76	Originally filed claims and specification, including claim 39
77	Originally filed claims and specification, including claim 40
78	Originally filed claims and specification, including claim 37
79	Originally filed claims and specification, including claim 41
80	Originally filed claims and specification, including claim 42
81	Originally filed claims and specification, including claim 43
82	Originally filed claims and specification, including claim 44
83	Originally filed claims and specification, including claim 36, published paragraph [0192]
84	Originally filed claims and specification, including claim 36, published paragraph [0192]
85	Originally filed claims and specification, including published paragraph [0038]
86	Originally filed claims and specification, including claim 65, published paragraph [0152]
87	Originally filed claims and specification, including claim 35, published paragraph [0270]
88	Originally filed claims and specification, including claim 33, published

	paragraph [0271]
89	Originally filed claims and specification, including claim 46
90	Originally filed claims and specification, including claims 4, 5
91	Originally filed claims and specification, including claim 8
92	Originally filed claims and specification, including claim 26
93	Originally filed claims and specification, including claim 3
94	Originally filed claims and specification, including claims 9, 10
95	Originally filed claims and specification, including claims 9, 10
96	Originally filed claims and specification, including claims 56, 57
97	Originally filed claims and specification, including claims 56, 57
98	Originally filed claims and specification, including claim 53, published paragraph [0212]
99	Originally filed claims and specification, including claim 59
100	Originally filed claims and specification, including claim 59
101	Originally filed claims and specification, including claim 64
102	Originally filed claims and specification, including claim 66
103	Originally filed claims and specification, including claims 48, 49
104	Originally filed claims and specification, including claim 67
105	Originally filed claims and specification, including claim 68
106	Originally filed claims and specification, including claims 35, 69, published paragraphs [0038]-[0040], [0048], [0154], [0177], [0179], [0187], [0208], [0211]-[0213], [0284], [0404], [0409], [0460], [0464], [0468], [0473], [0478], and [0485]

III. Claim Objections and Rejections

Claims 47 and 49 were objected to for depending from a cancelled claim. Claims 2, 4, 8, 22, 26, 28, 56, 64, 65, 67, 68, 73, and 74 were rejected under U.S.C. § 103(a) as being unpatentable over Conte et al. (US 5,594,030; hereinafter "Conte"). Claims 2, 4, 8, 22, 26, 28, 33, 35-41, 44, 47, 49, 56, 60, 61, 64-68, 73 and 74 were rejected under U.S.C. § 103(a) as being unpatentable over Liang et al. (US 2006/0210630; hereinafter "Liang"). Claims 42-43 were rejected under U.S.C. § 103(a) as being unpatentable over Liang in view of Allphin et al. (US 2012/0076865; hereinafter "Allphin").

The cancellation of claims 2, 4, 8, 22, 26, 28, 33, 35-37, 39-44, 47, 49, 56, 60, 61, 64-68, 73, and 74 renders moot their objections and rejections.

IV. New Claims 75-105 Are Not Rendered Obvious by the Cited Art

New claim 75 is directed to a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the modified release portion comprises particles of gamma-hydroxybutyrate coated with a coating comprising (i) a polymer carrying free carboxylic groups, and (ii) a hydrophobic compound having a melting point equal or greater than 40°C, wherein the modified release formulation of gamma-hydroxybutyrate comprises gamma-hydroxybutryate in a unit dose suitable for administration only once nightly. New claim 106 is directed to modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the modified release portion comprises particles of gamma-hydroxybutyrate coated with a coating comprising (i) a polymer carrying free carboxylic groups, and (ii) a hydrophobic compound having a melting point equal or greater than 40°C, wherein the gamma-hydroxybutryate is present in a unit dose of 4.5 grams or more.

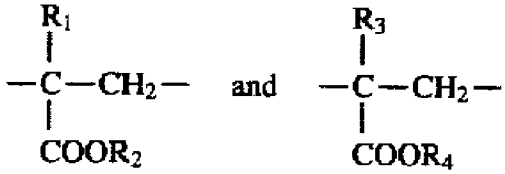
For claimed subject matter to be *prima facie* obvious under 35 U.S.C. § 103 in view of prior art, the prior art references must individually disclose or suggest all of the elements of the claim. Furthermore, there must be a reason for combining the elements in the manner claimed with a reasonable expectation of success.[1]

(a) Conte

New independent claims 75 and 106 incorporate limitations from previous claim 35, which was not rejected as being obvious is view of Conte. Applicant notes that Conte does ***not*** disclose or suggest a gamma-hydroxybutyrate composition that is coated with a polymer bearing free carboxylic groups and a hydrophobic compound.

[1] M.P.E.P. §§ 2143-2143.03 and *KSR* 550, U.S. at 417-18; M.P.E.P. § 2143.02(I) and (III) (citing *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986) and *Ex parte Erlich*, 3, USPQ2d 1011, 1016 (Bd. Pat. App. & Inter. 1986)).

Rather, Conte discloses gamma-hydroxybutyrate compositions covered by a film coating comprising copolymers having the following repeating units:



wherein R_1 is H or methyl, R_2 is methyl or ethyl, R_3 is methyl, and R_4 is $-CH_2CH_2N^{(+)}(CH_3)_3Cl^{(-)}$. Thus, the coating of Conte's compositions comprises copolymers that do not carry free carboxylic groups, and the coating does not contain a hydrophobic compound, as required in claims 75 and 106. Moreover, Conte provides no suggestion or rationale that would lead a person of ordinary skill in the art to modify the film coatings disclosed therein and include a polymer having free carboxylic groups and a hydrophobic compound.

Furthermore, Conte does ***not*** disclose or suggest a gamma-hydroxybutyrate composition in a unit dose suitable for administration only once nightly (as required by claim 75) or in a unit dose of 4.5 grams or more (as required by independent claim 106). By contrast, the largest tablet Conte prepared contained only 1 g of gamma-hydroxybutyrate.[2] Importantly, ***Conte could not have increased the dosage*** because the purpose of the invention was to relieve addictive cravings while awake. Increasing the dosage and thereby putting the patient to sleep would have been contrary to the intended purpose of Conte – *i.e.*, to relieve addictive cravings while the patient is awake. Consequently, the patients in Conte could not take too much gamma-hydroxybutyrate due to the purpose of the invention.

In fact, Conte teaches away from the claimed invention. As noted above, Conte developed his formulations for purposes entirely different than the present invention. Conte formulated gamma-hydroxybutyrate ***to relieve addictive cravings while the patient is awake***. By definition, the patient could not take too much gamma-hydroxybutyrate because he or she needed to stay awake. The largest tablet Conte

[2] Conte, see tables in column 6.

prepared contained only 1 g of gamma-hydroxybutyrate.[3] Conte also had no reason to be concerned with how much gamma-hydroxybutyrate remained in the patient's system at the end of the day because the patient would be going to sleep anyhow. **As such, there is no disclosure or suggestion in Conte for gamma-hydroxybutryate in a unit dose suitable for administration only once nightly (as required by independent claim 75), or in a unit dose of 4.5 grams or more (as required by independent claim 106).** According to the M.P.E.P., "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." M.P.E.P. 2143.01.V. Thus, as governed by the M.P.E.P., there is no suggestion or motivation to combine with Conte to arrive at the currently claimed invention.

By requiring multiple doses (2 or more) during the day, and at substantially lower dosages to alleviate addiction symptoms in an awake state, Conte clearly teaches away from the currently claimed invention.

> "In view of the foregoing, the active ingredient has to be administered many times day, in particular, at least 4 times in order to assure a desirable pharmacological effect in patients showing a marked craving who need a continuous and constant therapy, especially in the first period of the treatment."[4]

> "[S]aid compositions being suitable in particular for the treatment of alcoholism, opium like substances addiction, heroin addiction, food and nicotine addiction, as well as in the treatment of depressive and anxious states."[5]

In stark contrast to Conte, the inventors of the claimed invention formulated gamma-hydroxybutyrate to induce sleep, and to induce sleep for a continuous period of 8 hours from a single dose (*i.e.*, in a unit dose suitable for administration only once nightly). The gamma-hydroxybutyrate is administered at night immediately before the patient goes to sleep and is able to reduce the symptoms of narcolepsy during the day. The formulation has two important features that make it extremely valuable for this use

[3] *Id.*
[4] *Id.*, column 2, lines 64-67 and column 3, lines 1-2.
[5] *Id.*, column 1, lines 14-17.

– high bioavailability and low C_{8h}. The bioavailability (AUC^{6}) of a 7.5 g dose exceeds 340 hr•microgram/mL ("hr•mcg/mL"), which is more than 80% of the bioavailability achieved by an equal dose of immediate release gamma-hydroxybutyrate administered in divided doses. (See Table 18d of the instant specification, reporting a mean AUC_{inf} for 2 x 3.75 g doses of immediate release gamma-hydroxybutyrate as 432 hr•mcg/mL). The residual concentration of gamma-hydroxybutyrate remaining in the bloodstream after 8 hours of sleep (C_{8h}) of the claimed formulation is less than 130% of the C_{8h} achieved by an equal dose of immediate release gamma-hydroxybutyrate administered in divided doses.

Furthermore, current claim 104 requires that the claimed formulation be present in an amount "effective to treat narcolepsy Type 1 or Type 2" by "reducing excessive daytime sleepiness or reducing the frequency of cataplectic attacks." Similarly, current claim 105 requires that the claimed formulation be present in an amount "effective to induce sleep for eight consecutive hours." The formulation is capable of producing sleep for a full eight hours because of the large unit dose; the formulation is effective to treat narcolepsy because it is capable of producing eight hours of consecutive sleep.

In view of the above, it is respectfully submitted that new independent claims 75 and 106 are not rendered obvious by Conte. Claims 76-105, which depend from and incorporate all the limitations of claim 75, likewise are not obvious in view of Conte for the same reasons stated above with respect to claims 75 and 106.

(b) Liang

Liang fails to disclose or suggest each and every element of independent claims 75 and 106. Rather, Liang discloses gamma-hydroxybutyrate compositions comprising an immediate release component and a delayed/controlled release component, wherein the delayed/controlled release component comprises a pH sensitive enteric coating. The pH sensitive enteric coating comprises pH-sensitive polymers.[7] However, the enteric coating of the delayed/controlled release component of Liang is devoid of a

[6] When "AUC" is written herein, it will be understood to refer to AUC_{inf} or, when AUC_{inf} is not reported, AUC_{last}.
[7] Liang, paragraphs [0082], [0082], and the Examples.

hydrophobic compound, as required in independent claims 75 and 106. The Office states that Liang's compositions comprise hydrogenated vegetable oils.[8] However, said hydrophobic compound is present in the immediate release component of the immediate release core and **not** in the coating of the delayed/controlled release component. Liang states:

> "Examples of these pharmaceutically acceptable excipients in the immediate release component of the current invention include … hydrogenated vegetable oils …."[9]

> "Examples of these pharmaceutically acceptable excipients in the immediate release core of the current invention include … hydrogenated vegetable oils …."[10]

Thus, the gamma-hydroxybutyrate compositions disclosed in Liang comprise an the immediate release component comprising hydrogenated vegetable oils and a delayed/controlled release component comprising an immediate release core (comprising hydrogenated vegetable oils) that is coated with a enteric coating comprising pH-sensitive polymers. Stated another way, the coating of Liang's delayed/controlled release component does not contain hydrogenated vegetable oils or any other hydrophobic compound, as required in claims 75 and 106.

Furthermore, Liang teaches that the compositions disclosed therein provide "a convenient once nightly or once daily dose regiment for the oral delivery of one or more gamma-hydroxybutyric acid salts."[11] Thus, Liang provides no teaching or suggestion that would prompt a person of ordinary skill in the art to modify the coating of the delayed/controlled release component disclosed therein and arrive at the claimed formulation with a reasonable expectation of success.

In view of the above, Applicant respectfully submits that claims 75 and 106 are not rendered obvious by Liang. Claims 76-105, which depend from and incorporate all the limitations of claim 75, likewise are not obvious in view of Liang for the same reasons stated above with respect to claims 75 and 106.

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[8] Office action, dated May 3, 2018, page 9.
[9] Liang, paragraph [0055], emphasis added.
[10] *Id.*, paragraph [0061], emphasis added.
[11] *Id.*, [0012].

(c) Liang and Allphin

The teachings of Liang are discussed above. Allphin discloses gamma-hydroxybutyrate dosage forms comprising an immediate release component and a controlled release (CR) component, wherein the core of CR component (*i.e.*, CR core) comprises hydrogenated castor oil, hydrogenated vegetable oil.[12] The Office states that it would have been obvious for one of ordinary skill in the art to use the hydrogenated castor oil of Allphin in place of the hydrogenated vegetable oil of Liang.[13] However, replacing Liang's hydrogenated vegetable oil with Allphin's hydrogenated castor oil will produce to a delayed/controlled release formulation comprising a core comprising hydrogenated castor oil, wherein the core is coated with an enteric coating comprising pH sensitive polymers. Such a formulation, however, differs structurally from the claimed formulation, which requires a coating comprising both a polymer carrying free carboxylic groups and a hydrophobic compound.

In light of the forgoing, it is respectfully submitted the pending claims are not made obvious by Liang and Allphin.

V. The Claimed Formulations Produce Unexpected Results

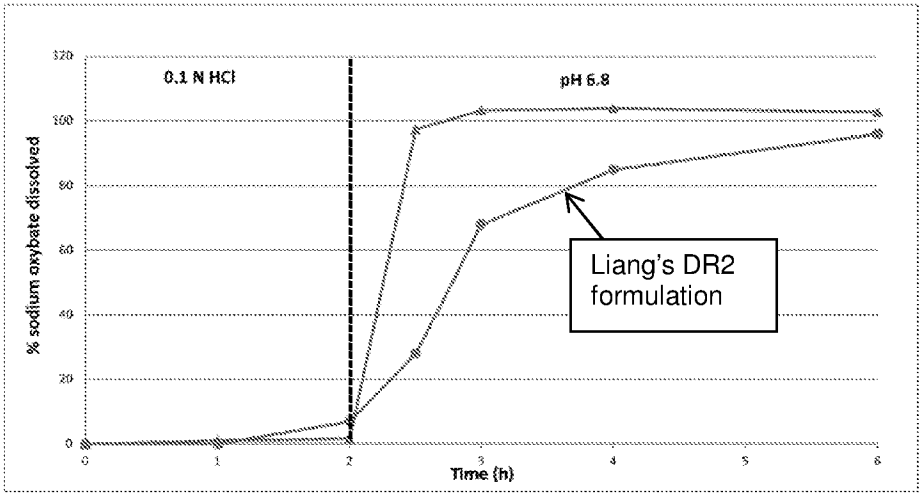
The claimed modified release formulations of gamma-hydroxybutyrate differ structurally and functionally from those of the prior art. In particular, the claimed formulations have increased bioavailability as compared to the previous modified release formulations of gamma-hydroxybutyrate. According to M.P.E.P. 715.12(a), unexpected results or superior properties are evidence of nonobviousness.

As detailed in the 37 C.F.R. § 1.132 Declaration of Hervé Guillard, Ph.D., submitted herewith (hereinafter, "the Declaration"), the inventors overcame the deficiencies of the prior art by utilizing two different release mechanisms in the coating of the modified release component of the formulation. The modified release component has a "time-dependent" release that is triggered after a specific period of time in the

[12] Allphin, paragraph [0045].
[13] Office action dated May 3, 2018, page 12.

stomach, and a "pH-dependent" release that is triggered by the increase in pH upon entry into the intestine. As explained in the Declaration:

> "As a consequence of this dual release triggering mechanism, it is my belief that release of gamma-hydroxybutyrate from our modified release particles is more rapid and more extensive after the pH increase than that achieved by previous modified release formulations of gamma-hydroxybutyrate, resulting in increased bioavailability. The different release profiles of our modified release particles (▲) and the DR2 formulation of Liang (●) are presented below (*i.e.*, Figure 4 of the pending application)."



> "Thus, a significant amount of the gamma-hydroxybutyrate was released from our modified release particles within the first hour at the elevated pH, whereas significantly less of the gamma-hydroxybutyrate was released from Liang's DR2 formulation after several hours hour at the elevated pH."[14]

The improved dissolution profile of the claimed formulation results in an increased bioavailability (AUC) of gamma-hydroxybutyrate relative to that achieved by previous modified release formulations of gamma-hydroxybutyrate. As shown in Table 18c of the pending application, a 4.5 g dose of the claimed modified release formulation provides a relative bioavailability of about 89% as compared to 2 x 2.25 g doses of the reference immediate release formulation. Dr. Guillard explains in his declaration:

[14] 37 C.F.R. § 1.132 Declaration of Hervé Guillard, Ph.D., paragraph 14.

> "In contrast, Allphin reported two different treatments that included modified release and immediate release components of gamma-hydroxybutyrate (Treatments D and E), compared to Treatment A that only included an immediate release dose administered in divided doses. Two 3 g doses of Treatment A achieved an AUC_{inf} of 285.79 hr•mcg/mL; 4 g of Treatment D achieved an AUC_{inf} of 62.55 hr•mcg/mL (equivalent to 93.82 hr•mcg/mL for a 6g dose); and 8 g of Treatment E achieved an AUC_{inf} of 218.12 hr•mcg/mL (equivalent to 163.59 hr•mcg/mL for a 6g dose) (see Allphin's Table 6). On a dose adjusted basis, Treatments D and E achieved a relative bioavailability compared to Treatment A of only 32.8% and 57.2%. Consequently, Allphin's formulations are substantially inferior to our claimed formulations. Furthermore, as Allphin shows in Figures 12 and 14, his formulations suffered from an excess of residual gamma-hydroxybutyrate in the bloodstream at 8 hours (i.e., C_{8hr})."[15]

> "Furthermore, Liang's delayed release formulations also suffered from low bioavailability (see, Table 3 in Liang). Regarding $C_{8hr,}$ Liang teaches that absorption of gamma-hydroxybutyrate decreases along the gastrointestinal tract (paragraph [0010]). However, Liang showed that replacing Eudragit L100-55 in the coating for the formulation targeting the duodenum (DR2 formulation) by Eudragit FS30D (DR1 formulation) resulted in a slight increase in the duration of absorption but a significant decrease of AUC (*see* Figure 7). As a consequence, it could not be predicted that relative bioavailability and C_{8hr} targets could be both achieved in a modified release formulation of gamma-hydroxybutyrate."[16]

Thus, the claimed formulation achieves superior bioavailability and low residual plasm concentrations as compared to the modified release formulations of the prior art. As stated in the Declaration:

> "The improved dissolution and pharmacokinetic profiles of our modified release formulation of gamma-hydroxybutyrate were surprising and unexpected considering the less than optimal performances (*i.e.*, reduced bioavailability and suboptimal residual plasma concentrations) of previous modified release formulations of gamma-hydroxybutyrate. Our findings were also surprising because there is no teaching or suggestion in the prior art that time-dependent release with a predetermined lag time in combination with pH-dependent release could improve the dissolution, bioavailability, and pharmacokinetics of gamma-hydroxybutyrate so effectively."[17]

[15] *Id.*, paragraph 16.
[16] *Id.*, paragraph 17.
[17] *Id.*, paragraph 18.

In summary, the claimed formulations differ structurally from those of the prior art, and the claimed formulation have unexpected and superior functional properties over the prior art formulations. The Applicant, therefore, respectfully submits that pending claims 75-106 are patentable, and requests allowance of the pending claims.

VI. Conclusion

In view of the foregoing, the Applicant respectfully requests entry of the claim amendments and new claims, withdrawal of the claim objections and rejections, and solicits an allowance of all the pending claims. The Examiner is invited to contact the undersigned practitioner should any issues remain unresolved.

Respectfully submitted,

POLSINELLI PC

Date: September 04, 2018

/J. Morgan Kirley/

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Attorney for Applicant

Atty. Docket No. 092677-602918

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Flamel Ireland Limited		
Inventor(s):	Claire Mégret et al.	Art Unit:	1615
Serial No:	15/655,924	Examiner:	Aradhana Sasan
Filed:	July 21, 2017	Conf. No.:	5196
For:	MODIFIED RELEASE GAMMA- HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS		

DECLARATION UNDER 37 C.F.R. § 1.132 OF HERVÉ GUILLARD. PH.D.

I, Hervé Guillard, Ph.D., declare and state as follows:

1. I am a co-inventor of the subject matter of the above captioned application (Serial No. 15/655,924; hereinafter the "Application").

2. My current position is Pharmaceutical Technology Team Leader at Flamel Technologies in Vénissieux, Rhône, France. I have held this position since 2017 and, prior to that, I was a Research and Development Engineer for 9 years and a Development Engineer for 4 years at Flamel Technologies. My previous employment experience includes 6 years as a Research and Development Engineer at Polymage, and one year as a Research Engineer at Commissariat à l'Energie Atomique.

3. My educational background includes a degree in Chemical Engineering from the National College of Chemical Engineering of Clermont-Ferrand in 1996, a Ph.D. degree in Physical Chemistry from Aix-Marseille University in 2001, and a six month traineeship at Sollac, Montataire, Oise, France. A copy of my résumé is attached to this Declaration.

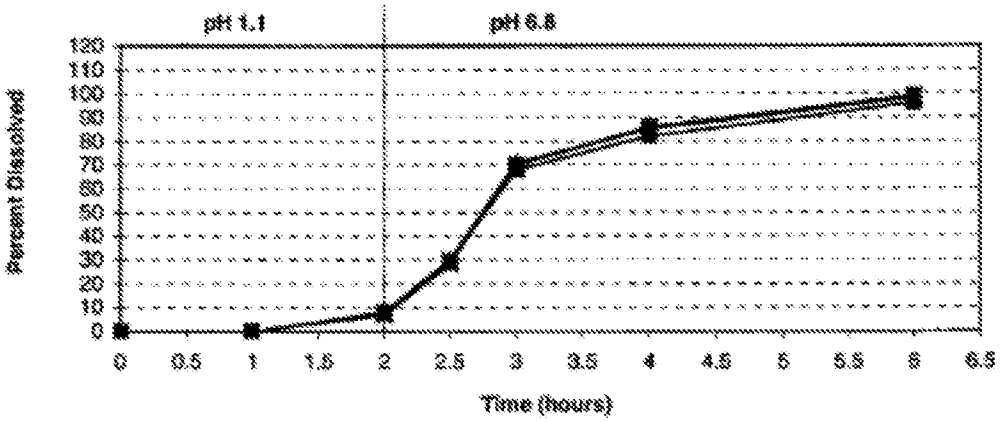
4. I have read and understand the Application and the pending claims of the Application. Claim 75 is directed to modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the modified release portion comprises particles of gamma-hydroxybutyrate coated with a coating comprising (i) a polymer carrying free carboxylic groups, and (ii) a hydrophobic compound having a melting point equal or greater than 40°C, wherein the modified release formulation of gamma-hydroxybutyrate comprises gamma-hydroxybutryate in a unit dose suitable for administration only once nightly. Claim 106 is directed to modified release

formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the modified release portion comprises particles of gamma-hydroxybutyrate coated with a coating comprising (i) a polymer carrying free carboxylic groups, and (ii) a hydrophobic compound having a melting point equal or greater than 40°C, wherein the gamma-hydroxybutryate is present in a unit dose of 4.5 grams or more.

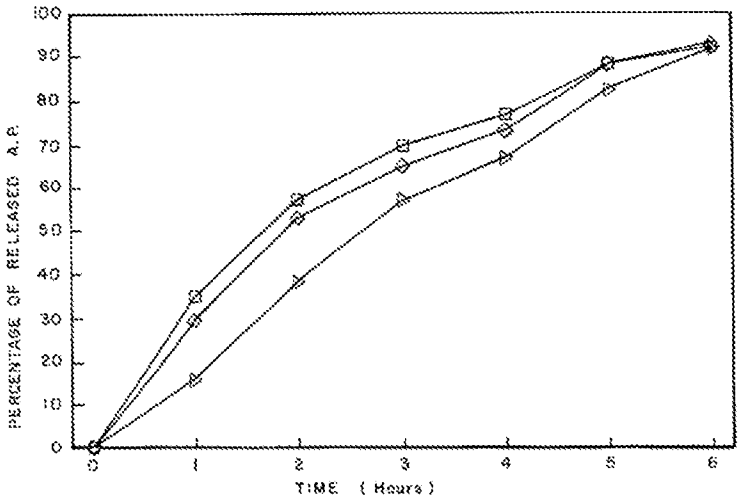
5. I also have read and understand the contents of the Office Action dated May 3, 2018 and the references cited within (*i.e.*, U.S. Pat. No. 5,594,030 to Conte; U.S. Publication 2006/0210630 to Liang; and U.S. Publication 2012/0076865 to Allphin). It is my understanding that Conte is directed to a completely different problem, namely, treatment of addiction symptoms during the daytime. Further, it is my understanding that Conte uses a substantially lower dosage that the present invention. Finally, it is my understanding that the modified release formulation of gamma-hydroxybutyrate of the currently claimed invention would be unsuitable for the intended purpose of Conte because, in short, it would knock them out (*i.e.*, induce sleep) during the daytime instead of merely alleviating their addiction symptoms.

6. My co-inventors and I developed a once-nightly modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release components, wherein the formulation provides comparable bioavailability as an equal dose of an immediate release formulation of gamma-hydroxybutyrate administered twice nightly and the formulation has low plasma concentrations at 8 hours (*i.e.*, C_{8hr}). Developing a modified release formulation of gamma-hydroxybutyrate with these properties was challenging because previous modified release formulations of gamma-hydroxybutyrate have reduced bioavailability as compared to immediate release formulations. Moreover, replacing two doses of an immediate release formulation with one dose of a modified release formulation requires developing a dosage form with high levels of gamma-hydroxybutyrate that is acceptable to and can be readily administered to patients.

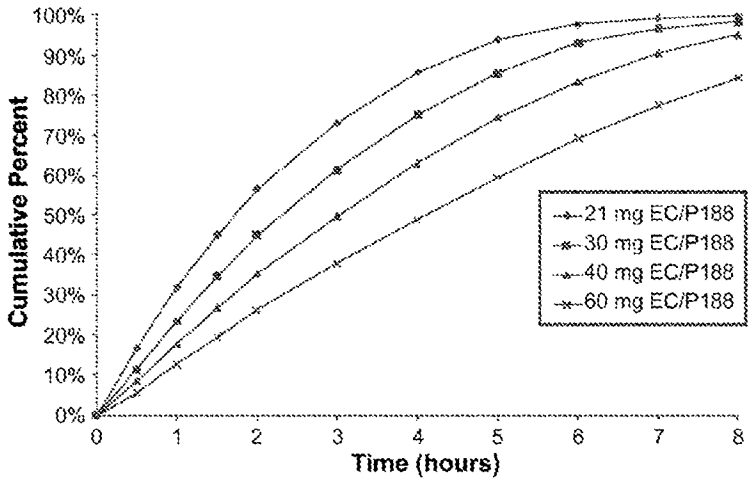
7. Previous modified release formulations of gamma-hydroxybutyrate relied on several different mechanisms for modifying release. One approach was to utilize pH-dependent release mechanisms. For example, Liang encapsulated particles of gamma-hydroxybutyrate in a pH sensitive enteric coating. Enteric coatings are resistant to the acidic conditions of the stomach and only dissolve under the higher pH conditions of the intestine. The delayed/controlled release particles of Liang, however, exhibited a slow release of gamma-hydroxybutyrate after the shift to a higher pH level. In particular, less than about 80% of the gamma-hydroxybutyrate was released from Liang's DR2 formulation within one hour after the pH shift, as shown in Figure 3 of Liang, reproduced below.



8. Another approach for preparing modified release formulations of gamma-hydroxybutyrate was to utilize film coatings that slow or retard release over time. For example, Conte coated gamma-hydroxybutyrate cores with a film coating comprising alkyl(meth)acrylate and ammonio methacrylate copolymers. Figure 3 of Conte, reproduced below, shows the release of gamma-hydroxybutyrate in HCl as a function of the percentage of film coating (□ 3.7%; ◇ 4.9%; △ 8.2%). The release of gamma-hydroxybutyrate release was reduced at higher film coating percentages.

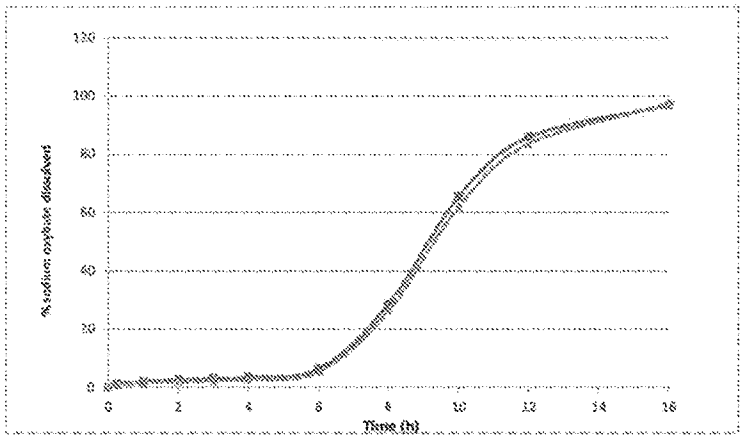


9. Similarly, the controlled release component of the modified release gamma-hydroxybutyrate formulation of Allphin comprises a functional coating that reduces release over time. The release of gamma-hydroxybutyrate in water from coatings comprising different amounts of ethylcellulose (EC) is shown in Figure 3 of Allphin, which is reproduced below. As with the coating of Conte, release of gamma-hydroxybutyrate is reduced as the percentage of ethylcellulose in the coating increased.



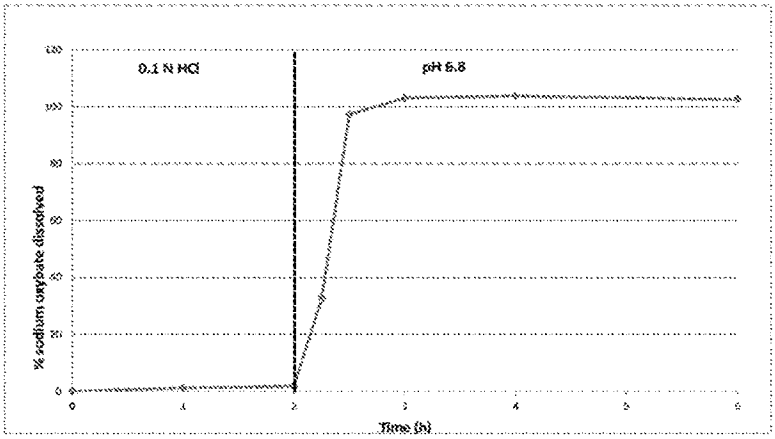
It should be noted that the functional coatings of both Conte and Allphin exhibited slow, steady release of gamma-hydroxybutyrate from the onset (*i.e.*, there is no lag period).

10. My co-inventors and I solved the problem of reduced bioavailability of modified release formulations gamma-hydroxybutyrate by utilizing a pH-dependent release mechanism and a time-dependent release mechanism that has a predetermined time lag. We prepared modified release particles by coating particles of gamma-hydroxybutyrate with a coating comprising pH-dependent polymer(s) and hydrophobic compound(s). Release of gamma-hydroxybutyrate from our modified release particles in 0.1N HCL is shown below (*i.e.*, Figure 9 of the Application).



Thus, gamma-hydroxybutyrate is released from our modified release particles after a period of time <u>even at acidic pH levels</u>.

11. The pH-dependent release of our modified release particles is shown below (*i.e.*, Figure 3 of the Application).

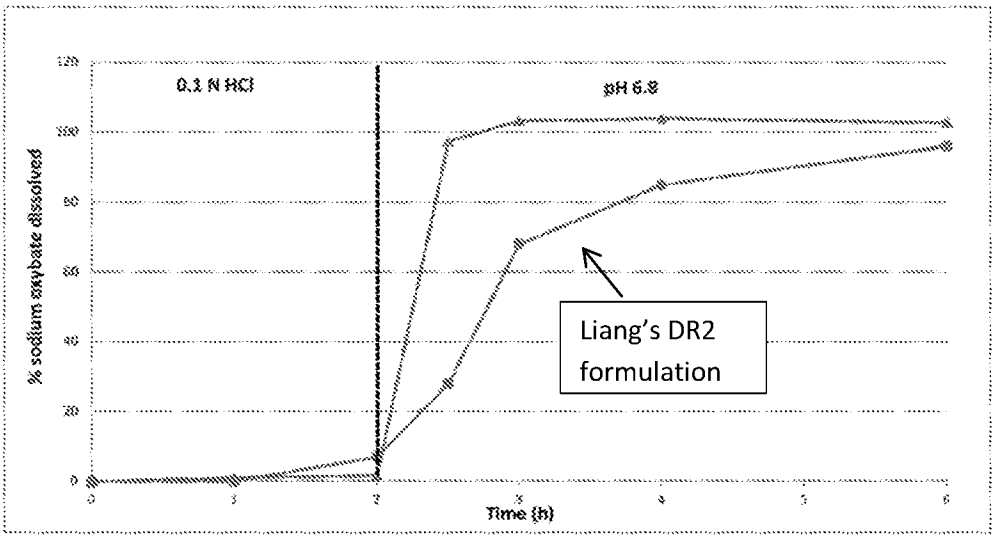


A significant amount of the gamma-hydroxybutyrate was released within one hour after the shift to the higher pH level (also, *see*, Figure 17 of the pending application).

12. Thus, our modified release particles have a "time-dependent" release that is triggered after a specific period of time in the stomach, and a "pH-dependent" release that is triggered by the increase in pH upon entry into the intestine.

13. My co-inventors and I discovered that utilizing both a time-dependent release that is triggered after a lag period and a pH-dependent release that is triggered by the higher pH of the intestine ensures a high degree of control and reliability. In particular, release of gamma-hydroxybutyrate is guaranteed after a preset latency period, even if the variation in pH does not intervene as a trigger, *i.e.*, even if the formulation does not pass from the stomach to the intestine.

14. As a consequence of this dual release triggering mechanism, it is my belief that release of gamma-hydroxybutyrate from our modified release particles is more rapid and more extensive after the pH increase than that achieved by previous modified release formulations of gamma-hydroxybutyrate, resulting in increased bioavailability. The different release profiles of our modified release particles (▲) and the DR2 formulation of Liang (●) are presented below (*i.e.*, Figure 4 of the Application).



Thus, a significant amount of the gamma-hydroxybutyrate was released from our modified release particles within the first hour at the elevated pH, whereas significantly less of the gamma-hydroxybutyrate was released from Liang's DR2 formulation after several hours hour at the elevated pH.

15. The improved release profile of our modified release particles results in an increased bioavailability of gamma-hydroxybutyrate relative to that achieved by previous modified release formulations of gamma-hydroxybutyrate. As shown in Table 18c of the Application, a 4.5 g dose of our modified release formulation provides a relative bioavailability of about 89% as compared to 2 x 2.25 g doses of the reference immediate release formulation.

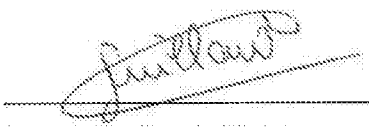
16. In contrast, Allphin reported two different treatments that included modified release and immediate release components of gamma-hydroxybutyrate (Treatments D and E), compared to Treatment A that only included an immediate release dose administered in divided doses. Two 3 g doses of Treatment A achieved an AUC_{inf} of 285.79 hr•mcg/mL; 4 g of Treatment D achieved an AUC_{inf} of 62.55 hr•mcg/mL (equivalent to 93.82 hr•mcg/mL for a 6g dose); and 8 g of Treatment E achieved an AUC_{inf} of 218.12 hr•mcg/mL (equivalent to 163.59 hr•mcg/mL for a 6g dose) (*see* Allphin's Table 6). On a dose adjusted basis, Treatments D and E achieved a relative bioavailability compared to Treatment A of only 32.8% and 57.2%. Consequently, Allphin's formulations are substantially inferior to our claimed formulations. Furthermore, as Allphin shows in Figures 12 and 14, his formulations suffered from an excess of residual gamma-hydroxybutyrate in the bloodstream at 8 hours (*i.e.*, C_{8hr}).

17. Furthermore, Liang's delayed release formulations also suffered from low bioavailability (see, Table 3 in Liang). Regarding $C_{8hr,}$ Liang teaches that absorption of gamma-hydroxybutyrate decreases along the gastrointestinal tract (paragraph [0010]). However, Liang showed that replacing Eudragit L100-55 in

the coating for the formulation targeting the duodenum (DR2 formulation) by Eudragit FS30D (DR1 formulation) resulted in a slight increase in the duration of absorption but a significant decrease of AUC (*see* Figure 7). As a consequence, it could not be predicted that relative bioavailability and C_{6hr} targets could be both achieved in a modified release formulation of gamma-hydroxybutyrate.

18. The improved dissolution and pharmacokinetic profiles of our modified release formulation of gamma-hydroxybutyrate were surprising and unexpected considering the less than optimal performances (*i.e.*, reduced bioavailability and suboptimal residual plasma concentrations) of previous modified release formulations of gamma-hydroxybutyrate. Our findings were also surprising because there is no teaching or suggestion in the prior art that time-dependent release with a predetermined lag time in combination with pH-dependent release could improve the dissolution, bioavailability, and pharmacokinetics of gamma-hydroxybutyrate so effectively.

19. I further declare that all statements made herein are of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Hervé Guillard, Ph.D.

September 3rd, 2019

Date

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CHEMICAL ENGINEER/PhD
PHARMACEUTICAL DEVELOPMENT:
FORMULATION – INDUSTRIAL TRANSFER
14 YEARS EXPERIENCE

WORK EXPERIENCES AND ACHIEVEMENTS

2017 to date (20 months): **Flamel Technologies (now Avadel Pharmaceuticals since 2017)** (Vénissieux – Rhône / France)

Pharmaceutical Technology Team Leader

- Development of innovative pharmaceutical formulations for the oral route (microparticles, tablets, capsules, sachets/stick-packs and suspensions)
- Monitoring of CMOs development activities
- Identification/evaluation of new technologies/manufacturing processes for the controlled release of active substances
- Responsibility/training of a team of 1-3 engineers and 4-9 technicians

2004 (1 year) then 2009-2016 (9 years): **Flamel Technologies** (Vénissieux – Rhône / France)

Research and Development Engineer (9 years)

- Development of innovative pharmaceutical formulations and achievement of feasibility studies for industrial partners in the field of:
  - the modified release of drugs for oral route (development of microparticles, tablets, capsules, sachets/stick-packs and suspensions)
  - the improvement of the oral bioavailability of poorly soluble drugs
  - the development of injectable sustained release formulations by subcutaneous route by using self-associative polymers as carriers for drugs
  - the development of anti-abuse formulations of opioids

  ⇒ Manufacturing of preclinical batches and GMP Phase 1 clinical batches
  ⇒ Several patents (granted or under examination)
  ⇒ One project now in Phase III clinical study
- Monitoring of CMOs development activities, support to scale-up activities and clinical/GMP batches manufacturing (up to registration batches)
- Writing of the CMC section of regulatory dossiers: IMPD-IND (from Phase I to Phase III studies) and NDA
- State of the art (literature, patents) and evaluation of the Freedom To Operate (FTO)/patentability of the formulations under development
- Responsibility/training of a team of 3-5 technicians

2005-2008 (4 years): **Flamel Technologies** (Pessac – Gironde / France)

Development Engineer

- Launching of a production unit for the manufacturing of 'Coreg CR' (modified-release formulation of beta-blocking agent Carvedilol) for GlaxoSmithKline/GSK:
  - Qualification of the production equipment
  - Adaptation of the manufacturing process to the production equipment
  - Redaction of the master batch records
  - Supervision of technical batches and validation batches
  - Training of operators and production managers
  - Technical support to the production unit
- Development of dosage forms in partnership with pharmaceutical companies:
  - Scale-up of the manufacturing of controlled-release pellets in fluid bed coater (from lab scale batches -1kg to pilot scale-140kg)
  - Formulation of capsules and tablets comprising controlled-release pellets

- Manufacturing of GMP batches
- Responsibility/training of 12 operators and technicians

1998- 2004 (6 years): **Polymage**, société d'ingénierie (Nice - Alpes-Maritimes / France)

Research and Development Engineer

- Achievement of studies and development of products for customer companies in the field of "smart" materials :
  - Development of adaptive materials allowing to control daylight and solar energy using liquid crystals and polymer gels: monomer organic synthesis, formulation, electro-optical characterizations and elaboration of « smart windows » prototypes

1998- 2001: Doctorate (PhD) in partnership with the Laboratory of Macromolecular Chemistry from the University of Aix-Marseille I. Subject: 'Electroswitchable polymer-liquid crystal micro composite films'.

  - Studies of piezochromic and thermochromic materials: synthesis and characterizations.

⇒ one granted patent and one patent application / several publications

- Scientific responsibility of 2 european research programs co-financed by the European Union
- Training of an engineer

1996-1997 (1 year): **Commissariat à l'Energie Atomique** (Fontenay-aux-Roses **-** Hauts-de-Seine / France)

Research Engineer (military service)

- Corrosion studies of alloys during incineration and vitrification of nuclear radioactive waste (corrosion by hot temperature gases, molten glasses and molten salts)
- Achievement of expertises on damaged equipments
- Training of a technician and an engineer-trainee

⇒ Deeper understanding of the corrosion mechanisms occuring during waste treatment

1996 (6 mois): **Sollac** (**Arcelor-Mittal group**) **-** (Montataire – Oise / France)

Development Engineer (trainee)

- Study of the adhesion mechanisms involved during sticking of lubricated galvanized steels, analysis of the corrosion resistance and stamping ability provided by dry lubricants

⇒ Development of lubricants for the automotive industry

EDUCATION

1998-2001 Aix-Marseille University: **PhD degree in physical chemistry**

1993-1996 National College of Chemical Engineering of Clermont-Ferrand**:** degree of **Chemical Engineer**, major in **Materials**

Clermont-Ferrand University: **Diplôme d'Etudes Approfondies** (post graduate diploma taken before completing a PhD), major in **materials**

LANGUAGES

French: native language
English: fluent
Spanish: notions

COMPUTER SKILLS

use of Word, Excel, Sigma Plot, Paint Shop Pro, PowerPoint, Origin, MS project

SPARE TIME ACTIVITIES

Reading (favourite writers E. Zola, L. Tolstoï, E. Wharton), cinema, cross-country skiing.

EXHIBIT C

REMARKS

I. Status of the Claims and Amendments to the Claims

Upon entry of this amendment, claims 1-24 are pending. Claims 1-13 are amended. Claims 14-24 are new. The amendments do not add any new matter and are supported by the originally filed specification and claims. Support for the amendment "in a human subject" and "in need thereof" can be found in paragraph [0313] of the specification as filed. The term "bioequivalent" was added to claims 15-24 and is expressly supported by paragraph [0148] of the specification as filed and throughout the specification (e.g., [0151], [0350], [0371], [0521]). The term "once-nightly" was added to claims 1-24 and is expressly supported by paragraph [0019], [0351], and [0372] of the originally filed specification, and the originally filed claims. Additional support for claims 14-24 can be found in originally filed claims 1-13.

II. Claim Objections

Claims 9 and 10 are objected to under MPEP 608.1(m) for lack of punctuation at the end of the claims. The issue has been corrected in the currently amended claims.

III. Claim Rejections – 35 USC § 112

Claims 1-8 and 13 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Specifically, claims 1-8 and 13 recite the limitation "substantially as depicted in Figure …" (emphasis added). The term "substantially" in claims 1-8 and 13 is a relative term which renders the claim indefinite.

In an effort to expedite prosecution, the term "substantially" has been removed from the currently amended claims 1-13. The rejection under §112 is rendered moot.

In the interest of further clarity, the term "bioequivalent" has been added to claims 15-24 and is expressly supported by paragraph [0148] of the specification as filed and throughout the specification (e.g., [0151], [0350], [0371], [0521]). The term "bioequivalent," as defined in the specification, is well understood and established in the

pharmaceutical industry, and is further concretely supported by FDA's March 2003 Guidance for Industry on BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS – GENERAL CONSIDERATIONS, which is also expressly referenced in the specification.

IV. 35 U.S.C. § 103 Rejection

Claims 1-13 are rejected under 35 U.S.C. 103 as being unpatentable over Liang et al. (US 2006/0210630 A1). Per the Office Action, "Liang et al. disclose controlled release compositions of gamma-hydroxybutyrate containing an immediate release component of gamma-hydroxybutyric acid, and one or more delayed/controlled release components of gamma-hydroxybutyric acid (Abstract, Examples 1-8 and claims 1-53). A daily dose of 4.5 to 9 g of sodium gamma-hydroxybutyrate or Xyrem® is disclosed ([0005]). Example 8 discloses a canine PK study including the mean GHB (sodium gamma-hydroxybutyrate or sodium oxybate – [0002]) concentrations (µg/mL) at different time points, as well as the Tmax, Cmax, AUC last and Rel BA (Relative Bioavailability) ([0114] – [0115]). Liang et al. disclose that the immediate release component has the highest bioavailability, and an AUClast of 601.0 µg/mL (TABLE 3). "The results show that the lower in the GI, the lower the bioavailability (BA); i.e., absorption is higher at upper GI. The immediate release component has the highest BA, so GHB may be absorbed better in its acid form. The BAs for the delayed release components with or without an neutralizer in the barrier coat do not very much so the neutralizer helps the coating-in tum the gastro-stability but does not affect the BA" ([0115])." In addition, per the Office Action, "Regarding instant claims 1-13, the limitations of the 4.5 g, 6.0 g or 7.5 g dose (instant claim 1), the 4.5 g dose (instant claim 2), and 4.5 g, 7.5 g or 9.0 g dose (instant claim 13) of the formulation would have been obvious over the daily dose of 4.5 to 9 g of sodium gamma-hydroxybutyrate, as taught by Liang et al. ([0005]). The limitations of the plasma concentration versus time curve when administered once-nightly (instant claims 1-2 and 13) and the dissolution profile (claims 3-12) would have been obvious over the mean GHB concentrations (µg/mL) as disclosed in TABLE 3 and

FIG. 7; and the dissolution profiles as disclosed in FIGS. 1-6 and Example 7 by Liang et al., unless there is evidence of criticality or unexpected results."

A. The Prior Art Fails to Provide Teachings Required by Claimed Invention

As provided in the attached expert declaration of Dr. Jason Vaughn at ¶ 10, ¶ 11, and ¶ 12, submitted herewith, the cited prior art fails to provide the necessary teachings of the claimed invention.

10. Turning now to the cited reference, Liang, there are a number of failings that preclude a finding of obviousness. The first is that **nowhere in the Liang reference is the claimed invention administered to a human subject**. The data cited by the Office Action is canine/dog data, and dogs are not humans. Moreover, dog pharmacokinetic profiles are not an adequate teaching for a human pharmacokinetic profile, nor are they capable of providing a reasonable expectation of success for a specific pharmacokinetic profile in a different animal. Dissolution profiles do not cure this defect. This is a key problem because the current claims refer to in vivo pharmacokinetic data in a human subject, and this is nowhere taught by Liang.

11. Even if a scientist were to ignore the fact that the data in Liang is canine/dog data (instead of human), another problem is that the data in Liang does not remotely match the currently claimed profiles. By way of illustration, here is FIG. 7 of Liang in a side-by-side comparison with Figure 12, as recited in claim 1. **They don't match at all.** There is no meaningful correlation. This isn't evidence of obviousness. **This is evidence of non-obviousness.**

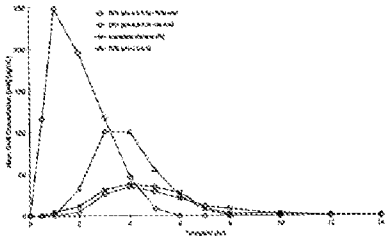

Figure 7

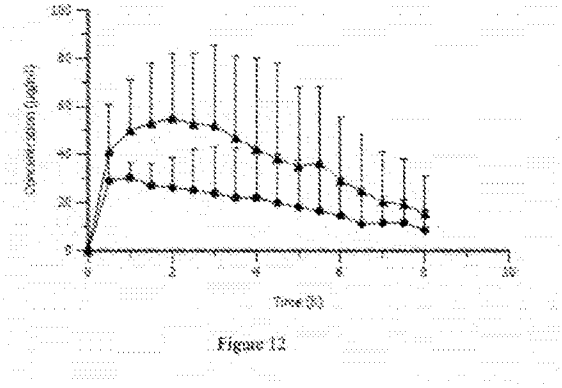

Figure 12

12. Upon close examination, it is clear that Example 8, TABLE 3, and FIG. 7 of Liang do not refer to the claimed composition, but only to immediate and delayed release formulations administered **separately**. Thus, taken

> as a whole, Liang provides no in vivo data whatsoever about the claimed composition, which requires both an immediate release and modified release portion. **Using Liang to guess the in vivo pharmacokinetic profile of the claimed invention would be pure speculation**. Pure speculation cannot provide a reasonable expectation of success—particularly in an unpredictable field—and therefore cannot be a basis for obviousness in the present circumstance.

In order to establish a *prima facie* case of obviousness, the prior art must teach or suggest all claim limitations. Here, the prior art fails to provide any teaching of the claimed pharmacokinetic profile in a human subject. These claimed features are nowhere present in the prior art. In view of the above, the obviousness rejection should be withdrawn.

B. High Level of Unpredictability in the Field

As provided in the attached expert declaration of Dr. Jason Vaughn at ¶ 9, there is a high level of unpredictability in the field.

> 9. Before discussing the prior art, it is highly important to note that the pharmaceutical arts are a highly unpredictable field. Moreover, the pharmacokinetic profile of gamma hydroxybutyrate is additionally unpredictable because of a significant food effect that tends to alter the pharmacokinetics. For example, as noted in the article entitled "The Influence of Gender and Food on the Pharmacokinetics of Sodium Oxybate Oral Solution in Healthy Subjects":[1]
>
> "Food **significantly altered** the bioavailability of oxybate by decreasing mean peak plasma concentration, increasing median time-to-peak concentration, and decreasing the area under the plasma concentration-time curve."
>
> Thus, the current claim limitation "approximately two hours after a standardized evening" is important because the prior art is unpredictable in this regard, and the current invention provides unexpected results by solving a problem previously unaddressed by the prior art.

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[1] *J Clin Pharmacol*. 2003 Jan;43(1):59-65. Available at: https://pubmed.ncbi.nlm.nih.gov/12520629/

The obviousness argument by the Patent Office does not provide a reasonable basis to override the **significant unpredictability** in the field and regarding pharmacokinetic profiles for gamma hydroxybutyrate in particular. Because the prior art lacks key teachings (as discussed above) and the field is also highly unpredictable, there is no reasonable expectation of success to support obviousness in the present case.

C. The Claimed Invention Provides Unexpected Results and Addresses Unmet Need

As provided in the attached expert declaration of Dr. Jason Vaughn at ¶ 13, the claimed invention provides unexpected results and addresses an unmet need.

> 13. The Office Action states at pg. 7 that the asserted obviousness may further be refuted if "there is evidence of criticality or unexpected results." In my expert opinion, the currently claimed invention is critical, unexpected, and meets a previously unmet need. Indeed, there has been great unpredictability in gamma hydroxybutyrate formulations in the prior art, and there has been a critical need to provide a formulation as currently claimed, which is nowhere found in the prior art.

Because the prior art fails to provide the necessary teachings, the field is highly unpredictable, and the claimed invention provides unexpected results, the Applicant respectfully requests the rejection under §103 be withdrawn.

V. Double Patenting

Claims 1-13 are provisionally rejected on the ground of nonstatutory double patenting as being allegedly unpatentable over claims 1-89 of U.S. Patent No. 10,272,062 B2 (the '062 Patent), over claims 1-52 of U.S. Patent No. 10,736,866 B2 (the '866 Patent), over claims 1-20 of copending Application No. 16/419,516 (the '516 Application), and over claims 1-10 of copending Application No. 16/431,219 (the '219 Application). The Applicant respectfully asserts that once the claims are found allowable, the Applicant will submit any necessary terminal disclaimer(s).

VI. Conclusion

In view of the foregoing, the Applicant respectfully requests entry of the claim amendments, withdrawal of the objections and rejections, and allowance of all the pending claims. The Examiner is invited to contact the undersigned practitioner should any issues remain unresolved.

Respectfully submitted,

POLSINELLI PC

Date: September 17, 2020 /J. Morgan Kirley/

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Chicago, IL 60606
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Attorney for Applicant

Atty. Docket No. 107884-626095

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Flamel Ireland Limited		
Inventor(s):	Claire Megret	Art Unit:	1615
Serial No.:	16/419,616	Examiner:	SASAN, ARADHANA
Filed:	May 22, 2019	Conf. No.:	4034
For:	MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS		

DECLARATION UNDER 37 C.F.R. § 1.132 OF JASON VAUGHN, PH.D.

I, Jason Vaughn, Ph.D., declare and state as follows:

1. I am currently the Senior Vice President of Technical Operations for Avadel Pharmaceuticals plc, which is the corporate parent of Flamel Ireland Limited, the Applicant for U.S. Serial No. 16/419,616 ("the '616 Patent Application"). Although I am not an inventor of the instant application, in my leadership role in Technical Operations, I am deeply familiar with the '616 Patent Application and the history underlying the development of the claimed invention. Among other factors, I am familiar with the numerous technical difficulties and obstacles overcome in arriving at the claimed invention.

2. Including my current role, my employment history includes over fifteen years of experience in formulation, process development, research, and operations for pharmaceuticals and life science companies. From 2005-2009, I was employed at PharmaForm LLC, ultimately rising to the level of Vice President of Operations. From 2009-2011, I was the Director of Formulation Development for DPT Laboratories. From 2011-2012, I was the Director of Research of Enavail. From 2012-2019, I was the Director and Vice President of Formulation and Process Development at Patheon Inc. Finally, from November 2019 to the present, I have been Senior Vice President of Technical Operations for Avadel Pharmaceuticals plc.

3. My educational background includes a Ph.D. in Pharmaceutics and a Bachelor of Sciences (B.S.) degree in Pharmacy, both from The University of Texas at Austin. During my doctoral studies, my Ph.D. dissertation was directed to the "Improved Bioavailability and Site Specific Delivery of Poorly Water Soluble Drugs through the Production of Stabilized Drug Nanoparticles."

4. Given my credentials, high level of education, and 15 years of formulations experience in the pharmaceutical industry, I am qualified and authorized to make this Declaration. In the context of the claimed invention of the '616 Patent Application, I am a person of skill in the art.

5. I have read and understand the '616 Patent Application and the pending claims of the '616 Patent Application. In its current iteration, claim 1 is directed to, "A once-nightly modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the once-nightly formulation yields a plasma concentration versus time curve when administered once-nightly in a human subject at a dose of 4.5g or 6.0g approximately two hours after a standardized evening meal as depicted in Figure 12 for the corresponding dose."

6. I also have read and understand the contents of the Non-Final Office Action dated August 19, 2020 and the references cited therein. In particular, I am familiar with Liang et al. (U.S. Publication 2006/0210630; hereinafter "Liang").

7. Based off of pg. 5 of the Non-Final Office Action, it is my understanding that the Patent Office interprets Liang as follows: "Liang et al. disclose controlled release compositions of gamma-hydroxybutyrate containing an immediate release component of gamma-hydroxybutyric acid, and one or more delayed/controlled release components of gamma-hydroxybutyric acid (Abstract, Examples 1-8 and claims 1-53). A daily dose of 4.5 to 9 g of sodium gamma-hydroxybutyrate or Xyrem® is disclosed ([0005]). Example 8 discloses a canine PK study including the mean GHB (sodium gamma-hydroxybutyrate or sodium oxybate – [0002]) concentrations (µg/mL) at different time points, as well as the Tmax, Cmax, AUC last and Rel BA (Relative Bioavailability) ([0114] – [0115]). Liang et al. disclose that the immediate release component has the highest bioavailability, and an AUClast of 601.0 µg/mL (TABLE 3). "The results show that the lower in the GI, the lower the bioavailability (BA); i.e., absorption is higher at upper GI. The immediate release component has the highest BA, so GHB may be absorbed better in its acid form. The BAs for the delayed release components with or without an neutralizer in the barrier coat do not very much so the neutralizer helps the coating-in tum the gastro-stability but does not affect the BA" ([0115])."

8. It is further my understanding from the Office Action at pg. 6-7 that the asserted obviousness includes the following: "The limitations of the plasma concentration versus time curve when administered once-nightly (instant claims 1-2 and 13) and the dissolution profile (claims 3-12) would have been obvious over the mean GHB concentrations (µg/mL) as disclosed in TABLE 3 and FIG. 7; and the dissolution profiles as disclosed in FIGS. 1-6 and Example 7 by Liang et al., unless there is evidence of criticality or unexpected results.").

9. Before discussing the prior art, it is highly important to note that the pharmaceutical arts are a highly unpredictable field. Moreover, the pharmacokinetic profile of gamma hydroxybutyrate is additionally unpredictable

because of a significant food effect that tends to alter the pharmacokinetics. For example, as noted in the article entitled "The Influence of Gender and Food on the Pharmacokinetics of Sodium Oxybate Oral Solution in Healthy Subjects":[1]

"Food **significantly altered** the bioavailability of oxybate by decreasing mean peak plasma concentration, increasing median time-to-peak concentration, and decreasing the area under the plasma concentration-time curve."

Thus, the current claim limitation "approximately two hours after a standardized evening" is important because the prior art is unpredictable in this regard, and the current invention provides unexpected results by solving a problem previously unaddressed by the prior art.

10. Turning now to the cited reference, Liang, there are a number of failings that preclude a finding of obviousness. The first is that **nowhere in the Liang reference is the claimed invention administered to a human subject**. The data cited by the Office Action is canine/dog data, and dogs are not humans. Moreover, dog pharmacokinetic profiles are not an adequate teaching for a human pharmacokinetic profile, nor are they capable of providing a reasonable expectation of success for a specific pharmacokinetic profile in a different animal. Dissolution profiles do not cure this defect. This is a key problem because the current claims refer to in vivo pharmacokinetic data in a human subject, and this is nowhere taught by Liang.

11. Even if a scientist were to ignore the fact that the data in Liang is canine/dog data (instead of human), another problem is that the data in Liang does not remotely match the currently claimed profiles. By way of illustration, here is FIG. 7 of Liang in a side-by-side comparison with Figure 12, as recited in claim 1. **They don't match at all.** There is no meaningful correlation. This isn't evidence of obviousness. **This is evidence of non-obviousness.**

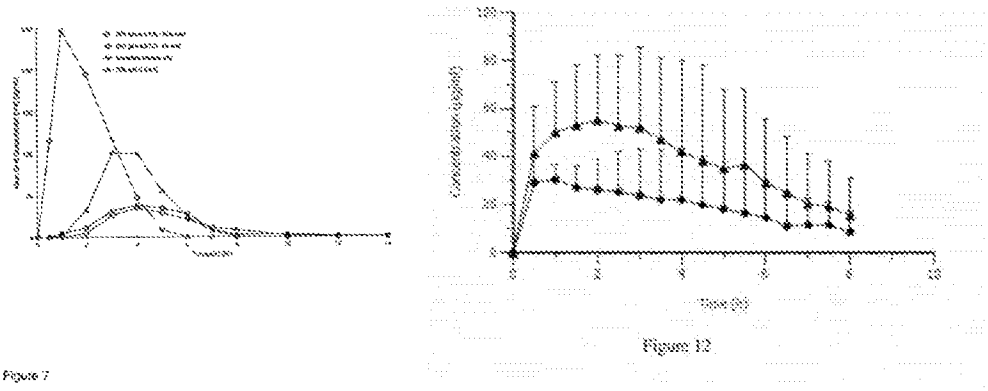


Figure 7

Figure 12

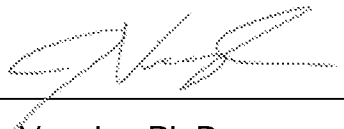
[1] *J Clin Pharmacol*. 2003 Jan;43(1):59-65. Available at: https://pubmed.ncbi.nlm.nih.gov/12520629/

12. Upon close examination, it is clear that Example 8, TABLE 3, and FIG. 7 of Liang do not refer to the claimed composition, but only to immediate and delayed release formulations administered **separately**. Thus, taken as a whole, Liang provides no in vivo data whatsoever about the claimed composition, which requires both an immediate release and modified release portion. **Using Liang to guess the in vivo pharmacokinetic profile of the claimed invention would be pure speculation**. Pure speculation cannot provide a reasonable expectation of success—particularly in an unpredictable field—and therefore cannot be a basis for obviousness in the present circumstance.

13. The Office Action states at pg. 7 that the asserted obviousness may further be refuted if "there is evidence of criticality or unexpected results." In my expert opinion, the currently claimed invention is critical, unexpected, and meets a previously unmet need. Indeed, there has been great unpredictability in gamma hydroxybutyrate formulations in the prior art, and there has been a critical need to provide a formulation as currently claimed, which is nowhere found in the prior art.

14. In summary, the current Office Action makes an argument for obviousness, but it should be withdrawn in view of the evidence presented herein. The Liang reference provides flawed data for canine/dog PK profiles that do not remotely match or suggest the currently claimed invention in human subjects. Moreover, the Liang reference cannot be used to extrapolate the currently claimed invention because of high unpredictability in the art and gamma hydroxybutyrate formulations in particular.

15. I further declare that all statements made herein are of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Jason Vaughn, Ph.D.

September 14, 2020

Date

EXHIBIT D

AMENDMENTS TO THE CLAIMS

1. (currently amended). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion; and

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

2. (original). The formulation of claim 1, wherein the suspending or viscosifying agent is present at 1% to 15% by weight of the formulation, and the acidifying agent is present at 1.2% to 15% by weight of the formulation.

3. (currently amended). The ~~modified release~~ formulation of claim 2, wherein:

the suspending or viscosifying agent is a mixture of xanthan gum, carrageenan gum, and hydroxyethylcellulose, or a mixture of xanthan gum and carrageenan gum, and

the acidifying agent is malic acid or tartaric acid.

4. (original). The formulation of claim 1, wherein the formulation further comprises a lubricant or glidant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate, glycerol behenate, sodium stearyl fumarate, talc, or colloidal silicon dioxide.

5. (original). The formulation of claim 1, wherein the formulation is a dry particulate formulation or a powdered formulation.

6. (original). The formulation of claim 1, wherein the formulation comprises 4.5 g, 6.0 g, 7.5 g, or 9.0 g of gamma-hydroxybutyrate.

7. (original). The formulation of claim 1, wherein the formulation comprises gamma-hydroxybutyrate in the form of sodium oxybate.

8. (original). The formulation of claim 1, wherein modified release portion comprises a hydrophobic compound having a melting point equal to or greater than 40°C.

9. (original). The formulation of claim 1, wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

10. (original). The formulation of claim 1, wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

11. (original). The formulation of claim 1, wherein a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

12. (original). The formulation of claim 1, wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

13. (original). The formulation of claim 1, wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of

immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

14. (original). The formulation of claim 1, wherein the formulation releases at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C and a paddle speed of 75 rpm.

15. (original). The formulation of claim 1, wherein the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37°C and a paddle speed of 75 rpm.

16. (original). The formulation of claim 1, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C and a paddle speed of 75 rpm.

17. (original). The formulation of claim 1, wherein the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37°C and a paddle speed of 75 rpm.

18. (original). The formulation of claim 1, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours in a dissolution test started in 750 mL of 0. 1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37°C and a paddle speed of 75 rpm.

19. (original). The formulation of claim 1, wherein the immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37°C and a paddle speed of 75 rpm.

20. (currently amended). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate; and

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness (“EDS”) in narcolepsy.

21. (original). The formulation of claim 20, wherein:

the suspending or viscosifying agent is selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

the acidifying agent is selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid.

22. (original). The formulation of claim 20, wherein:

the suspending or viscosifying agent is a mixture of xanthan gum, carrageenan gum, and hydroxyethylcellulose, or a mixture of xanthan gum and carrageenan gum, and

the acidifying agent is malic acid or tartaric acid.

23. (original). The formulation of claim 20, wherein the formulation further comprises a lubricant or glidant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate, glycerol behenate, sodium stearyl fumarate, talc, and colloidal silicon dioxide.

24. (original). The formulation of claim 20, wherein the formulation is a dry particulate formulation or a powdered formulation.

25. (original). The formulation of claim 20, wherein the formulation comprises 4.5 g, 6.0 g, 7.5 g, or 9.0 g of gamma-hydroxybutyrate.

26. (original). The formulation of claim 20, wherein the formulation comprises gamma-hydroxybutyrate in the form of sodium oxybate.

27. (original). The formulation of claim 20, wherein the modified release portion comprises a hydrophobic compound having a melting point equal to or greater than 40°C.

28. (original). The formulation of claim 20, wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

29. (original). The formulation of claim 20, wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

30. (original). The formulation of claim 20, wherein a dose of the formulation achieves a median T_{max} within one hundred fifty minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

31. (original). The formulation of claim 20, wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

32. (original). The formulation of claim 20, wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

33. (original). The formulation of claim 20, wherein the formulation releases at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C and a paddle speed of 75 rpm.

34. (original). The formulation of claim 20, wherein the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37°C and a paddle speed of 75 rpm.

35. (original). The formulation of claim 20, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic

potassium phosphate buffer pH 6.8 at a temperature of 37° C and a paddle speed of 75 rpm.

36. (original). The formulation of claim 20, wherein the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37°C and a paddle speed of 75 rpm.

37. (original). The formulation of claim 20, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours in a dissolution test started in 750 mL of 0. 1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37°C and a paddle speed of 75 rpm.

38. (original). The formulation of claim 20, wherein the immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37°C and a paddle speed of 75 rpm.

39. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent for improving the formulation's viscosity and pourabilty after mixing with a liquid, the suspending or viscosifying agent being selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent for ensuring that the formulation's release profile remains unchanged for at least 15 minutes after mixing with a liquid, the acidifying agent being selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid,

boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

40. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent for improving the formulation's viscosity and pourabilty after mixing with a liquid; and

from 1.2% to 15% of an acidifying agent for ensuring that the formulation's release profile remains unchanged for at least 15 minutes after mixing with a liquid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate; and

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy.

41. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate and a coating comprising a hydrophobic compound having a melting point equal to or greater than 40°C;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

42. (new) A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate and a coating comprising a hydrophobic compound having a melting point equal to or greater than 40°C;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate; and

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy.

43. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid

solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

44. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

45. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

46. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

47. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

48. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

49. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

50. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

51. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

52. (new). A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness (“EDS”) in narcolepsy; and

wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

REMARKS:

I. Status of the Claims

Claims 1-52 are pending.

II. Amendments to the Claims

The Applicant has amended claims 1, 3, and 20, and added new claims 39-52. The claims amendments and new claims are supported by the specification and do not add new matter. Support for the amendments to claims 1 and 20 can be found, for example, in paragraphs [0157] and [0328) and Table 1c of the specification as filed. Claim 3 is amended to correct a typographical error. Support for new claims 39 and 40 can be found, for example, in original claims 1 and 20, respectively, and paragraphs [0238] and [0252] of the specification as filed. Support for new claims 41 and 42 can be found in original claims 1 and 20, respectively, and paragraphs [0189]-[0194] of the specification as filed. Support for new claims 43 and 44 can be found, for example, in original claims 1 and 20, respectively, and original claims 9 and 28, respectively. Support for new claims 45 and 46 can be found, for example, in original claims 1 and 20, respectively, and original claims 10 and 29, respectively. Support for new claims 47 and 48 can be found, for example, in original claims 1 and 20, respectively, and original claims 11 and 30, respectively. Support for new claims 49 and 50 can be found, for example, in original claims 1 and 20, respectively, and original claims 12 and 31, respectively. Support for new claims 51 and 52 can be found, for example, in original claims 1 and 20, respectively, and original claims 13 and 32, respectively.

III. 35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1-38 under 35 U.S.C. § 103 as being unpatentable over Liang et al. (US 2006/0210630; hereinafter "Liang").

The Applicant notes that obviousness requires a suggestion of all the elements in a claim[1] and an explicit, apparent reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed invention does[2] with a reasonable expectation of success.[3]

Claim 1, as amended, is directed to a formulation of gamma-hydroxybutyrate comprising an immediate release portion comprising gamma-hydroxybutyrate, a modified release portion comprising gamma-hydroxybutyrate, a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof, and an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid, wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion, wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35. The claimed formulation, therefore, includes several separate and distinct entities, *e.g.*, the suspending/viscosifying agent is separate and distinct from the acidifying agent, and both are separate and distinct from the immediate and modified release portions.

Liang fails to disclose or suggest each and every element of the claimed formulation. Liang discloses dosage forms containing an immediate release component of gamma-hydroxybutyric acid and one or more delayed/controlled release component of gamma-hydroxybutyric acid (abstract). Liang also discloses that the immediate release component can comprise one or more excipients ([0052]) such as microcrystalline cellulose, xanthan gum, carrageenan, malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, or benzoic acid ([0055]) and the

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[1] *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003); *In re Royka*, 490 F.2d 981, 985 (CCPA 1974); M.P.E.P. §2143.03.
[2] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731, 1741 (2007); M.P.E.P. §2142).
[3] *KSR Int'l Co.* at 1727; *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986); M.P.E.P. §2143.02.

immediate release core of the delayed/controlled release component further comprises one or more excipients ([0058]) such as microcrystalline cellulose, malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, or benzoic acid ([0061]). The total amount of "excipients in the immediate release component is from about 0% to about 80% by weight" ([0054]) and the total amount of "excipients in the immediate release core is from about 1% to about 80% by weight" ([0060]).

The immediate release cores of Liang are prepared by "dry blending, milling, dry granulation, wet granulation, pelletization, direct pelletization, extrusion, melt-extrusion, spheronization, drug layering, compaction, or compression" ([0069]) such that the salts of gamma-hydroxybutyric acid and the one or more excipients are mixed together to form immediate release particles/pellets ([0096]). Thus, the excipients of Liang are integral elements of both the immediate release component and the core of the delayed/controlled release component. Stated another way, Liang's only teaching regarding excipients is that they have to be actually part of Liang's immediate release and delayed/controlled release components. As such, nowhere does Liang disclose or suggest a formulation having a suspending/viscosifying agent and an acidifying agent that are separate and distinct from the immediate release component and the delayed/controlled release component of the formulation, as required in claim 1.

Liang also describes dosage forms in which the immediate release component is present together with delayed/controlled release components, or the immediate release component is separate from the delayed/controlled release components ([0046]). For example, the immediate release component, which comprises up to 100% of the one or more gamma-hydroxybutyric acid salts and optional excipients, is a powder to be stirred into a drink or food along with the delayed/controlled release component ([0048]). Alternatively, the immediate release component is an aqueous solution of the one or more gamma-hydroxybutyric acid salts, stabilized with one or more excipients, to be mixed with the delayed/controlled release component and then ingested ([0050]). Importantly, none of the dosage forms envisioned by Liang specifies a suspending/viscosifying agent and an acidifying agent that are separate and distinct from the immediate release and delayed/controlled release components.

Thus, the claimed formulation comprising suspending/viscosifying and acidifying agents that are separate and distinct from the immediate release and modified release portions differs structurally from the dosage forms of Liang. Moreover, a person of ordinary skill in the art would not be prompted by the disclosure of Liang to modify the dosage forms disclosed therein and arrive at the claimed formulation with a reasonable expectation of success.

For at least the reasons stated above, the Applicant respectfully submits that claim 1 is not rendered obvious by Liang. Claims 2-19, which depend from and incorporate all the limitations, likewise are not obvious in view of Liang for the same reasons stated above with respect to claim 1.

Claim 20 is similar to claim 1 in that it also requires that the suspending/viscosifying and acidifying agents are separate and distinct from the immediate release and modified release portions. Thus, claim 20 and its dependent claims (21-38) are also not obvious in view of Liang for the same reasons articulated above with respect to claim 1.

In view of the above, the Applicant respectfully request withdrawal of the 103 rejections of claims 1-38 in view of Liang.

IV. New Claims 39-52 Are Patentable

New claims 39 and 40 specify that the suspending/viscosifying agent improves the formulation's viscosity and pourability after mixing with a liquid, and the acidifying agent ensures that the formulation's release profile remains unchanged for at least 15 minutes after mixing with a liquid. Liang does not disclose or suggest including excipients such as a suspending/viscosifying agent and an acidifying agent in the dosage forms along the immediate release and delayed/controlled release components for improving the viscosity and pourability of the formulation after mixing with a liquid and for ensuring the formulation's release profile remains unchanged for at least 15 minutes after mixing with a liquid, respectively.

New claims 41 and 42 specify that the modified release portion comprises a coating comprising a hydrophobic compound having a melting temperature equal to or

greater than 40°C. Liang discloses that the immediate release component can comprise hydrogenated vegetable oils ([0055]) and the immediate release core of the delayed/controlled release component can comprise hydrogenated vegetable oils ([0058]). However, Liang fails to disclose or suggest including a hydrophobic compound (*e.g.*, vegetable oil) in the coating of the delayed/controlled release component.

New claims 43 and 44 specify that the formulation achieves a relative bioavailability of greater than 80% when compared to an immediate release liquid solution. Liang discloses the relative bioavailability of various delayed release components and an immediate release component (Table 3). The delayed release components exhibit much lower bioavailability, ranging from 22% to 53%, relative to the immediate release component. As stated in paragraph [0013] of the pending application as filed, one can easily calculate that any of the combinations of immediate release and delayed controlled release components envisioned in Liang "will not give a relative bioavailability greater than 78%."

New claims 45 and 46 specify that the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal. Liang discloses AUC_{last} values for delayed release components or the immediate release component (Table 3) but does not disclose or suggest any AUC values for the dosage forms disclosed therein. As such, the mean AUC_{8h} to mean AUC_{inf} ratio of the dosage forms of Liang is unpredictable. Moreover, because of the differences between the claimed formulation and the dosage forms of Liang, a person of ordinary skill in the art would expect that the pharmacokinetics would also differ.

New claims 47 and 48 specify that a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal. Liang discloses T_{max} values for delayed release components or the immediate release component (Table 3) but does not disclose or suggest said values for the dosage forms disclosed therein. Thus, comparisons between Liang's dosage forms and immediate release formulations are unpredictable.

Moreover, because the dosage forms of Liang differ from the claimed formulation, a person of ordinary skill in the art would expect that pharmacokinetic properties would also differ.

New claims 49 and 50 specify that a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal. Liang fails to disclose or suggest concentration (C) values at various time points for the dosage forms disclosed therein. As such, comparisons between Liang's dosage forms and immediate release formulations are unpredictable. Moreover, because of the differences between the claimed formulation and the dosage forms of Liang, a person of ordinary skill in the art would expect that the pharmacokinetics would also differ.

New claims 51 and 52 specify that a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal. Liang does not disclose or suggest $AUC_{inf/last}$ or C_{8hr} values for the dosage forms disclosed therein. Thus, comparisons between Liang's dosage forms and immediate release formulations are unpredictable. Moreover, because the dosage forms of Liang differ from the claimed formulation, a person of ordinary skill in the art would expect that pharmacokinetic properties would also differ.

For all the reasons stated above, the Applicant respectfully submits that new claims 39-52 are patentable.

V. Conclusion

In view of the foregoing, the Applicant respectfully requests entry of the claim amendments and new claims, withdrawal of the claim rejections, and solicits an allowance of all the pending claims. The Examiner is invited to contact the undersigned practitioner should any issues remain unresolved.

Respectfully submitted,

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Date: March 18, 2020

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EXHIBIT E

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a single daily dose to said human, the single daily dose comprising an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises

opening a sachet containing a gamma-hydroxybutyrate formulation,

mixing the formulation with water, and

orally administering the mixture.

2. (Original) The method of claim 1, wherein the orally administering occurs at bedtime.

3. (Original) The method of claim 1, wherein the mixing occurs shortly before the orally administering.

4. (Original) The method of claim 1, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.

5. (Original) The method of claim 1, wherein said administering results in inducing said human to sleep for 6 to 8 hours.

6. (Original) The method of claim 1, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g of sodium oxybate.

7. (Original) The method of claim 1, wherein the mixture is a suspension.

8. (Original) The method of claim 1, wherein the mixing comprises pouring the gamma-hydroxybutyrate formulation from the sachet into a container containing the water.

9. (Original) The method of claim 8, wherein the container contains 50 mL of water prior to the pouring.

10. (Original) A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a 4.5 g dose of gamma-hydroxybutyrate to said human that yields a pharmacokinetic profile as shown in Figure 11,

wherein the dose comprises immediate release and modified release portions.

11. (Currently Amended) A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, at a dose of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized evening meal that yields a plasma concentration versus time curve ~~substantially as~~ bioequivalent to that depicted in Figure 12.

12. (Currently Amended) A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, at a dose of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized evening meal that yields a plasma concentration versus time curve ~~substantially as~~ bioequivalent to that depicted in Figure 13.

13. (Currently Amended) A method of treating narcolepsy Type 1 or Type 2, the method comprising:

administering a single daily dose to a human in need thereof, the single daily dose comprising an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises

opening a sachet containing a gamma-hydroxybutyrate formulation,

mixing the formulation with water, and

orally administering the mixture.

14. (Original) The method of claim 13, wherein the orally administering occurs at bedtime.

15. (Original) The method of claim 13, wherein the mixing occurs shortly before the orally administering.

16. (Original) The method of claim 13, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.

17. (Original) The method of claim 13, wherein said administering results in inducing said human to sleep for 6 to 8 hours.

18. (Original) The method of claim 13, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g of sodium oxybate.

19. (Original) The method of claim 13, wherein the mixture is a suspension.

20. (Original) The method of claim 13, wherein the mixing comprises pouring the gamma-hydroxybutyrate formulation from the sachet into a container containing the water.

21. (Original) The method of claim 20, wherein the container contains 50 mL of water prior to the pouring.

22. (Currently Amended) A method of treatment of narcolepsy Type 1 or Type 2, the method comprising:

administering a single daily dose to a human in need thereof, the single daily dose comprising an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate,

wherein, compared to a dosing regimen consisting of administering half the dose at t_0 and another half of the dose at t_{4h} of an immediate release liquid solution of sodium oxybate, the method produces less confusion, less depressive syndrome, less incontinence, less nausea, or less sleepwalking.

23. (Currently Amended) A method of reducing narcolepsy-related excessive daytime sleepiness or frequency of cataplectic attacks, the method comprising:

administering a single daily dose to a human in need thereof, the single daily dose comprising an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises

opening a sachet containing a gamma-hydroxybutyrate formulation,

mixing the formulation with water, and

orally administering the mixture.

24. (Original) The method of claim 23, wherein the orally administering occurs at bedtime.

25. (Original) The method of claim 23, wherein the mixing occurs shortly before the orally administering.

26. (Original) The method of claim 23, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.

27. (Original) The method of claim 23, wherein said administering results in inducing said human to sleep for 6 to 8 hours.

28. (Original) The method of claim 23, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g of sodium oxybate.

29. (Original) The method of claim 23, wherein the mixture is a suspension.

30. (Original) The method of claim 23, wherein the mixing comprises pouring the gamma-hydroxybutyrate formulation from the sachet into a container containing the water.

31. (Original) The method of claim 30, wherein the container contains 50 mL of water prior to the pouring.

REMARKS:

I. Status of the Claims

Claims 1-31 are presently pending. By this amendment, claims 1, 11, 12, 13, 22, and 23 are amended for clarification purposes. The amendments are fully supported by the originally filed specification and claims. No new matter has been added. The clarifying amendments are believed to place all claims in condition for allowance.

II. Claim Objections

Claims 1, 13, 22, and 23 are objected to because of the following informalities: "In each of claim 1 (line 3), claim 13 (line 2), claim 22 (line 2), and claim 23 (line 3), the phrase "administering a single daily dose to a human in thereof an amount of …" should be amended to recite either "administering **in** a single daily dose to a human in thereof an amount of…" or "administering a single daily dose to a human in thereof, **the single daily dose comprising** an amount of …" (Emphasis Original).

The Applicants thank Examiner Sasan for the suggestion and have incorporated the latter language, "**the single daily dose comprising"** into claims 1, 13, 22, and 23.

III. 35 U.S.C. § 112 Indefiniteness Rejection

Claims 11-12 are rejected under 35 U.S.C. 112(b) as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter for the use of the term "substantially" as in "**substantially** as depicted in Figure…"

The term **"substantially"** has been replaced with "**bioequivalent**" as expressly supported by the specification, which is well-defined in the industry as noted in the specification by FDA's March 2003 Guidance for Industry on Bioavailability and Bioequivalence studies for Orally Administered Drug Products.

IV. 35 U.S.C. § 103 Rejections

1. Claims 1-12 and 23-31 are rejected under 35 U.S.C. 103 as being unpatentable over Liang et al. (US 2006/021630) in view of Cook et al. (US 2002/0077334).

As admitted by the Patent Office, "Liang do not expressly disclose opening a sachet containing a gamma hydroxybutyrate formulation, mixing the formulation with water and orally administering the mixture." Cook is alleged to cure the deficiency of Liang by reference to suspensions or powders admixed with an aqueous medium and dissolving a pouch containing GHB with water.

The Patent Office, however, cannot effectively rely on the Cook for the missing teachings of Liang. There are a number of problems with Cook, which make it an unacceptable to support a rejection under §103, including the following:

- Cook ***teaches away*** from a sachet as currently claimed. As noted in [0078] of Cook, Cook describes a twin-pouch having "inherent problems" with preservatives and stability and abandons the twin-pouch with "inherent problems" in favor of a purely liquid formulation. One of skill in the art reading Cook would view the twin-pouch as a problematic temporary arrangement used in the clinical trial, before returning to a liquid formulation, as that is how it was characterized by Cook. Importantly, Cook never identifies a way of fixing or mitigating the "inherent problems" of instability with the twin-pouch.
- There is no reasonable expectation of success in combining Cook with Liang. As expressly noted by Cook, there are known problems of instability, microbial growth, and/or degradation of the GHB active ingredient into GBL. To quote the Cook specification at [0010], "Problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pHand thus, GHB's stability." As such, there is ***high level of unpredictability regarding combination or modification*** of references dealing with GHB.
- The legal precedent is also clear that the Patent Office cannot maintain an obviousness rejection when there is a plain material difficulty preventing

success. For example, in *Endo Pharmaceuticals Inc. v. Actavis LLC*, a majority of the Federal Circuit panel found that skilled artisans would not have had a reasonable expectation of success in combining the cited references because one of the references disclosed a material difficulty with using catalytic hydrogenation to purify the API to the FDA-mandated level.

- The unpredictability of GHB formulations is not merely academic. As noted by the owner of the Cook reference (Jazz Pharmaceuticals Inc.) in its Citizen Petition to FDA, "Formulation differences may affect in vivo absorption of generic gamma hydroxybutyrate products and the safety and efficacy of the drug."[1] As such, there is no reasonable predictability with respect to GHB formulations, even if a skilled artisan were trying to copy a formulation exactly. It's simply too unpredictable.
- As an additional matter, it is also worth noting that Cook does not teach a "single daily dose" as currently claimed. Cook's immediate release formulations are short-lived and only last 4 hours, as evidenced by the 4-hour dosing schedule. See Cook at [0146].

In summary, it is respectfully submitted that the cited art fails to disclose or suggest each and every claim element and, given the ***teachings away*** by Cook, fail to provide an apparent reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed invention does with a reasonable expectation of success, as required by the law.[2]

Withdrawal of the § 103 rejections is respectfully requested.

2. Additional Basis for Non-Obviousness of Claims 10-12

According to the Patent Office at pg. 8, "Regarding instant claims 10-12, the limitations of the pharmacokinetic profile as recited in claim 10, claim 11, and claim 12 are alleged to be obvious over the mean GHB concentrations as disclosed in TABLE 3

[1] See https://investor.jazzpharma.com/static-files/f9cdf771-cb99-4374-a276-d5d3fd40a23f

[2] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731, 1741 (2007); M.P.E.P. §2142

and FIG. 7, as disclosed by Liang, unless there is evidence of criticality or unexpected results."

Claims 10-12 are non-obvious for a number of reasons, including the following:

- The claims 10-12 all recite pharmacokinetic profiles in a "human in need thereof" but the Patent Office is citing to Table 3 and Figure 7 of Liang which is dog/canine data. ***Dog/canine data cannot teach the currently claimed human pharmacokinetic profile.***
- The pharmaceutical arts are highly unpredictable with respect to pharmacokinetic profiles. As noted in legal precedent *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018), there must be a finding that that skilled artisans could extrapolate the claimed pharmacokinetic performance data. Here, the Patent Office does not have the necessary evidence to make a *prima facie* case for a human pharmacokinetic profile. The Patent Office has cited to no authority that dog/canine data can be extrapolated into human pharmacokinetics for GHB formulations, as is legally required. Because the formulations are materially different with different excipients, preservatives, and solvents, *Endo Pharm. Sols., Inc. v. Custopharm Inc.* also states that inherency is legally impermissible.

3. Additional Basis for Non-Obviousness of Claims 4 and 26

According to the Patent Office at pg. 9, "Regarding instant claims 4 and 26, the limitations of the oral administration occurring approximately 2 hours after said human has eaten a meal would have been obvious over the at least three hours which elapsed between the completion of dinner and the administration of the GHB dose, as taught by Cook et al., unless there is evidence of criticality or unexpected results."

As noted previously, there is high unpredictability with regard to GHB formulations and particularly regarding food effect:

- As noted by the owner of the Cook reference (Jazz Pharmaceuticals Inc.) in its Citizen Petition to FDA, "Generic Sodium Oxybate Formulation

Differences Could Alter the Food Effect Seen with Xyrem [Immediate Release GHB]." Among other factors, "Due to the variability of this effect on poorly metabolized and poorly permeable drugs [such as GHB], changes in absorption continue to be difficult to model and are an area of active research."[3] As such, there is no predictability with respect to GHB formulations and food effect, even if a skilled artisan were trying to copy a formulation exactly.

- Here, again, there is the additional technical difference of an immediate release formulation of Cook versus a "single daily dose" as currently claimed. Cook's immediate release formulations are short-lived and only last 4 hours, as evidenced by the 4-hour dosing schedule. See Cook at [0146].

4. Claims 1-31 are rejected under 35 U.S.C. 103 as being unpatentable over Liang et al. (US 2006/021630) in view of Cook et al. (US 2002/0077334) and Scammell, Thomas ("Narcolepsy," The New England Journal of Medicine 373;27, December 31, 2015, pp. 2654-2662).

Per the Office Action at pg. 12, "The teachings of Liang et al. and Cook et al. are discussed above. Although Liang et al. and Cook et al. disclose the treatment of narcolepsy, these references do not expressly disclose a method of treating narcolepsy Type 1 or Type 2 as recited in instant claims 13 and 22." Scammell is cited for the purpose of teaching two types of narcolepsy, Type 1 or Type 2.

The deficiencies of Liang and Cook, as described above, are herein incorporated by reference and reasserted with respect to the instant rejection. Whether considered alone or in combination with Liang and Cook, Scammell does not cure the teachings away of Cook, the unpredictability in the field, and the lack of reasonable expectation of success. Scammell provides additional basis of teachings away and uncertainty by

[3] See https://investor.jazzpharma.com/static-files/f9cdf771-cb99-4374-a276-d5d3fd40a23f

stating that existing GHB formulations must be taken every "2.5 to 4 hours." As such, Scammell teaches away from a "single daily dose," as currently claimed.

> Unlike the medications discussed above, which are taken in the morning or several times during the day, sodium oxybate (the sodium salt of γ-hydroxybutyrate) is a highly sedating liquid given at bedtime and 2.5 to 4 hours later. It pro-

Scammell also teaches away from the sachet, and instead teaches the "highly sedating liquid." Again, it should be noted that Cook stated that the twin-pouch had stability and preservative problems, and was abandoned in favor of the liquid formulation. Scammell therefore reinforces the unpredictability and teachings away of Cook. In view of the above, withdrawal of all rejections and allowance of all claims is respectfully requested.

V. Obviousness-Type Double Patenting Rejections

Claims 1-31 have been provisionally rejected for obviousness-type double patenting in view of US 10,272,062, US 10,736,866, US Application 16/431,219, in view of Cook and/or Scammell. Applicants respectfully assert that the double patenting rejections are provisional in nature, and will be addressed once the current claims are in condition for allowance (e.g., by filing any appropriate terminal disclaimer at that time).

VI. Conclusion

In view of the foregoing, the Applicant respectfully requests entry of the claim amendments, withdrawal of the claim rejections, and allowance of all the pending claims. The Examiner is invited to contact the undersigned practitioner should any issues remain unresolved.

Respectfully submitted,

POLSINELLI PC

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EXHIBIT F

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	)	C.A. No. 21-cv-1138-MN
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	)	C.A. No. 21-cv-1594-MN

DEFENDANT'S INITIAL INVALIDITY CONTENTIONS

Pursuant to Paragraph 4(d) of the Default Standard for Discovery and the Scheduling Order entered in the above-captioned actions on December 21, 2021 (*see* D.I. 29),[1] Defendant Avadel CNS Pharmaceuticals, LLC ("Defendant" or "Avadel"), hereby provide Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited ("Plaintiffs") its initial invalidity

[1] Both matters listed in the caption above are proceeding on a coordinated schedule. All docket cites are to matter C.A. No. 21-cv-1138-MN unless otherwise noted.

contentions regarding the asserted claims of U.S. Patent Nos. 11,077,079 (the "'079 patent") and 11,147,782 (the "'782 patent") (collectively the "Jazz Resinate Patents"). Under separate cover, Defendant provides its document production accompanying these contentions.

I. GENERAL STATEMENTS

Defendant submits these initial invalidity contentions based upon information presently available. Discovery is ongoing and the terms of the asserted claims have not yet been construed by the Court. Therefore, Defendant reserves the right to supplement, alter, amend and/or modify these contentions based on further investigation, fact or expert discovery, evaluation of the scope and content of the prior art, any claim construction by the Court, or as a result of Plaintiffs' asserted claims and contentions.

To the extent that Plaintiffs are permitted to assert additional claims not presently identified in their initial infringement contentions, Defendant reserves the right to address the invalidity of such claims. Defendant's invalidity positions in these contentions may be in the alternative and do not constitute any concession by Defendant for purposes of claim construction or infringement. *See, e.g.*, *Vanmoor v. Wal-Mart Stores, Inc.*, 201 F.3d 1363, 1366 (Fed. Cir. 2000). Furthermore, these contentions are provided without prejudice to Defendant's right to introduce at trial any subsequently-discovered evidence or expert opinions relating to currently-known facts and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently-discovered facts. Moreover, facts, documents, and things now known may be imperfectly understood and, accordingly, such facts, documents, and things may not be included in the following contentions. Defendant reserves the right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, expert opinion testimony, documents, and things notwithstanding the written statements herein. Defendant further reserves its right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial,

any and all facts, documents, and things that are not currently recalled but might be recalled at some time in the future.

Defendant objects to the disclosure of information that is protected by the attorney-client privilege, the attorney work-product immunity, the common interest privilege, or any other applicable privilege or immunity. To the extent that Defendant inadvertently discloses information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege, or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

The information set forth below is provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other action, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time. Defendant further reserves the right to amend and/or supplement these contentions in accordance with the Federal Rules of Civil Procedure and/or the Rules of this Court. Defendant reserves the right to allege the invalidity of the asserted claims on bases other than those disclosed herein.

II. BACKGROUND

On December 7, 2021, Plaintiffs provided Defendant with their initial infringement chart pursuant to Paragraph 4(c) of the Delaware Default Standard. In this initial infringement chart, Plaintiffs asserted that the product described in Defendant's NDA infringes claims 1-3, 5-12, and 14-18 of the '079 patent, and claims 1-24 of the '782 patent.

In view of Plaintiffs' initial infringement chart, the following initial invalidity contentions address the asserted claims of the Jazz Resinate Patents.

III. PRIORITY DATES

The '079 patent issued on August 3, 2021 and was filed on December 10, 2020. The '079 patent is a continuation of U.S. Application No. 16/448,598, filed on June 21, 2019, now abandoned; which is a continuation of U.S. Application No. 15/047,586, filed on February 18, 2016, which issued as U.S. Patent No. 10,398,662, which claims priority to Provisional Application No. 62/117,889 (the "'889 application"), filed on February 18, 2015.

However, for the reasons discussed in Section VII, the asserted claims of the '079 patent are not entitled to claim priority to the '889 application, and should be entitled to a priority date no earlier than December 10, 2020.

The '782 patent issued on October 19, 2021, and was filed on March 23, 2021. The '782 patent is a continuation of U.S. Application No. 17/118,041, now the '079 patent, which is a continuation of U.S. Application No. 16/448,598, filed on June 21, 2019, now abandoned; which is a continuation of U.S. Application No. 15/047,586, filed on February 18, 2016, which issued as U.S. Patent No. 10,398,662, which claims priority to the '889 application, filed on February 18, 2015.

However, for the reasons discussed in Section VII, the asserted claims of the '782 patent are not entitled to claim priority to either the '889 application or the '586 application, but instead should be entitled to a priority date no earlier than March 23, 2021.

IV. PRIOR ART

At this time, Defendant contends that at least the following prior art references anticipate and/or render obvious, either alone or in combination, the asserted claims of the '079 patent:

1. U.S. Patent Publication No. 2006/0210630 ("Liang 2006");

2. U.S. Patent No. 8,529,954 to Lebon et al. issued on September 10, 2013 ("Lebon 2013");

3. E.U. Patent No. EP2825188B1 to Comiskey et al, granted Jan. 2015 ("Comiskey 2015");

4. U.S. Patent App. 2012/0076865 to Allphin et al., published March 29, 2012 ("Allphin 2012");

5. PHARMACEUTICAL SUSPENSIONS: FROM FORMULATION DEVELOPMENT TO MANUFACTURING, 2010 (Kulshreshtha et al. Eds.) ("PHARMACEUTICAL SUSPENSIONS 2010");

6. The 46th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations - TRS, No. 970 (June 1, 2012) ("WHO 2012");

7. Robert J. Balch & Andrea Trescot, *Extended-release morphine sulfate in treatment of severe acute and chronic pain*, 3 J. PAIN RSC. 191 (2010) ("Balch 2010");

8. Alexandra F. Bowles, *Development of a multiparticulate-based platform for delivering functionalized capability as an oral liquid dosage form*, UCL SCHOOL OF PHARMACY, 2013 ("Bowles 2013");

9. Nina Bladh et al., A *New Esomeprazole Packet (Sachet) Formulation for Suspension: In Vitro Characteristics and Comparative Pharmacokinetics Versus Intact Capsules/Tablets in Healthy Volunteers*, 29 CLINICAL THERAPEUTICS 640 (2007) ("Bladh 2007");

10. Emmanuel J. M. Mignot, *A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes*, 9 NEUROTHERAPEUTICS, 739 (2012) ("Mignot 2012");

11. The Nexium (esomeprazole magnesium) delayed-release capsules for oral use and Nexium (esomeprazole magnesium) for delayed-release oral suspension 2014 label ("Nexium 2014 label");

12. Fang Liu et al., *Patient-Centered Pharmaceutical Design to improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations*, 74 DRUGS, 1871 (2014) ("Liu 2014");

13. XYREM® (sodium oxybate) oral solution label, revised April 2014 ("Xyrem 2014 Label").

In addition, for the reasons discussed in Section VII, the '079 patent is entitled to a priority date no earlier than December 10, 2020. The following additional prior art references therefore anticipate and/or render obvious, either alone or in combination, the asserted claims of the '079 patent under the correct priority date:

14. Avadel's U.S. Patent Publication No. 2019/0274990 published on September 12, 2019 ("the '986 patent publication") , which eventually issued as Avadel's U.S. Patent No. 10,952,986 on March 23, 2021 ("the '986 patent");

15. Avadel's U.S. Patent Publication No. 2019/0183836 ("the '866 patent publication") published on June 20, 2019, which eventually issued as Avadel's U.S. Patent No. 10,736,866 on August 11, 2020 ("the '866 patent");

16. Avadel's '866 patent;

17. Avadel's U.S. Patent Publication No. 2018/0021284 ("the '062 patent publication") published on January 25, 2018, which eventually issued as Avadel's U.S. Patent No. 10,272,062 issued on April 10, 2019 ("the '062 patent");

18. Avadel's '062 patent.

At this time, Defendant contends that at least the following prior art references anticipate and/or render obvious, either alone or in combination, the asserted claims of the '782 patent:

1. Lebon 2013;

2. Allphin 2012;

3. Liang 2006;

4. U.S. Patent No. 5,540,912 to Roorda et al. issued on July 30, 1996 ("Roorda 1996");

5. U.S. App. No. 11/486,454 to Dang et al. January 25, 2007 ("Dang 2007");

6. WO Pat. App. No 2011/107865 to Gandhi et al. published on September 9, 2011 ("Gandhi 2011");

7. Farhan AlHusban et al., *Formulation of multiparticulate systems as lyophilized orally disintegrating tablets (ODTs)*, EUROPEAN J. PHARM & BIOPHARMACEUTICS 627, 629, 633 (2011) ("AlHusban 2011");

8. PHARMACEUTICAL SUSPENSIONS 2010;

9. PHARMACEUTICAL DOSAGE FORMS: DISPERSE SYSTEMS (Herbert A. Lieberman et al., eds), 1996 ("PHARMACEUTICAL DOSAGE FORMS 1996");

10. U.S. Pub. No. 2014/0287038 to Mehta 2014 et al. published on September 25, 2014 ("Mehta 2014");

11. Quillivant XR 2012 Label revised in September 2012 ("Quillivant XR 2012 Label");

12. Jones et al, *Concentration-Time Profiles of Gamma-Hydroxybutyrate in Blood After Recreational Doses are Best Described by Zero-Order Rather than First-Order Kinetics*, J. ANALYTICAL TOXICOLOGY, 332, 332 (2009) ("Jones 2009");

13. Harmik Sohi et al, *Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches*, 30 DRUG DEV. & IND. PHARM 429 (1991) ("Sohi 1991");

14. Xyrem 2014 Label;

15. Y. Kawashima et al., *Preparation of controlled-release microspheres of ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method*, 75 INT'L. J. PHARMA. 25 (1991) ("Kawashima 1991");

16. P. Nykanen et al., *Organic acids as excipients in matrix granule for colon-specific drug delivery*, 184 INT'L J. PHARMA. 251 (1999) ("Nykanen 1999");

17. P. Nykanen et al., *Citric acid as excipient in multiple-unit enteric-coated tablets for targeting drugs on the colon*, 229 INT'L J. PHARMA. 155 (2001) ("Nykanen 2001");

18. P. Nykanen et al., *Citric acid as pH-regulating additive in granules and the tablet matrix in enteric-coated formulations for colon-specific drug delivery*, 59 PHARMAZIE 268 (2004) ("Nykanen 2004").

In addition, for the reasons discussed in Section VII that the '782 patent is entitled to a priority date no earlier than March 23, 2021. The following additional prior art references anticipate and/or render obvious, either alone or in combination, the asserted claims of the '079 patent under the correct priority date:

19. Avadel's '986 patent publication;

20. Avadel's '866 patent publication;

21. Avadel's '866 patent;

22. Avadel's '062 patent publication;

23. Avadel's '062 patent.

V. THE ASSERTED CLAIMS OF THE '079 AND '782 PATENTS ARE INVALID UNDER 35 U.S.C. § 102 AND/OR 35 U.S.C. § 103

For the reasons set forth below, as well as set forth in the claim charts attached as Appendices A and B, the asserted claims of the Jazz Resinate Patents are invalid as anticipated and/or obvious over the prior art.

Under 35 U.S.C. § 102(a), a person is not entitled to a patent if the "claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention."

Under 35 U.S.C. § 103, an applicant is not entitled to a patent "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious" to a person of ordinary skill in the art ("POSA") at the time the invention was made. The relevant factual inquiries include:

(a) determining the scope and content of the prior art;

(b) ascertaining the differences between the prior art and the claims at issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966). The Supreme Court reiterated the applicability of the Graham factors in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

Defendant's contentions are based, in part, on Plaintiffs' interpretation of the claims, as set forth in their December 7, 2021 infringement contentions. Defendants do not concede that Plaintiffs' implicit claim constructions are correct. Nevertheless, to the extent Plaintiffs continue to assert that Defendant's product infringes the claims of the '079 and '782 patents, then the asserted claims of those patents are invalid for the reasons set forth below.

A. The '079 patent

The asserted claims of the '079 patent, according to Plaintiffs' infringement contentions, are generally directed to a method of treating narcolepsy with a single-dose oxybate formulation comprising opening a sachet containing a solid oxybate formulation comprising a mixture of immediate release and controlled release components and mixing the formulation with water for

oral administration to a patient. As set forth in Appendix A and as discussed below, all of the asserted claims of the '079 patent (claims 1-3, 5-12, 14-18) are invalid as anticipated and/or obvious over the prior art in view of the knowledge of a POSA.

Further, for the reasons discussed in Section VII and Appendix A, the '079 patent is entitled to a priority date no earlier than December 10, 2020, and all of the asserted claims of the '079 patent are invalid as anticipated and/or obvious over at least Avadel's '866 patent, '062 patent, and '986 patent publication under the correct priority date.

1. Claim 1

Asserted claim 1 of the '079 patent is invalid as anticipated by Liang 2006 and Lebon 2013 and/or obvious over Liang 2006 and/or Lebon 2013 in view of the knowledge of a POSA.

Claim 1 is reproduced below:

> 1. A method of treating narcolepsy in a patient in need thereof, the method comprising:
> administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:
> opening a sachet containing a solid oxybate formulation,
> mixing the formulation with water, and
> orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

Claim 1 is anticipated by Liang 2006. Liang 2006 discloses an oral solid dosage form of gamma-hydroxybutyric acid ("GHB") containing "an immediate release component of [GHB], and one or more delayed/controlled release components of [GHB]." Liang 2006 at Abstract. Liang 2006 teaches that GHB can be used to treat narcolepsy. *See id.* at ¶¶ 1, 2, 3, 5, 40. Liang also teaches that it could be a single daily dose. *Id.* at ¶¶ 12, 32. It further discloses that the amount in the dosage could be between 4.5 g to 9 g. *Id.* at ¶ 5. As in the '079 patent, Liang 2006 also discloses that the solid dosage form could be a sachet. *Id.* at ¶ 45. Further, Liang 2006 discloses

that the formulation could be stirred into a drink, and water is the most common form of drink. *Id.* at ¶ 48.

Claim 1 is likewise anticipated by Lebon 2013. Lebon 2013 discloses an oral solid dosage form of GHB containing an immediate release component and a controlled release component. *See id.* at col. 2:25-29 ("The present invention relates to a granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts."); col. 4:34-47 (adding a sustained-release coating "enables a modified or delayed release of the active constituents (modified-release granulates)"). Lebon 2013 also teaches that GHB can be used to treat narcolepsy. *Id.* at col. 1:31. Lebon 2013 further teaches administering a GHB formulation in a single daily dose. *See id.* at col 1:46-48 (describing current dosing regimen for narcolepsy as "repeated every 3 to 4 hours. . . in the middle of the night."); col. 2:1-5 (stating that the object of the invention is to "reduce the daily dose and number of times it is taken per day"). Lebon 2013 also discloses the dosage to be between 4 to 9 g per day. *Id.* at col. 1:46-47. Lebon 2013 discloses providing the solid dosage form in a "sachet" wherein the granules can be "dispersed in a solution." *Id.* at 5:49-51, 60-62.

To the extent Liang 2006 or Lebon 2013 are found not to anticipate claim 1 of the '079 patent, claim 1 would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the prior art. As described below, a POSA would have been motivated to develop a method for treating narcolepsy by administering a single daily dosage of GHB containing an immediate release component and a controlled release component in a sachet form, wherein the GHB formulation was administered by opening the sachet, mixing it with water, and administering it

orally. Claim 1 would therefore have been obvious to a POSA as of the earliest asserted priority date of the '079 patent.

a. **"A method of treating narcolepsy in a patient in need thereof, the method comprising"**

To the extent that the preamble is limiting, a POSA would have been motivated to develop a method of treating narcolepsy in a patient in need thereof. Liang 2006 teaches that GHB can be used "in the treatment of narcolepsy." *Id.* at ¶ 1; *see also id.* at ¶ 2, ("Sodium gamma-hydroxybutyrate (GHB or sodium oxybate) . . . has broad indications including narcolepsy."); ¶ 5 ("Xyrem® is prescribed to narcolepsy patients.").

Similarly, Lebon 2013 teaches that Xyrem "is used for the treatment of narcolepsy in adult patients exhibiting cataplexy." *Id.* at col. 1:28-31. Lebon 2013 however explains that "the major drawback of GHB in terms of effectiveness is linked to its pharmacokinetic profile" which limits the effectiveness of GHB and requires the administration of multiple doses repeated every few hours. *Id.* at col. 1:36-52. Lebon 2013 explains that the object of the present invention is therefore to provide a "novel galenic form based on gamma-hydroxybutyric acid or one of its salts (in particular sodium) which makes it possible to circumvent the aforementioned drawbacks" associated with the administration of GHB. *Id.* col. 1:64-67.

For the reasons set forth above Liang 2006 and Lebon 2013 disclose methods of treating narcolepsy in a patient in need thereof.

b. **"administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate"**

Liang 2006 is directed to a formulation that provides a single daily dose of sodium oxybate for the treatment of narcolepsy. *Id.* at ¶ 1. In addition, Liang 2006 discloses that combining the immediate release and "delayed/controlled release components" of GHB "can constitute a

complete once-nightly or once-daily dose." *Id.* at ¶ 32. It clarifies that the term combining can mean supplying and consuming all components "simultaneously in the same presentation or dosage form." *Id.* Liang 2006 further discloses that the "delayed/controlled release" particles and immediate release component can be "supplied as pre-mixed doses," thus comprising a single dosage. *Id.* at ¶ 33. Liang 2006 also describes the single daily dosage to be convenient, because "a patient does not need to wake up and take a second dose during the night." *Id.* at ¶ 36.

Liang 2006 also discloses a daily dose comprising an amount of oxybate equivalent to from 4 to 12 grams. Specifically, Liang 2006 discloses that "a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients." *Id.* at ¶ 5. Further, the '079 patent identifies no unique or unexpected properties associated with the recited range of oxybate amount, and a POSA would have arrived at the recited dosage ranges from the ranges disclosed in Liang 2006 as a result of routine optimization. Liang 2006 also teaches that Xyrem® is composed of sodium GHB. *Id.* at ¶ 3. In addition, Liang 2006 teaches that the GHB dosage can be adjusted beyond the daily dose expressly recited in Liang 2006: "the immediate release component can be at a slightly higher than normal dose, and the delayed release dose can be at a normal dose or at a reduced dose." Liang 2006 at ¶ 41. Further, the prior art taught that a single dose of GHB can have "a range of about 500 mg to about 12 g of drug." Allphin 2012 at ¶ 42. Thus, a POSA would have also been motivated to modify the amount of sodium oxybate in the single daily dose described in Liang 2006 to arrive at the claimed range of 4.0 g to 12.0 g of sodium oxybate.

Similarly, Lebon 2013 is directed to a formulation that provides a single daily dose of sodium oxybate. Lebon 2013 states the object of the invention is to "reduce the daily dose and number of times [GHB] is taken per day," *id.* at col. 1:46-48, compared to the current dosing regimen for narcolepsy which requires that the dosing be "repeated every 3 to 4 hours. . . in the

middle of the night." *Id.* at col. 1:46-48; *see also id.* at col. 1:28-29 (describing Xyrem® as "comprising as [sic] active constituent a sodium salt of GHB"); Xyrem® 2014 Label, at 3-4 (describing the dosing regimen of Xyrem®: one dose taken at bedtime and one taken 2.5-4 hours later). Further, Lebon 2013 discloses that the "present invention" "reduce[s] . . . the number of times it is taken per day." *Id.* at col. 2:1-4.

Lebon 2013 also discloses a daily dose of 4 to 12 grams. Lebon 2013 discloses that the current dosing regimen involves "a substantial daily dose of 4 to 9 g." *Id.* at col. 1:46-47. Further, the '079 patent identifies no unique or unexpected properties associated with the recited range of oxybate amount, and a POSA would have arrived at the recited dosage ranges from the ranges disclosed in Lebon 2013 as a result of routine optimization. Further, the prior art taught that a single dose of GHB can have "a range of about 500 mg to about 12 g of drug." Allphin 2012 at ¶ 42. Thus, a POSA would have also been motivated to modify the amount of sodium oxybate in the single daily dose described in Lebon 2013 to arrive at the claimed range of 4.0 g to 12.0 g of sodium oxybate.

For the reasons set forth above, this limitation would have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA. *Id.* at ¶ 45.

c. **"opening a sachet containing a solid oxybate formulation"**

Liang 2006 discloses that the immediate release component can be administered in, among other forms, a sachet. Liang 2006 at ¶ 45. Liang 2006 further discloses, however, that the immediate release and controlled release components can be a pre-mixed powder. *Id.* at ¶47 ("[T]he immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed-controlled release particles"); *id.* at ¶ 48 ("[T]he immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion."). Thus, to the extent that Jazz contends

that its disclosure in the priority application is sufficient to disclose this limitation, then Liang 2006's disclosure of the use of sachets for the storage of solid oxybate formulations comprising both immediate and "delayed/controlled release" formulations would likewise disclose this limitation. Further, a POSA would understand that administration of the GHB formulation in a sachet would require opening the sachet.

Likewise, Lebon 2013 also discloses the use of a sachet to store the GHB formulation. *Id.* at col. 5:49-51 ("The granulates according to the invention may be packaged in individual containers, for example in sachets, sticks, paper bags or bottles, and preferably in plastic ampoules.").

A POSA would have been motivated to select a sachet from among the various dosage forms disclosed in Liang 2006 and Lebon 2013 because of the well-known advantages a sachet provides. Sachet formulations are known to be a flexible method of drug administration. For example, WHO 2012 teaches that "powders and multiparticulates . . . provided in sachets" "possess great flexibility." *Id.* at 213. Similarly, Liu 2014 teaches that single-use sachet can "increas[e] the portability of a medicine," and can be beneficial for ease of administration. *Id.* at 1881-82. Thus, sachet formulations, including sustained release formulations, were routinely used in the art at the time of the priority date of the '079 patent. *See e.g.*, Bowles 2013 at 57 ("It can be seen that commercially available multiparticulates are mainly supplied for administration in capsules, sachets, or multi-use containers."); WHO 2012 at 215 (describing sachet as a formulation dosage form for sustained-release formulation); Balch 2010 at 195 (teaching the use of a sachet form of an extended-release formulation of morphine for treatment of chronic pain); Nexium 2014 Label at 6 (Nexium, a delayed-release formulation of esomeprazole magnesium, has a sachet dosage form).

A POSA would have had additional motivation to select a sachet for use with the disclosed GHB formulation because the prior art teaches that GHB for the treatment of narcolepsy needs to be formulated in large doses. *See, e.g.*, Liang 2006 at ¶ 31 (disclosing that the dosage needed for oxybate is "high"); Allphin 2012 at ¶ 29 (disclosing that GHB "requires a relatively high dose" and, therefore, "should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration"). Further, the prior art taught that sachet drug forms, when the contents are reconstituted as a suspension, are more easily swallowed compared to other conventional solid dosage forms.[2] *See, e.g.*, Bowles 2013 at 64 ("By using a suspension form, we allow for swallowability and reduce the challenges of other multiparticulate administration methods such as food compatibility, choking or the use of expensive proprietary technologies."). A POSA would therefore have been motivated to use a sachet form to facilitate administration of the large dose of GHB known to be required in the art for the treatment of narcolepsy.

Finally, a POSA would have been motivated to use a sachet for the storage of the disclosed GHB formulation because sachets were known to be a more convenient method for storage compared to an oral solution, and to provide enhanced stability characteristics. *See* Liu 2014 at 1881 (explaining that oral liquid may require refrigeration, and may require more preservatives than a sachet formulation); Bowles 2013 at 77 (explaining that oral solution requires many different excipients and in higher levels compared to solid dosage form). A POSA would have been motivated to provide the claimed GHB formulation in a sachet for this additional reason.

[2] For a discussion on administration with water and the resulting oral suspension, see *infra* Section V.A.1.d. and V.A.6.

For the foregoing reasons, this limitation would have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

d. **"mixing the formulation with water and orally administering the mixture to the patient,"**

Liang 2006 discloses that the GHB formulation can be mixed with water and orally administered to the patient. In discussing the immediate release component, Liang 2006 teaches that the GHB formulation can be a "powder . . . stirred into a drink or food along with the delayed/controlled release beads/pellets/mini tabs." *Id.* at ¶ 48. Water is the most common form of drink, and suspensions are routinely prepared using water. *See, e.g.*, PHARMACEUTICAL SUSPENSIONS at 45 ("Suspensions are prepared by insoluble solids in dispersion medium, mostly water."). Thus a POSA would have understood Liang 2006 to disclose mixing the contents of a sachet with water, which can then be orally administered to a patient.

Similarly, Lebon 2013 teaches that the GHB formulation can be mixed with a solution and orally administered to the patient. Lebon 2013 discloses that the granulates "may be ingested directly or may be dispersed in a solution, or mixed in dietary support such as yoghurt or a compote." *Id.* at col. 5:60-62. As discussed above, suspensions of a drug product were commonly made using water, and a POSA would have therefore understood Lebon 2013 to describe mixing the contents of a sachet with water, which can then be orally administered to a patient. *See, e.g.*, PHARMACEUTICAL SUSPENSIONS at 45.

In addition, mixing the contents of a sachet with water and orally administering the mixture to the patient was well known in the art. WHO 2012 teaches that a sachet can be used as a single-dose administration, and that one way of administering it is to "reconstitute the product with . . . boiled and cooled water." *Id.* at 212. Similarly, Bowles 2013 provides an overview of ways of administering multiparticulate formulations, including a sachet, one of which is

"administering a multiparticulate in a suspension." *Id.* at 59. Liu 2014 further teaches that "[m]ultiparticulates . . . presented in sachets or capsules. . . can be reconstituted in a drink to provide solutions or suspensions." *Id.* at 1881. A POSA would have understood that the multiparticulate formulations discussed in WHO 2012, Bowles 2013, and Liu 2014 are all intended for oral administration.

Further, the Nexium 2014 Label discloses step-by-step instructions for administering a sachet form of delayed-release esomeprazole magnesium. For oral administration, it teaches that one should "empty the contents of . . . a NEXIUM packet into a container containing water," "stir the packet contents into the water," "leave 2 to 3 minutes to thicken," and "stir and drink within 30 minutes." *Id.* at 6. The label also teaches that Nexium forms an "oral suspension." *Id.* In view of the disclosures in the art teaching administering a drug formulation stored in a sachet by mixing it with water, a POSA would have been motivated to administer the GHB formulation stored in a sachet by mixing it with water and administering it orally.

Thus, this limitation would have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

e. **"wherein the oxybate formulation comprises an immediate release component and a controlled release component"**

Liang 2006 is directed to a GHB formulation with both an immediate release and a controlled release component. Liang 2006 discloses that "[t]he dosage forms of the current invention comprise an immediate release component . . . wherein the immediate release component is present together with (or separated contained from) one or more pH sensitive delayed/controlled release particles." *Id.* at ¶ 27; *see id.* at ¶ 29 ("In one of the preferred embodiments, the composition comprises multiple delayed release pellets or beads (used interchangeably herein) and an immediate release component.). Liang 2006 further teaches that "combining the immediate

release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete . . . dose." *Id.* at ¶ 32. Liang 2006 further discloses that the "delayed/controlled release" particles and immediate release component can be "supplied as pre-mixed doses," thus comprising a single dosage. *Id.* at ¶ 33. Further, it discloses a preferred embodiment where "an immediate release component is combined with . . . delayed/ controlled release particles." *Id.* at ¶ 38.

Lebon 2013 discloses that the oxybate formulation can comprise an immediate release component and a controlled release component. Lebon 2013 discloses that "[t]he present invention relates to a granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2:25-29. Lebon 2013 further discloses that "[a]ccording to a particular embodiment, the core of the granulates may however comprise particles of gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2:51-53. A solid core supported by the gamma-hydroxybutyric acid or one of its salts, without any other excipients, would have been understood by a POSA to possess an immediate release profile.

Lebon 2013 further discloses granulates of GHB having a controlled release profile. Lebon 2013 discloses that adding a sustained-release coating "enables a modified or delayed release of the active constituents (modified-release granulates)." Lebon 2013 at col. 4:34-47 ; *see also* claims 5, 15. Lebon 2013 further discloses that the coating can consist of "copolymers of methacrylates and acrylates, Eudragit(R) S100, shellac, cellulose derivatives, in particular ethylcellulose, and acrylic derivatives." *Id.* at col. 4:38-41. Further, a POSA would understand that granulates of GHB with a controlled-release profile would need to be combined with GHB granulates having an immediate release profile in order to treat a patient suffering from narcolepsy.

For the reasons set forth above, claim 1 would have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

2. Claim 2

Claim 2, which depends on claim 1, further recites "wherein the orally administering occurs at night." Liang 2006 discloses that the described GHB formulations can be used for a once nightly dosing regimen. *See id.* at ¶ 12 ("With the compositions of the present invention, a patient does not need to wake up at night to take a second dose then go back to sleep."). Lebon 2013 discloses that GHB is administered at night for narcoleptic patients. *See id.* at col. 1:47-49 (describing the dosing regimen as involving "doses repeated every 3 to 4 hours, and in particular in the middle of the night for narcoleptic patients"). Further, a POSA would understand that a treatment for narcolepsy should be administered at night. For example, the Xyrem® 2014 Label discloses that the oral administration should occur at night. *See id.* at 3 (instructing patients to take the first dose at bedtime and the second dose 2.5 to 4 hours later), 4 ("Patients should take both doses of Xyrem while in bed and lie down immediately after dosing.").

Claim 2 would therefore have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

3. Claim 3

Claim 3, which depends on claim 1, further recites "wherein the oxybate formulation is mixed with water immediately prior to administration." Claim 3 is rendered anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 for the reasons discussed in claim 1. In addition, a POSA would have understood that the oxybate formulation would need to be mixed immediately prior to administration to avoid the negative effects of the particles settling out of suspension.[3] *See*

[3] For a discussion on why the mixture would result in a suspension, *see infra* Section V.A.6.

e.g., PHARMACEUTICAL SUSPENSION at 110 ("When left undisturbed for a long period of time the suspension particles will aggregate, sediment, and eventually cake."); Bladh 2007 at 640 ("the packet formulation was stable for up to 60 minutes after reconstitution."). The Nexium 2014 Label also instructs that the administration must happen "within 30 minutes" of the mixing with water. Nexium 2014 Label at 6.

Claim 3 would therefore have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

4. Claim 5

Claim 5, which depends on claim 1, further recites "wherein the administering promotes the patient to sleep for 6 to 8 hours."

Liang 2006 discloses administering the dosage in a way that promotes the patient to sleep for 6 to 8 hours. It teaches that the twice-nightly Xyrem® solution requires that the patient wake up after four hours to take a second dose. Liang 2006 at ¶ 3 ("Patients take an initial dose of sodium gamma-hydroxybutyrate around bedtime and must wake up four hours later to take a second dose."). A POSA would have therefore understood that Liang discloses the use of GHB to promote a total of approximately eight hours of sleep.

Similarly, Lebon 2013 discloses that the narcoleptic patient needs to take a dose of GHB every 3-4 hours in the middle of the night. *Id.* at col. 1:46-49. A POSA would have understood the disclosure in Lebon 2013 to mean that each dose of Xyrem® causes the patient to sleep for 3-4 hours, resulting in a total of 6-8 hours of sleep. *See* Xyrem® 2014 Label at 3 (instructing patients to take the first dose at bedtime and the second dose 2.5 to 4 hours later).

Further, to the extent a POSA would not understand Liang 2006 or Lebon 2013 as disclosing promoting the patient to sleep for 6-8 hours, it was well known in the art as of the priority date of the '079 patent that 6 to 8 hours of sleep per night was considered optimal for

patients taking sodium oxybate. For example, Mignot 2012 provides a review of methods of administering sodium oxybate to narcolepsy patients so that the patient can "fully consolidate a six to eight hour night." *Id.* at 746. Thus, Mignot 2012 would have provided a POSA with further motivation to promote the patient to sleep for 6 to 8 hours.

Claim 5 would therefore have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

5. Claim 6

Claim 6, which depends on claim 1, further recites "wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate." All of these dosages were disclosed by Liang 2006. A POSA would have understood that milliequivalent (mEq) measures the amount of solute in mg equal to 1/1000th gram of the equivalent weight of the substance. It can be converted to weight for any given solute. (mEq=(mg/atomic weight)*valence). According to this conversion, 36 mEq of oxybate is about 4.4 grams, 45 mEq is about 5.7 g, 60 mEq is about 7.5 g, and 70 mEq is about 8.8 g.

Liang 2006 discloses that "a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients." *Id.* at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1:46-47. Liang 2006 and Lebon 2013 therefore disclose dosing regimens for GHB falling within 4 g to 9 g.

Claim 6 would have therefore been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

6. Claim 7

Claim 7, which depends on claim 1, further recites "wherein the mixture is a suspension." Claim 7 is anticipated and/or obvious over Liang 2006 for the same reasons as claim 1. As discussed above, Liang 2006 discloses a sachet dosage form of GHB that is mixed with water. A

POSA would have understood that mixing the claimed formulation with water would necessarily result in a suspension. *See e.g.*, Bowles 2013 at 59 ("Wet administration of a multiparticulate is being taken to be administering a multiparticulate in a suspension."); Liu 2014 at 1881 ("Multiparticulates . . . presented in sachets or capsules. . . can be reconstituted in a drink to provide solutions or suspensions."). For the same reason, a POSA would understand that the sachet form disclosed in Lebon 2013 would be mixed with water to create a suspension of the mixture of GHB particles. *See id.* at col. 5:49-51 (disclosing a sachet); col. 5:60-61 (disclosing that the granulates "may be dispersed in a solution").

Claim 7 would therefore have been anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

7. Claim 8

Claim 8, which depends on claim 1, further recites "wherein the oxybate formulation further comprises an acid." Liang 2006 discloses an oxybate formulation that includes an acid, such as citric acid and malic acid.

Liang 2006 discloses adding acid to a sodium oxybate formulation. Specifically, Liang 2006 discloses that the solid GHB dosage form could be stored in a sachet, and that the formulation comprises an acid such as citric acid and malic acid. *Id.* at ¶ 55. Further, Liang 2006 claims a dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *Id.* at claim 3.

Further, this claim would have been obvious over Lebon 2013. A POSA would have been motivated to modify the GHB formulation disclosed in Lebon 2013 through the addition of acid.[4]

[4] For a detailed discussion on adding acid, *see infra* at Section V.B.1.e.

Claim 8 would therefore have been anticipated and/or obvious in view of Liang 2006 and the knowledge of a POSA.

8. Claim 9

Claim 9, which depends on claim 1, further recites "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid."

Liang 2006 discloses adding acid to a sodium oxybate formulation. Specifically, Liang 2006 discloses and claims a GHB dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *Id.* at claim 3.

Further, for the reasons set forth above for claim 8, a POSA would have been motivated to modify the GHB formulation disclosed in Lebon 2013 to include an acid, including the acids recited in claim 9, all of which were well-known in the art. *See, e.g.*, Liang 2006 at claim 3.[5]

Claim 9 would therefore have been anticipated and/or obvious in view of Liang 2006 and the knowledge of a POSA.

9. Claim 10

Claim 10 recites:

> "10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:
>
> administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:
>
> opening a sachet containing a solid oxybate formulation,

[5] For a detailed discussion on adding acid, *see infra* at Section V.B.1.e.

> mixing the formulation with water, and
>
> orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component."

Claim 10 is identical to claim 1 other than the preamble, which recites "[a] method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy."

To the extent that the preamble is limiting, it is disclosed by Liang 2006, which teaches that GHB can be used "in the treatment of narcolepsy." *Id.* at ¶ 1; *see also id.* at ¶¶ 2, 3, 5. Similarly, Lebon 2013 teaches that Xyrem® "is used for the treatment of narcolepsy in adult patients exhibiting cataplexy." *Id.* at col. 1:28-31. Lebon 2013 however explains that "the major drawback of GHB in terms of effectiveness is linked to its pharmacokinetic profile" which limits the effectiveness of GHB and requires the administration of multiple doses repeated every few hours. *Id.* at col. 1:36-52. Lebon 2013 explains that the object of the present invention is therefore to provide a "novel galenic form based on gamma-hydroxybutyric acid or one of its salts (in particular sodium) which makes it possible to circumvent the aforementioned drawbacks" associated with the administration of GHB. *Id.* at col. 1:64-67. Further, the prior art taught that sodium oxybate was useful for the treatment of cataplexy and excessive daytime sleepiness associated with narcolepsy. *See, e.g.*, Xyrem® 2014 Label at 3 (teaching the use of sodium oxybate to treat cataplexy and excessive daytime sleepiness in narcolepsy).

Because the remaining limitations of claim 10 are identical to the limitations of claim 1, claim 10 is anticipated and/or obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA as set forth above for claim 1.

10. Claim 11

Claim 11, which depends on claim 10, further recites "wherein the orally administering occurs at night." This limitation is also recited in claim 2. Claim 11 is rendered anticipated and/or obvious for the same reasons as claim 2.

11. Claim 12

Claim 12, which depends on Claim 10, further recites "wherein the oxybate formulation is mixed with water immediately prior to administration." This limitation is also recited in claim 3. Claim 12 is rendered anticipated and/or obvious for the same reasons as claim 3.

12. Claim 14

Claim 14, which depends on claim 10, further recites "wherein the administering promotes the patient to sleep for 6 to 8 hours." This limitation is also recited in claim 5. Claim 14 is rendered anticipated and/or obvious for the same reasons as claim 5.

13. Claim 15

Claim 15, which depends on claim 10, further recites "wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate." This limitation is also recited in claim 6. Claim 15 is rendered anticipated and/or obvious for the same reasons as claim 6.

14. Claim 16

Claim 16, which depends on claim 10, further recites "wherein the mixture is a suspension." This limitation is also recited in claim 7. Claim 16 is rendered anticipated and/or obvious for the same reasons as claim 7.

15. Claim 17

Claim 17, which depends on claim 10, further recites "wherein the oxybate formulation further comprises an acid." This limitation is also recited in claim 8. Claim 17 is rendered anticipated and/or obvious for the same reasons as claim 8.

16. Claim 18

Claim 18, which depends on claim 17, further recites "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid." This limitation is also recited in claim 9. Claim 18 is rendered anticipated and/or obvious for the same reasons as claim 9.

B. The '782 Patent

As set forth in Appendix B and as discussed below, all of the asserted claims of the '782 patent (claims 1-24) are invalid as obvious over the prior art in view of the knowledge of a POSA. The asserted claims of the '782 patent, according to Plaintiffs' infringement contentions, are generally directed to a formulation or a unit dose of GHB with specific viscosity enhancing agents, acid, lubricants, amounts of GHB, or blood concentrations of GHB following administration of the claimed formulation.

Further, for the reasons discussed in Section VII and Appendix B, the '782 patent is entitled to a priority date no earlier than March 23, 2021, and all of the asserted claims of the '079 patent are invalid as anticipated by and/or obvious over at least Avadel's '866 patent, '062 patent, and '986 patent publication under the correct priority date.

1. Claim 1

Asserted claim 1 of the '782 patent is invalid as obvious over Lebon 2013 and/or Liang 2006 in view of the knowledge of a POSA. Claim 1 is reproduced below:

1. A formulation of gamma-hydroxybutyrate comprising:

> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;
>
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

In light of the art as of the priority date of the '782 patent, a POSA would have had the requisite knowledge to develop the claimed formulation of GHB disclosed in claim 1, would have had the requisite motivation to do so, and would have had a reasonable expectation of success in doing so.

Liang 2006 is directed to an oral solid dosage form of GHB "containing an immediate release component of [GHB], and one or more delayed/controlled release components of [GHB]." Liang 2006 at Abstract. Liang 2006 states that "an immediate release component in the form of particles and one or more pH sensitive delayed/controlled release particles are supplied as pre-mixed doses." *Id.* at ¶ 33. Liang 2006 discloses adding a viscosity enhancing agent, and specifically "suspending agents, thickening agents, [and] gelling agents," to a sodium oxybate formulation. *Id.* at ¶ 53. Liang 2006 also discloses adding acid to a sodium oxybate formulation. Specifically, Liang 2006 discloses and claims a dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *See, e.g.*, *id.* at claim 3.

Thus, Liang 2006 discloses all of the limitations of claim 1 other than a viscosity enhancing agent and acid that are separate from the immediate release and modified release particles.

Although Liang 2006 is listed on the face of the '782 patent, it was not cited or discussed by the Examiner during prosecution.

Lebon 2013 describes "granulate[s] of gamma-hydroxybutyric acid or of one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported gamma-hydroxybutyric acid or one of its salts is supported." Lebon 2013 at col. 2:25-29. Lebon 2013 thus discloses granulates of GHB acid or one of its pharmaceutically acceptable salts, capable of immediate release of GHB. *Id.* It describes granulates as "a shape which is quite regular, homogeneous and quasi-spherical," "intended for oral administration," and "hav[ing] a characteristic structure of the core/shell type, wherein the core is of a different nature from the active constituents which form the shell." *Id.* at col. 2:33-43. Lebon 2013 further discloses that granulates of GHB may optionally have modified-release characteristics. *Id*. at col. 4:34-44. Further, Lebon 2013 discloses the "development of a novel oral multi-particle form" that consists of granulates intended for oral administration. *Id.* at col. 2:63-67.

Thus, Lebon 2013 discloses all of the limitations of claim 1 other than a viscosity enhancing agent and an acid that are separate from the immediate release and modified release particles. Although Lebon 2013 is listed on the face of the '782 patent, it was not cited or discussed by the Examiner during prosecution.

Allphin 2012 is directed to "controlled release dosage forms for delivery of a drug selected from GHB and pharmaceutically acceptable salts . . . [that] may incorporate both controlled release and immediate release formulations in a single unit dosage form." Allphin 2012 at Abstract. Allphin 2012, in describing Xyrem® sodium oxybate oral solution, discloses adding malic acid to a formulation of sodium oxybate in order to adjust the pH to 7.5. Allphin 2012 at ¶

9. The label for Xyrem® states that the oral solution is made up of sodium oxybate, purified water, and malic acid only. Xyrem® 2014 Label at 25.

During prosecution of the '782 patent, Allphin 2012 was cited and described by the Examiner as disclosing each and every limitation of the '782 patent except for a "viscosity enhancing agent and an acid [that] are separate from the GHB-containing particles." 8/2/2021 Applicant Arguments/Remarks Made in an Amendment, at 7-8 (noting that "[t]he Examiner cites *Allphin* for allegedly teaching formulations and unit doses that contain immediate release and modified release GHB-containing portions, a viscosity enhancing agent and an acid"). The Examiner repeated this observation in the "Reasons for Allowance": "The closest prior art, Allphin . . . discloses controlled release dosage forms that may incorporate both controlled release and immediate release (IR) formulations in a single unit dosage form," but "does not teach[] or suggest the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles." 9/9/2021 Notice of Allowance at 2.

As set forth below, the addition of an acid and/or a viscosity enhancing agent separate from the immediate and modified release particles was well-known in the art as part of a multi-particulate drug form. Further, a POSA would have been motivated to modify the formulations in Liang 2006 and/or Lebon 2013 to include an acid and/or viscosity enhancing agent separate from the immediate and modified release particles of GHB with a reasonable expectation of arriving at the claimed formulation.

a. **"A formulation of gamma-hydroxybutyrate"**

Liang 2006 and Lebon 2013 both disclose a formulation of gamma-hydroxybutyrate. Liang 2006 is "directed to pulse-released formulations of oxybate, or gamma-hydroxybutyric acid, salts." Liang 2006 at ¶ 1. Lebon 2013 is directed to " a granulate of gamma-hydroxybutyric acid or of one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on

which is supported the gamma-hydroxybutyric acid or one of its salts." Lebon 2013 at col. 2:25-29. Furthermore, Lebon 2013 claims a "granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, comprising: a solid core; and a shell layer constituted of the gamma-hydroxybutyric acid or one of its salts that is deposited around and supported by the solid core . . . ." *Id.* at claim 1. Thus, this claim limitation was disclosed by both Liang 2006 and Lebon 2013.

b. **"a plurality of immediate release particles comprising gamma-hydroxybutyrate"**

Liang 2006 and Lebon 2013 also both disclose a formulation of gamma-hydroxybutyrate comprising a plurality of immediate release particles comprising gamma-hydroxybutyrate. For example, Liang 2006 discloses that the "immediate release component" can be "in the form of particles." Liang 2006 at ¶ 33. Liang 2006 also discloses that the immediate release component may be a solid pellet, bead or minitablet or the like. *Id.* ¶ 56. Thus, a POSA would have understood that Liang 2006 disclosed a plurality of immediate release particles.

Lebon 2013 discloses that "[t]he present invention relates to a granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2:25-29. Lebon 2013 further discloses that "[a]ccording to a particular embodiment, the core of the granulates may however comprise particles of gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2:51-53. A solid core supported by the gamma-hydroxybutyric acid or one of its salts, without any other excipients, will be understood to display an immediate release profile. Lebon 2013 also discloses that the granulates are for "a novel oral multi-particle form," *id*. at col. 2:63-67; and that they can be packaged in individual containers, "such as in sachets, sticks, paper

bags, or bottles," *id.* at col. 5:49-51, 8:7-8. Lebon 2013 therefore also describes having a plurality of the disclosed immediate release particles.

Thus, this claim limitation was disclosed by both Liang 2006 and Lebon 2013.

c. **"a plurality of modified release particles comprising gamma-hydroxybutyrate"**

Liang 2006 and Lebon 2013 both teach a formulation of gamma-hydroxybutyrate comprising a plurality of modified release particles comprising gamma-hydroxybutyrate. Liang 2006 discloses that the "delayed/controlled release components are particles containing GHB." *See, e.g.*, Liang 2006 at claim 2. "Specifically, at the essence of the present invention is a dosage form comprising one or more pH sensitive delayed/controlled release particles (e.g., beads, granules, minitabs or pellets)." Liang 2006 at ¶ 26. Thus, a POSA would have understood that Liang 2006 disclosed a plurality of modified release particles.

Lebon 2013 is directed to a granulate of GHB acid with a modified or delayed release characteristic. Lebon 2013 discloses that adding a sustained-release coating "enables a modified or delayed release of the active constituents (modified-release granulates)." Lebon 2013 at col. 4:34-47 ; *see also* claims 5, 15. Lebon 2013 further discloses that the coating can consist of "copolymers of methacrylates and acrylates, Eudragit(R) S100, shellac, cellulose derivatives, in particular ethylcellulose, and acrylic derivatives." *Id.* at col. 4:38-41. Lebon 2013 also discloses that the granulates are for "a novel oral multi-particle form," *id.* at col. 2:63-64; and that they can be packaged in individual containers, "such as in sachets, sticks, paper bags, or bottles," *id.* at col. 5:49-51, 8:7-8. Lebon 2013 therefore also discloses having a pluarilty of modified release particles.

Thus, this claim limitation was disclosed by both Liang 2006 and Lebon 2013.

d. **"a viscosity enhancing agent . . . wherein the viscosity enhancing agent [is] separate from the immediate release particles and the modified release particles"**

The prior art teaches the addition of a viscosity enhancing agent wherein the viscosity enhancing agent is separate from the immediate release particles and the modified release particles.

Liang 2006 discloses that pharmaceutically acceptable excipients such as "suspending agents/thickening agents/gelling agents" may be used in the formulations of GHB. *See* Liang 2006 at ¶¶ 53, 55. Liang 2006 also discloses the use of other common viscosity enhancing agents such as xanthan gum, microcrystalline cellulose, hydroxypropylmethylcellulose, and hydroxypropyl cellulose. *Id.*; *see also* '782 patent claim 2 (identifying these excipients as viscosity enhancing agents); PHARMACEUTICAL SUSPENSION at 113 (disclosing excipients as suspending or viscosity enhancing agents).

Further, to the extent that the claims are construed to cover oral suspensions, a POSA would have been motivated to add such a viscosity enhancing agent to improve the physical stability of the oral suspension. *See* PHARMACEUTICAL SUSPENSION at 110-12 (stating that viscosity enhancing agents are often added to formulations containing a plurality of drug particles for oral suspension to improve the physical stability of an oral suspension and decrease sedimentation rate). Adding a viscosity enhancing agent to an oral suspension is a common pharmaceutical practice in order to help maintain the suspension and prevent the suspended material from settling. *See* PHARMACEUTICAL DOSAGE FORMS 1996 at 151, 161 (teaching that "a typical suspension" may contain a "suspending agent" and that "[s]uspending agents are used to impart increased viscosity and retard sedimentation" and can include "cellulose derivatives, clays, natural gums, synthetic gums, and miscellaneous agents"). For that reason, the inclusion of a viscosity enhancing agent was a well-established technique commonly used in the art. *See e.g.*, Roorda 1996 at Abstract, col. 7:43-62 (disclosing a formulation of a controlled-release, anesthetic composition for localized

application comprising an even suspension prepared by mixing minipellets with an aqueous solution containing a viscosity-elevating solute); AlHusban 2011 at 627 (disclosing adding viscosity enhancing agents such as gelatin, carrageenan, and alanine to the suspending solution to formulate the oral disintegrating tablet made of enteric coated multiparticulate); Dang 2007 at ¶ 92 (disclosing formulations for intranasal or ocular pharmaceutical compositions with "one or more water soluble viscosity enhancing agents"). These viscosity enhancing agents were often added to formulations containing a plurality of drug particles for oral suspension to improve the physical stability of an oral suspension and decrease sedimentation rate. PHARMACEUTICAL SUSPENSIONS at 110-12.

Viscosity enhancing agents were also disclosed in solid formulations to be prepared for oral suspension in a liquid. For example, Mehta 2014 is directed at an oral methylphenidate powder consisting of immediate and modified release particles for reconstitution into an oral aqueous sustained release formulation. Mehta 2014 at Abstract. Mehta 2014 discloses that the powder blend can contain "suspending agents." *Id.* at ¶ 78. A POSA would have understood suspending agent to encompass viscosity enhancing agent.

It would thus have been obvious to a POSA for the viscosity enhancing agent to be separate from the immediate release and modified release particles. Because the role of the viscosity enhancing agent is to modify the liquid in which the particles are added to enhance the stability of the oral suspension prior to administration of the immediate and modified release particles, a POSA would have been motivated to add the viscosity enhancing agent as a separate component from the immediate and modified release particles. In addition, it would have been obvious to try to formulate the viscosity enhancing agent to be separate from the immediate release and modified

release particles, as there are a finite number of ways to include the viscosity enhancing agent, and each way would have been obvious.

The prior art discloses the addition of a viscosity enhancing agent separate from the particles containing the drug product. For example, Gandhi 2011 is directed to a sustained release oral liquid suspension dosage form of pharmaceutical active ingredients. Gandhi 2011 at col. 1:3-5. It is directed specifically to active ingredients of high solubility to be administered once daily or twice daily. *Id.* at col. 1:19-21. Gandhi 2011 specifies that the viscosity enhancing agent is part of the aqueous media *separate* from the sustained release pellets. *See id.* at col. 5:13-18 ("Wherein the sustained release pellets are suspended with viscosity modifying agent or suspending agent. . . in a suspending media."); col. 5:27-29. It further teaches that "viscosity modifying agent . . . [is] also called as [sic] suspension stabilizers and they are intended to ensure that the individual doses removed have constant active ingredient content." *Id.* at col. 10:13-16. As another example, Mehta 2014 discloses that the powder blend can contain a diluent granule, ion exchange resin complex, and optionally "suspending agents." Mehta 2014 at ¶ 78.

Because adding a viscosity enhancing agent separately from the immediate and modified release particles was within the general knowledge of a POSA and was a more efficient manner of achieving the desired effect from such an agent, a POSA would have been motivated to modify the GHB formulations disclosed in Liang 2006 and Lebon 2013 to include a viscosity enhancing agent separate from the immediate and modified release particles.

e. **"an acid . . . wherein the acid [is] separate from the immediate release particles and the modified release particles"**

The prior art taught the addition of an acid wherein the acid is separate from the immediate release particles and the modified release particles.

The asserted '782 patent describes the addition of the acid as a pH-modifier: "[D]ue to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6 . . . In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating." '782 patent at col. 5:39-49. This ability of an acid to lower the pH and protect an enteric coating was well-known in the art. *See, e.g.*, Liang 2006 at ¶ 72 (disclosing adding acidifiers to "prevent[] these alkalinic salt from reacting with the enteric coat material").

Liang 2006 discloses and claims a dosage form comprising an acid, *i.e.*, "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *See, e.g.*, Liang 2006 at claim 3. Liang 2006 discloses the use of these acids for numerous reasons, including to adjust the target release/dissolution pH, *id.* at ¶ 88, to improve absorption in the gastrointestinal tract, *id.* at ¶ 68, as well as for gastro-stability of the GHB formulations. *Id.* at ¶ 72. The use of such acids in the barrier coat of the GHB formulations prevents the "release [of] any sodium gamma-hydroxybutyrate at pH 1.1 and pH 6.0 for up to 3 hours," thus improving the gastro-stability of the GHB formulations. *Id.* at ¶ 111; *see also id.* at ¶ 114.

A POSA would have been motivated to use acid as a pH-modifier in modified-release formulations, such as with gamma hydroxybutyrate, for controlling the dissolution of the formulation and for stability. In particular, a POSA would have been motivated to adjust the pH of modified release formulations of gamma hydroxybutyrate using acid given the knowledge of the buffering effect of oxybate due to its large dosage and "strongly alkalinic" properties. *See e.g.*,

Allphin 2012 (discussing the "high doses" required of sodium oxybate); Liang 2006 at ¶ 72 (referring to GHB salts as "strongly alkalinic").

As a result, the prior art contained numerous examples of modified-release formulations with acid in their formulation to modify the pH, thereby controlling the dissolution of the formulation and improving stability. For example, Allphin 2012 discloses the use of an acid to adjust the pH of sodium oxybate oral solutions. *See* Allphin 2012 at ¶ 9. Kawashima 1999 discloses a controlled-release suspension of ibuprofen-Eudragit RSPM microspheres. *Id*. at 25. The authors noted that the acidic pH was a prerequisite for the formulation of a stable suspension. *Id.* at 28. In addition to stabilizing the microparticle suspension, the acidity of the aqueous phase also prevented diffusion or loss of the acidic drug, ibuprofen (pKa5.2), into the suspending vehicle. *Id.* at 34. Further, Nykanen 1999 teaches adding an organic acid to the formulation. *Id.* at 251. And Nykanen 2001 and 2004 disclose adding citric acid to the formulation. Nykanen 2001 at 155; Nykanen 2004 at 268.

To the extent that the claims are construed to cover oral suspensions, a POSA would have been motivated to add acid separate from the immediate release particles and the modified release particles to, for example, modify the pH or modify the flavor of such an oral suspension, as described below.

(1) A POSA would have been motivated to add acid separately from the particles as a buffering agent

Acids were commonly added as a buffering agent to oral suspensions separately from the drug pellets containing active ingredient. *See, e.g.*, PHARMACEUTICAL DOSAGE FORMS 1996 at 151, 168 (teaching that "a typical suspension" may contain a "buffer system," and further teaching that acids such as citric acid are "typical buffering agents"). These acids were often added separately in oral suspensions to maintain the integrity of the coating of any modified release

components that dissolved in a neutral pH. As discussed above, oxybate was known to be alkalinic, and the addition of acids separately from the modified release components was known to prevent the modified release component, such as an enteric coating, from prematurely dissolving.

The use of an acid separate from the immediate and modified release components was disclosed in the art. *See, e.g.*, Gandhi 2011 at col. 1:3-5. In one example, the suspension formulation consists of "extended release granules" and *separately* "citric acid monohydrate." *Id.* at Ex. 3. Another example is Mehta 2014, which discloses the buffering agent as separate from the immediate release and modified release ion-exchange complex beads. *See* Mehta 2014 at Abstract ("a blend containing a combination of an uncoated methylphenidate-ion exchange resin complex, a barrier coated methylphenidate-ion exchange resin complex matrix, and a water soluble buffering agent."); ¶ 42 ("In one embodiment, the powder blend further comprises water-soluble diluent granules which contain at a minimum, a water soluble buffering agent"). Mehta 2014 further discloses that the buffering agent is "selected from the group consisting of one or more of a pharmaceutically acceptable acid consisting of citric acid, ascorbic acid, acetic acid, tartartic acid, phosphoric acid, a pharmaceutically acceptable salt of citric acid, ascorbic acid, acetic acid, tartartic acid, phosphoric acid, or a mixture of said pharmaceutically acceptable acid or salt, and mixtures thereof." *Id.* at ¶ 42, claim 15. Acid is also incorporated separately from the immediate and modified release components of Nexium®. *See* Nexium 2014 Label at 14.

(2) **A POSA would have been motivated to add acid separately from particles as a flavoring agent**

Acids were also routinely added for flavor modification purposes. Lebon 2013 discloses that for modified release formulations of gamma hydroxybutyrate, additives such as sweeteners, lubricants, flavourings, and colorings" may be added to the finished granulates before being

packaged into sachet or plastic ampules. Lebon 2013 at 8:3-8. It was also well known in the prior art that acid could advantageously be used as a flavor modifier. Sohi 1991 is a review article that discusses various methods of taste masking and teaches that citric acid can be used to mask the bitter taste of commonly associated with drugs. *Id.* at 430. It also lists citric acid as a flavor modifying agent in at least three examples. *Id.* at 431. Sohi 1991 also discusses a formulation of ibuprofen suspension that contains acid for the dual purpose for buffering and for taste masking. *Id.* at 433 ("The [ibuprofen suspension] composition is taste masked by primary taste-masking agents (sucrose/ sorbitol/glycerin) and also contains a buffer acid (citric acid/phosphoric acid) to adjust the pH of the suspension between 1.5 to 4.1.").

Further, Lebon 2013 teaches that additives such as flavorings "which may or may not be in the form of granulates may be added to the granulates in a mixer." Lebon 2013 at col 8:3-6. Because acid can be used as a flavor modifier, a POSA would have been motivated to add the acid separately from the granulates, consistent with its use in the prior art. Thus, a POSA would have been motivated to add an acid to the claimed formulation separately with a reasonable expectation of success that it would achieve flavor modification.

Claim 1 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 in view of the knowledge of a POSA.

2. Claim 2

Claim 2, which depends on claim 1, further recites "wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof."

Liang 2006 discloses adding a viscosity enhancing agent to a sodium oxybate formulation. Specifically, Liang 2006 discloses a dosage form comprising viscosity enhancing agents such as

xanthan gum, microcrystalline cellulose, hydroxypropylmethylcellulose, and hydroxypropyl cellulose. Liang 2006 at ¶¶ 53, 55; *see also*, *e.g.,* PHARMACEUTICAL SUSPENSION at 112 ("Generally used suspending agents in suspension include cellulosic derivatives (methylcellulose, carboxymethylcellulose, hydroxyethyl cellulose, and hydroxypropyl methylcellulose), synthetic polymers (carbomers, polyvinylpyrrolidone poloxamers, and polyvinyl alcohol), and polysaccharides and gums (alginates, xanthan, guar gum, etc.)."). It also discloses microcrystalline cellulose as a common viscosity enhancing agent. *Id*. at 113.

Another example is Gandhi 2011, which discloses examples of viscosity enhancing agent, including "xanthan gum," "hydroxy ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl- or ethylhydroxyethyl cellulose, carboxymethyl cellulose," and "microcrystalline cellulose." Gandhi 2011 at col. 10: 21-27.

Claim 2 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

3. Claim 3

Claim 3, which depends on claim 1, further recites: "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid."

Liang 2006 discloses adding an acid to a sodium oxybate formulation. Specifically, Liang 2006 claims a dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." Liang 2006 at claim 3; *see also* Mehta 2014 at ¶ 106 (disclosing that "[t]he pH adjuster may be a buffering agent which may include one of the following or may be selected from the group consisting of one or more of a pharmaceutically acceptable acid selected from the group consisting of citric acid, ascorbic acid, acetic acid, tartartic

acid, phosphoric acid"); PHARMACEUTICAL SUSPENSION at 86 (listing common acid used as a buffering agent, including boric acid, malic acid, citric acid, tartaric acid, phosphoric acid, among others).

Claim 3 would therefore have been obvious in light of Liang 2006 and/or Lebon 2013 and knowledge of a POSA.

4. Claim 4

Claim 4, which depends on claim 1, further recites: "wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate."

Liang 2006 discloses adding a lubricant to a sodium oxybate formulation. Specifically, Liang 2006 discloses that the lubricant may be "talc, sodium lauryl fumurate, fumed silicon dioxide, colloidal silica, titanium dioxide, kaolin, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, and sodium lauryl sulfate." Liang 2006 at ¶ 61. Lebon 2013 also discloses adding a lubricant to a sodium oxybate formulation. It teaches that a lubricant "may be made in particular of talc, magnesium stearate, silica derivatives (in particular Aerosil R) or waxes." Lebon 2013 at col. 4:45-52; *see also* Allphin 2012 at ¶ 45 (disclosing lubricants "selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate).

Claim 4 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

5. Claim 5

Claim 5, which depends on claim 1, further recites: "wherein the lubricant is magnesium stearate."

Liang 2006 and Lebon 2013 disclose the use of magnesium stearate as a lubricant. Liang 2006 at ¶ 61; Lebon 2013 at col. 4:45-52.

Claim 5 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

6. Claim 6

Claim 6, which depends on claim 1, further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate."

Liang 2006 discloses that the daily dose of Xyrem® is 4.5 to 9 grams. Liang 2006 at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1:46-47. Further, the '079 patent identifies no unique or unexpected properties associated with the recited range of oxybate amount, and a POSA would have arrived at the recited dosage ranges from the ranges disclosed in Liang 2006 as a result of routine optimization. Further, the prior art taught that a single dose of GHB can have "a range of about 500 mg to about 12 g of drug." Allphin 2012 at ¶ 42. Thus, a POSA would have also been motivated to modify the amount of sodium oxybate in the single daily dose described in Liang 2006 to arrive at the claimed range of 4.0 g to 12.0 g of sodium oxybate.

Claim 6 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

7. Claim 7

Claim 7, which depends on claim 1, further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium gamma-hydroxybutyrate." Liang 2006 discloses that the daily dose of Xyrem® is 4.5 to 9 grams. Liang 2006 at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1:46-47.

Claim 7 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

8. Claim 8

Claim 8, which depends on claim 1, further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate." Liang 2006 discloses that the daily dose of Xyrem® is 4.5 to 9 grams. Liang 2006 at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1:46-47.

Claim 8 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

9. Claim 9

Claim 9, which depends on claim 1, further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate." Liang 2006 discloses that the daily dose of Xyrem® is 4.5 to 9 grams. Liang 2006 at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1:46-47.

Claim 9 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

10. Claim 10

Claim 10, which depends on claim 1, further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate." Liang 2006 discloses that the daily dose of Xyrem® is 4.5 to 9 grams. Liang 2006 at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1:46-47.

Claim 10 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

11. Claim 11

Claim 11, which depends on claim 1, further recites: "wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL."

A blood concentration of 40 mg/mL is equivalent to 40,000 mg/L. A POSA would thus have understood a concentration of 40 mg/mL of GHB to be virtually impossible to achieve, or at least highly toxic to the human body. *See e.g.*, Jones 2009 at 332 (describing concentration in blood of ~900 mg/L of GHB as "probably . . . fatal"). Thus, a POSA would have understood the claimed limitation to mean that the blood concentration after 8 hours would be at least 10 mg/L.

This limitation is disclosed in Allphin 2012. Allphin 2012 teaches an embodiment for which "administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 µg/mL." Allphin 2012 at ¶ 35. It further specifies that the controlled release form can " provid[e] plasma concentrations of at least 10 µg/mL over . . . up to about 8 hours." *Id.* A POSA would thus have understood that the claimed range is disclosed in Allphin 2012. A POSA would further have been motivated to combine Liang 2006 and/or Lebon 2013 with Allphin 2012 because they are directed to a sustained release formulation of sodium oxybate.

Claim 11 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and in view of Allphin 2012.

12. Claim 12

Claim 12, which depends on claim 1, further recites: "wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL."

A blood concentration of 30 mg/mL is equivalent to 30,000 mg/L. For the same reasons discussed above for Claim 11, a POSA would thus have understood the claimed limitation to mean that the blood concentration after 8 hours would be at least 15 mg/L.

This claimed limitation is disclosed in Allphin 2012. Allphin 2012 teaches embodiment for which "administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 µg/mL." Allphin 2012 at ¶ 35. It further specifies that the controlled release form can "provid[e] plasma concentrations of at least 10 µg/mL over . . . up to about 8 hours." *Id.* Since the claimed range of sodium oxybate blood concentration fall within this range, a POSA would thus have understood that the claimed range is disclosed in Allphin.

Further, Figures 12 and 14 in Allphin 2012 further discloses a blood concentration within the claimed range 8 hours after administration. Fig. 12 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form (Treatment B) at a daily dose of 6 g. Allphin 2012 at ¶¶ 22, 99.

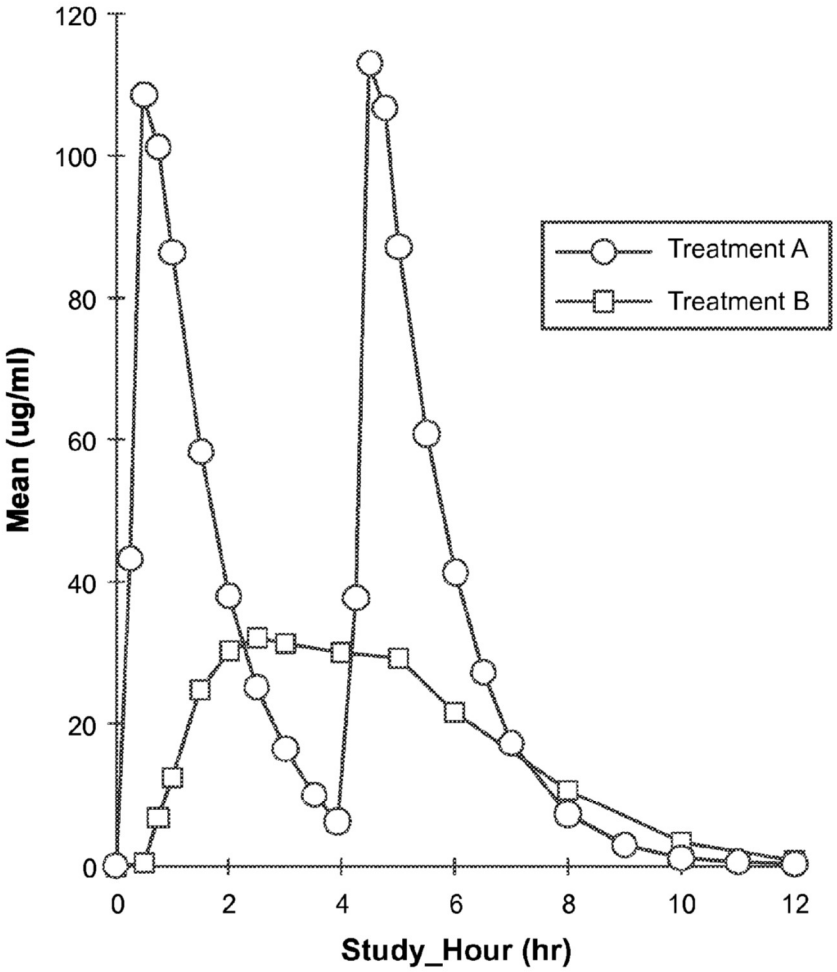

FIG. 12

FIG. 14. provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral Solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E). *Id.* at ¶ 24.

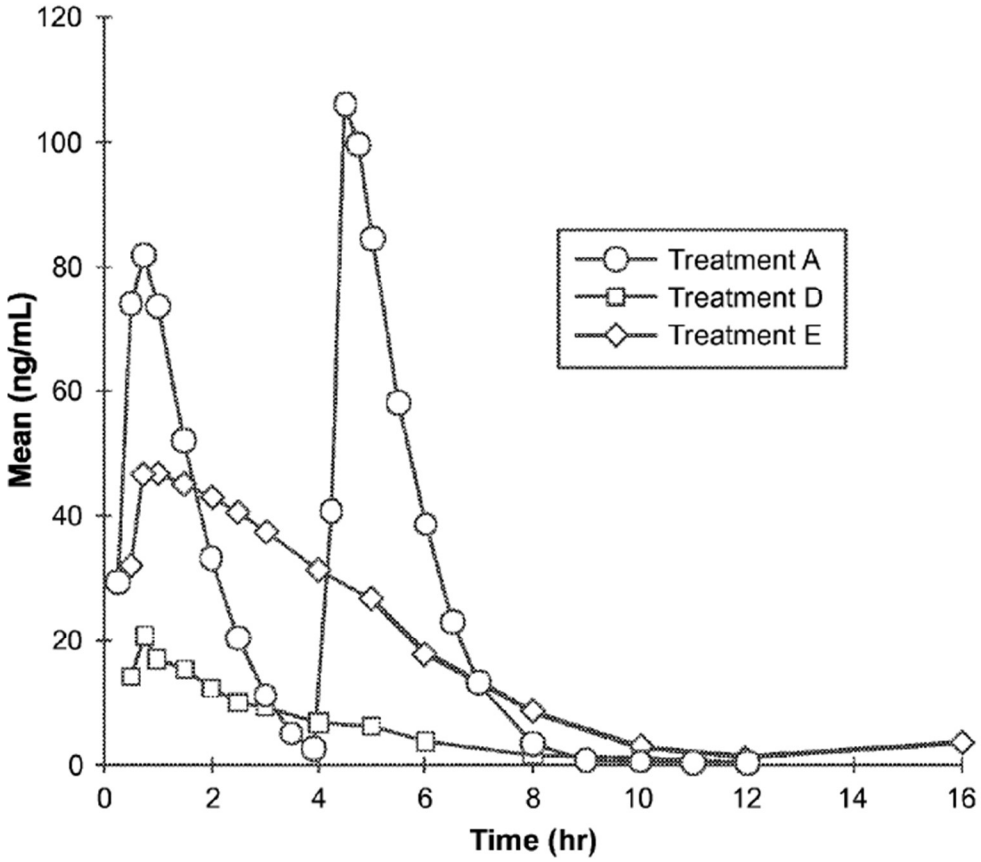

FIG. 14

By comparing Fig. 12 and Fig. 14, one would understand that at least for Treatment E (treatment group with a daily dosage of 8 g), the plasma concentration of sodium oxybate 8 hours after administration is around 15 μg/mL, or 15 mg/L.[6] Thus, a POSA would have understood that the claimed range of plasma concentration is disclosed in Allphin 2012. A POSA would further have been motivated to combine Liang 2006 and/or Lebon 2013 with Allphin 2012 because they are directed to a sustained release formulation of sodium oxybate.

[6] A POSA would understand the unit "ng/mL" in Fig. 14 is a typo and should be "μg/mL" instead. Table 6, which contains a summary of pharmacokinetic data presented in Figure 14, shows all units in μg/mL.

Claim 12 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 in view of Allphin 2012.

13. Claim 13

Claim 13, which depends on claim 1, further recites: "wherein the formulation is a multiparticulate composition."

Liang 2006 discloses that "the immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed-controlled release particles." *Id.* at ¶ 47. Lebon 2013 discloses that the invention could be used for a "novel oral multi-particle form." Lebon 2013 at col. 2:63-64. A POSA would thus have understood Liang 2006 and Lebon 2013 to disclose a multiparticulate formulation.

Claim 13 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

14. Claim 14

Claim 14 recites:

> A unit dose comprising a formulation of gamma-hydroxybutyrate, wherein the formulation comprises:
>
> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
> a viscosity enhancing agent; and
> an acid;
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

Claim 14 is identical to claim 1 other than the preamble, which recites "[a] unit dose comprising a formulation of gamma-hydroxybutyrate, wherein the formulation comprises."

To the extent the preamble is limiting, it is disclosed by Liang 2006 and Lebon 2013. Liang 2006 discloses that "[c]ombining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete once-nightly

or once-daily dose," and "combining" can mean "supplying and consuming all components . . .simultaneously in the same presentation or dosage form." Liang 2006 at ¶ 32.

Similarly, Lebon 2013 discloses that the granulates claimed can be formulated into a unit dose, and further explains that to mean the dose "per individual container containing the granulates." *Id.* at col. 5:53-57.

Claim 14 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

15. Claim 15

Claim 15, which depends on claim 14, further recites: "wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof." This limitation is also recited in claim 2. Claim 15 is rendered obvious for the same reasons as claim 2.

16. Claim 16

Claim 16, which depends on claim 14, further recites: "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid." This limitation is also recited in claim 3. Claim 16 is rendered obvious for the same reasons as claim 3.

17. Claim 17

Claim 17, which depends on claim 14, further recites: "wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate." This

limitation is also recited in claim 4. Claim 17 is rendered obvious for the same reasons as claim 4.

18. Claim 18

Claim 18 , which depends on claim 14, further recites: "wherein the lubricant is magnesium stearate." This limitation is also recited in claim 5. Claim 18 is rendered anticipated and/or obvious for the same reasons as claim 5.

19. Claim 19

Claim 19, which depends on claim 14, further recites: "wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL." This limitation is also recited in claim 12. Claim 19 is rendered obvious for the same reasons as claim 12.

20. Claim 20

Claim 20 recites, which depends on claim 14, further recites: "wherein the unit dose comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate." This limitation is also recited in claim 6. Claim 20 is rendered obvious for the same reasons as claim 6.

21. Claim 21

Claim 21, which depends on claim 14, further recites: "wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate." This limitation is also recited in claim 8. Claim 21 is rendered obvious for the same reason as claim 8.

22. Claim 22

Claim 22, which depends on claim 14, further recites: "wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate."

This limitation is also recited in claim 9. Claim 22 is rendered obvious for the same reason as claim 9.

23. Claim 23

Claim 23, which depends on claim 14, further recites: "wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate." This limitation is also recited in claim 10. Claim 23 is rendered obvious for the same reason as claim 10.

24. Claim 24

Claim 24, which depends on claim 14, further recites: "wherein unit dose is a sachet."

Liang 2006 discloses that the immediate release component can be administered in, among other forms, a sachet. Liang 2006 further discloses, however, that the immediate release and controlled release components can be a pre-mixed powder. *Id.* ¶ 47 ("[T]he immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed-controlled release particles"); *id.* at ¶ 48 ("[T]he immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion."). Thus, to the extent that Jazz contends that its disclosure in the priority application is sufficient to disclose this limitation, then Liang 2006's disclosure of the use of sachets for the storage of solid oxybate formulations comprising both immediate and "delayed/controlled release" formulations would likewise disclose this limitation.

Likewise, Lebon 2013 also discloses the use of a sachet to store the GHB formulation. Lebon 2013 teaches that granulates may be packaged in "individual containers, for example in sachets," and that a unit dose is the dosage "per individual container containing the granulates." *Id.* at col. 5:49-51; 5:53-57. Thus, a POSA would thus have understood that Lebon 2013 discloses this limitation.

A POSA would have been motivated to select a sachet from among the various dosage forms disclosed in Liang 2006 and Lebon 2013 because of the well-known advantages a sachet provides. Sachet formulations are known to be a flexible method of drug administration. For example, WHO 2012 teaches that "powders and multiparticulates . . . provided in sachets" "possess great flexibility." *Id.* at 213. Similarly, Liu 2014 teaches that single-use sachet can "increas[e] the portability of a medicine," and can be beneficial for ease of administration. *Id.* at 1881-82. Thus, sachet formulations, including sustained release formulations, were routinely used in the art at the time of the priority date of the '079 patent. *See e.g.*, Bowles 2013 at 57 ("It can be seen that commercially available multiparticulates are mainly supplied for administration in capsules, sachets, or multi-use containers."); WHO 2012 at 215 (describing sachet as a formulation dosage form for sustained-release formulation); Balch 2010 at 195 (teaching the use of a sachet form of an extended-release formulation of morphine for treatment of chronic pain); Nexium 2014 Label at 6 (Nexium, a delayed-release formulation of esomeprazole magnesium, has a sachet dosage form).

A POSA would have had additional motivation to select a sachet for use with the disclosed GHB formulation because the prior art teaches that GHB for the treatment of narcolepsy needs to be formulated in large doses. *See, e.g.*, Liang 2006 at ¶ 31 (disclosing that the dosage needed for oxybate is "high"); Allphin 2012 at ¶ 29 (disclosing that GHB "requires a relatively high dose" and, therefore, "should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration"). Further, the prior art taught that sachet drug forms, when the contents are reconstituted as a suspension, are more easily swallowed compared to other conventional solid dosage forms. *See, e.g.*, Bowles 2013 at 64 ("By using a suspension form, we allow for swallowability and reduce the challenges of other multiparticulate

administration methods such as food compatibility, choking or the use of expensive proprietary technologies."). A POSA would therefore have been motivated to use a sachet form to facilitate administration of the large dose of GHB known to be required in the art for the treatment of narcolepsy.

Finally, a POSA would have been motivated to use a sachet for the storage of the disclosed GHB formulation because sachets were known to be a more convenient method for storage compared to an oral solution, and to provide enhanced stability characteristics. *See* Liu 2014 at 1881 (explaining that oral liquid may require refrigeration, and may require more preservatives than a sachet formulation); Bowles 2013 at 77 (explaining that oral solution requires many different excipients and in higher levels compared to solid dosage form). A POSA would have been motivated to provide the claimed GHB formulation in a sachet for this additional reason.

Claim 24 would therefore have been obvious in view of Liang 2006 and/or Lebon 2013 and the knowledge of a POSA.

VI. THE ASSERTED CLAIMS OF THE '079 AND '782 PATENTS ARE INVALID UNDER 35 U.S.C. § 112

For the reasons set forth below, the asserted claims of the '079 and the '782 patent are invalid for failure to comply with the written description and enablement requirements of 35 U.S.C. § 112.

Pursuant to 35 U.S.C. § 112, ¶ 1, a patent specification "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]" *Id.* The Federal Circuit has held that this language creates two closely related, yet separate requirements for a specification: (i) a written description of the invention ("written description"), and (ii) a written description of the manner

and process of making and using the invention ("enablement"). *See Ariad Pharm., Inc. v. Eli Lilly Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc).

The test for sufficiency of a patent's written description "requires an objective inquiry into the four corners of the specification from the person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan to show that the inventor actually invented the invention claimed." *Id.* at 1351. A patent is invalid for inadequate written description unless "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.*

The requirement of enablement mandates that the disclosure in the specification describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the [invention]." 35 U.S.C. § 112, ¶ 1. For a patent's specification to be enabling, it "must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010). In determining whether undue experimentation is required to practice the claimed invention, a court may assess some or all of the so-called *Wands* factors, which include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence of absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A patent specification must enable the full scope of the claimed invention. *See ALZA Corp.*, 603 F.3d at 939 (affirming invalidity of the claims based on lack of enabling disclosure because

"developing non-osmotic oral dosage forms, such as tablets and capsules" requires undue experimentation).

A. The '079 Patent Is Invalid for Lack of Written Description

1. "controlled release component"

Each of asserted claims 1-3, 5-11, and 14-18 of the '079 patent contain the limitation "controlled release component." To the extent that "controlled release component" is construed to cover non-resinate components, the claims are invalid for failing to satisfy the written description requirement of 35 U.S.C. § 112.

Plaintiffs have broadly interpreted this claim limitation to capture non-resinate GHB formulations, such as Avadel's FT218 product. *See, e.g.*, Plaintiffs' 12/7/2021 Initial Infringement Contentions at 5. Under Plaintiffs' interpretation, the asserted claims would broadly cover any solid or liquid formulation with a "controlled release component" containing GHB, regardless of the composition of the "controlled release component." Thus, the claims broadly recite and claim a component with a desired functionality—controlled release of GHB—regardless of the means by which the claimed functionality is achieved.

In contrast to the breadth of the claims as interpreted by Jazz, the disclosures of the '079 patent are limited to resinate forms of GHB. The specification states that "the term 'controlled release' refers to compositions, for example GHB resinate compositions as described herein…" *Id.* col. 6:55-57. But the specification does not describe any GHB composition other than a resinate composition. Likewise, all of the embodiments disclosed in the specification are limited to resinate forms of GHB. *See, e.g.*, *id.* at Examples 1-7. While the specification contains a general disclosure of a "controlled release formulation of GHB" in combination with "an immediate release GHB formulation," such a generic disclosure, without any description of the corresponding formulation or method for achieving such controlled release, would not lead a POSA to believe the inventors

were in possession of a formulation containing a "controlled release component" other than resinate forms. *Id.* col. 4:14-20.

In addition, the specification repeatedly describes the invention being directed to resinate-containing compositions:

- "Any anion exchange suitable for pharmaceutical use can be employed ***in the compositions of the present invention***, particularly strong anion exchange resins." *Id.* col. 8:33-35.

- "For the ***oxybate resinate compositions of the present invention***, the amount of oxybate present in the resinate should be high to minimize the amount of resin required." *Id.* col. 9:6-8.

- "Formulation of such drugs ***as resinates according to the present invention*** permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights."[7] *Id.* col. 15:13-16.

- "In the dried state, the ***sustained release resinate beads of the present invention*** can hydrate more slowly if release-retarding agents are used." *Id.* col. 19:7-9.

- "If the Stomach has about 5 mEq chloride, then **about 30 mEq of additional exchangeable anion must be provided with the *resinate formulation of the present invention*** to ensure complete release of the oxybate." *Id.* col. 20:18-21.

- "These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after of ***administering the drug resinate (e.g. oxybate resinate) compositions of the present invention***, or simultaneously therewith." *Id.* col. 20:62-66.

Indeed, the specification of the '782 patent specifically denigrates other non-resinate forms of "controlled release" components containing GHB. *Id.* col. 5:57 ("…the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies").

[7] The inventor has defined "oxybate resinate compositions" as "i.e., oxybate ionically bound to an ion exchange matrix." '782 Patent File History, February 18, 2016, Allphin Declaration at ¶ 5.

In light of the specification's disclosures, a POSA would not have understood the inventors to be in possession of formulations containing a GHB controlled release component other than resinate forms of GHB. To the extent Jazz contends the claims of the '079 patent cover formulations containing non-resinate forms of GHB, they are invalid for lack of written description support.

2. "opening a sachet containing a gamma-hydroxybutyrate formulation"

Each of asserted claims 1-3, 5-11, and 14-18 of the '079 patent lack adequate description of "opening a sachet containing a gamma-hydroxybutyrate formulation." The lone description with regard to a sachet occurs at column 6, and recites that "some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user." '079 Patent at col. 6:8-10. There is no disclosure of opening a sachet or mixing its contents in water, as claimed, let alone to obtain the biological results recited in various dependent claims.

3. "wherein the administering promotes the patients to sleep for 6 to 8 hours"

Claims 5 and 14 lack adequate written description for "wherein the administering promotes the patient to sleep for 6 to 8 hours" because the specification does not disclose any data that would lead a POSA to believe that the inventors were in possession of a formulation that "promotes the patient to sleep for 6 to 8 hours." The specification only recites a desired functionality—a once nightly GHB formulation that promotes sleep for 6 to 8 hours—with no indication the inventors actually achieved it. *See e.g., id*. at col 4:4-6 ("One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours."). The specification contains no dissolution testing showing GHB levels over time, no animal model data, no clinical pharmacokinetic data, and clinical sleep studies or other tests in humans demonstrating efficacy in providing sleep for 6 to 8 hours. *See e.g., id.* at Examples 1-7.

Such data would be necessary to provide written description support, particularly where, as here, Jazz has broadly interpreted its claimed formulation to cover any mechanism of controlled release, including those the specification provides no examples or information for at all. Thus, a POSA would not believe that the inventors were in possession of an invention that "promotes the patient to sleep for 6 to 8 hours."

B. The '079 Patent Is Invalid for Lack of Enablement

A POSA would not be able to enable the full scope of the asserted claims of the '079 patent to encompass a non-resinate formulation of GHB. To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. As detailed above, the specification's disclosure of a controlled release component is limited to GHB-resinate forms. *See supra* at Section VI.A. It would require undue experimentation to make and use controlled release components that are not GHB-resinate forms, as confirmed by, *inter alia*, evidence demonstrating Plaintiffs' own failures to do so. The patent therefore fails to enable the full scope of possible "controlled release component," including controlled release particles that do not contain GHB resinates.

C. The '782 Patent Is Invalid for Lack of Written Description

1. "modified release particles"

Each of asserted claims 1-24 of the '782 patent contain the limitation "modified release particles." To the extent that "modified release particles" is construed to cover non-resinate particles, the claims are invalid for failing to satisfy the written description requirement of 35 U.S.C. § 112.

Plaintiffs have broadly interpreted this claim limitation to capture non-resinate GHB formulations, such as Avadel's FT218 product. *See, e.g.*, Plaintiffs' 12/7/2021 Initial Infringement

Contentions at 18. Under Plaintiffs' interpretation, the asserted claims would broadly cover any solid or liquid formulation with "modified release particles" containing GHB, regardless of the composition of the "modified release particles." Thus, under Jazz's interpretation, the claims broadly recite and claim particles with a desired functionality—modified release of GHB—regardless of the means by which the claimed functionality is achieved.

In contrast to Jazz's broad interpretation of the claims, the disclosures of the '782 patent are limited to resinate forms of GHB. A POSA would not believe the inventors were in possession of any "modified release particles" of GHB other than resinate forms. While the specification does contain a general disclosure of a GHB formulation with polymeric beads, *see* '782 patent col. 2:51-53 ("GHB formulation comprising polymeric beads and pharmaceuticals [sic] acceptable excipients"), there is no description of any form of polymeric beads or how such a GHB-containing bead would be made, other than using GHB resinate. There are also no embodiments disclosed in the specification other than to GHB resinate forms. *See, e.g.*, *id.* at Examples 1-7. Rather, the specification repeatedly describes the invention being directed to resinate-containing compositions.

- "Any anion exchange suitable for pharmaceutical use can be employed ***in the compositions of the present invention***, particularly strong anion exchange resins." *Id.* col. 8:34-36.
- "For the ***oxybate resinate compositions of the present invention***, the amount of oxybate present in the resinate should be high to minimize the amount of resin required." *Id.* col. 9:7-9.
- "Formulation of such drugs ***as resinates according to the present invention*** permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights."[8] *Id.* col. 15:38-41.

[8] The inventor has defined "oxybate resinate compositions" as "i.e., oxybate ionically bound to an ion exchange matrix." '782 Patent File History, February 18, 2016, Allphin Declaration at ¶ 5.

- "In the dried state, the ***sustained release resinate beads of the present invention*** can hydrate more slowly if release-retarding agents are used." *Id.* col. 19:33-35.

- "If the Stomach has about 5 mEq chloride, then **about 30 mEq of additional exchangeable anion must be provided with the *resinate formulation of the present invention*** to ensure complete release of the oxybate." *Id.* col. 20:44-47.

- "These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after of ***administering the drug resinate (e.g. oxybate resinate) compositions of the present invention***, or simultaneously therewith." *Id.* col. 21:21-25.

Indeed, the specification of the '782 patent specifically denigrates other non-resinate forms of "modified release particles" containing GHB. *Id.* col. 5:58 ("…the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies").

The specification also fails to adequately describe "modified release particles" because it does not define the term "modified release particle" or otherwise explain the composition or characteristics of the recited "modified release particle." Indeed the claimed term "modified release particle" is not found anywhere in the specification. The only discussion of "modified release" are in two passages discussing the general unsuitability of conventional approaches to modified release formulations of GHB, including traditional resinate GHB formulations:

- "Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for **modified release**, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies." *Id.* col. 5:55-61.

- "Drug-resin complexes including **modified release** drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable." *Id.* col. 6:21-32.

Thus, a POSA would understand the term "modified release particle" as used in the claims of the '782 patent to include any particle possessing modified release of GHB (as compared to an immediate release GHB formulation). This could include, but is not limited to, enteric coatings, ion exchanges, physical modifications, osmotic devices, and resins. As the specification is limited to embodiments and disclosures of resinate formulations, the specification does not support the full scope of the claims.

In light of the specification's disclosures, a POSA would not have understood the inventors to be in possession of formulations containing "modified release particles" containing GHB other than resinate forms of GHB. To the extent Jazz contends the claims of the '782 patent cover formulations containing non-resinate forms of GHB, they are invalid for lack of written description support.

2. "a viscosity enhancing agent…wherein the viscosity enhancing agent … [is] separate from the immediate release particles and the modified release particles"

Claims 1-24 lack adequate written description of "a viscosity enhancing agent… wherein the viscosity enhancing agent… [is] separate from the immediate release particles and the modified release particles." To the extent Plaintiffs allege claims 1-24 of the '782 patent cover any formulations containing "modified release particles" of GHB in combination with "a viscosity enhancing agent" that is separate from the particles, a POSA would not believe the inventors were in possession of the claimed formulation.

The specification is silent as to the arrangement of the viscosity enhancing agent vis-à-vis the "immediate release" and "modified release" particles. While the specification contains a general disclosure of possible viscosity enhancing agents, *see id*. at col. 14:56-61, the specification contains no description corresponding to the incorporation of a viscosity enhancing agent into a final formulation containing particles but "separate from" the particles. Nor does the specification

describe what amount of a viscosity enhancing agent would be needed to achieve a desired effect, or how to determine if the formulation was successful. Thus, a POSA would not understand, by the disclosures of the specification, that a viscosity enhancing agent added to the disclosed embodiments would be separate from the "immediate release particles" and "modified release particles."

3. "an acid wherein the . . . acid [is] separate from the immediate release particles and the modified release particles"

Claims 1-24 lack adequate written description of "an acid wherein the . . . acid [is] separate from the immediate release particles and the modified release particles." To the extent Plaintiffs allege claims 1-24 of the '782 patent cover any formulations containing "modified release particles" of GHB in combination with "an acid" that is separate from the particles, a POSA would not believe the inventors were in possession of the claimed formulation.

The specification is silent as to the arrangement of the acid vis-à-vis the "immediate release" and "modified release" particles. The specification contains no description corresponding to the incorporation of an acid into a final formulation containing particles but "separate from" the particles. Nor does the specification describe what amount of acid would be needed to achieve a desired effect, or how to determine if the formulation was successful. *See, e.g., id.* col. 2:22-32 (describing coating a resin bead with a coating comprising an acid to "provide further controlled release characteristics); *id.* col. 2:54-56 (describing stearic acid could be added to "control the release of GHB from within the polymeric bead"). Thus, a POSA would not understand, by the disclosures of the specification, that an acid added to the disclosed embodiments would be separate from the "immediate release particles" and "modified release particles."

4. Blood concentration ranges

Claims 11, 12, and 19 all claim blood concentration ranges of GHB eight hours after administration of the claimed formulation. Claim 11 claims a blood concentration range from "10 mg/L to about 40 mg/mL," and claims 12 and 19 claim a blood concentration range from "15 mg/L to about 30 mg/mL." A POSA would not believe the inventors were in possession of any GHB formulation or unit dose that could provide such blood concentration ranges.

The specification only mentions blood concentration in two places. In each disclosure the ranges are merely conclusory, with no examples of accompanying disclosures for how to achieve such a concentration or any testing data showing such a concentration had been achieved by the inventors.

- "One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours." *Id.* col. 4:5-7.
- "Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L [sic], maintained over a period of about 5-8 hours as described herein. For example, blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween [sic]." *Id.* col. 22:26-32.

Example 3 reports that "resinate beads" were administered to beagles, but that does not describe any blood level results and Jazz erroneously construes the claims to apply to non-resinate dosage forms, such that any such results would fail to demonstrate possession in any event. *Id.* at col. 23:54-58. A POSA would not believe that the inventors possessed any formulation or unit dose with the claimed blood concentration ranges because the specification discloses only "a mere wish or plan" for the stated blood concentration ranges. *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*, 636 F.3d 1341, 1350-51 (Fed. Cir. 2011) (finding a patent invalid for lack of written description where the specification did "not describe a single antibody that satisfies the claim limitations").

Even if the two conclusory disclosures were enough to provide support for the disclosed ranges, the claimed blood concentration ranges do not match those mentioned in the specification, and thus there is not adequate written description for the ranges. *See Indivior UK Limited v. Dr. Reddy's Laboratories S.A.*, 18 F.4th 1323, 1328 (Fed. Cir. 2021) (noting that the "specification must indicate with some clarity what the claim recites" and finding no written description support for claimed ranges that did not appear in the application). Normalizing the units of the claimed concentrations, claim 11 claims a concentration range of 10 mg/L to about 400,000 mg/L. Likewise, claims 12 and 19 claim a concentration range of 15 mg/L to about 30,000 mg/L. Nowhere are these ranges disclosed in the specification. Thus, claims 11, 12, and 19 are invalid for lack of written description.

D. The '782 Patent Is Invalid for Lack of Enablement

A POSA would not be able to enable the full scope of the claims to encompass a non-resinate formulation of GHB. To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. As detailed above, the specification's disclosure of modified release particles is limited to GHB-resinate forms. *See supra* at Section VI.C. It would require undue experimentation to make and use controlled release components that are not GHB-resinate forms, as confirmed by, *inter alia*, evidence demonstrating Plaintiffs' own failures to do so. The patent therefore fails to enable the full scope of possible "modified release particles," including modified release particles that do not contain GHB resinates.

Additionally, the specification does not enable a POSA to achieve the full range of possible blood concentrations achieved via the use of "modified release particles," as required by dependent claims 11, 12, and 19. Nowhere does the specification disclose examples or studies of how the claimed concentrations can be achieved. The only reference to a dosage amount that is

administered and then tested for blood concentration is Example 3, which discloses that dried GHB resinate beads were administered to beagle dogs, the dogs' blood were sampled for determination of plasma GHB content, but no results were disclosed. '782 Patent col. 23:54-58.

VII. THE '079 AND '782 PATENTS ARE INVALID FOR IMPROPER INVENTORSHIP AND/OR AS ANTICIPATED BY AVADEL PATENT PUBLICATIONS

The claims of the Jazz Resinate Patents are further invalid for improper inventorship under 35 U.S.C. § 101 and 115(a) because they were derived from the inventive work of Avadel. The inventive work by Avadel alternatively renders the claims of the Jazz Resinate Patents invalid as anticipated under post-AIA § 102.

Section 101 requires proper inventorship, as it requires that: "Whoever invents or discovers [an invention] may obtain a patent." 35 U.S.C. § 101. Section 115(a) similarly states that: "An application for patent . . . shall include . . . the name of the inventor." *See Belcher Pharm., LLC v. Hospira, Inc.*, No. 17-775-LPS, 2019 WL 2503159, at *1 (D. Del. June 5, 2019); *see also* MPEP § 2157 ("[W]here it is clear that the application does not name the correct inventorship . . . Office personnel should reject the claims under 35 U.S.C. [§] 101 and 35 U.S.C. [§] 115.").

Avadel's conception and reduction to practice of its once-nightly formulation and the publication of its associated patents prior to the filing of the claims in the Jazz Resinate Patents establishes that the claims of the Jazz Resinate Patents are invalid for improper inventorship. The Jazz named inventors did not conceive of or reduce to practice the claims in the Jazz Resinate Patents. Rather, Jazz, through its prosecution counsel, copied the claimed invention from the true inventors—Claire Megret, Herve Guillard, and Jean-Francois Dubuisson, who are the named inventors on Avadel's patents relating to its once-nightly formulation.

The Jazz Resinate Patents claim priority to U.S. provisional 62/117,889, filed February 18, 2015. However, as of September 2019, all of Jazz's issued and pending claims in that family were directed to ion exchange resins, commensurate with the only disclosures of the provisional and other applications of that family. At the time, Jazz was engaged in the prosecution of U.S. Application No. 16/448,598 ("the '598 Application"), a parent application to the applications that would eventually issue as the Jazz Resinate Patents. Unlike the claims of the Jazz Resinate Patents, the pending claims of the '598 Application were directed to a composition of oxybate that was ionically bound to an ion exchange matrix, such as an anion-exchange resin, as well as a method of preparing an oxybate resinate. *See* '598 Application File History at Claims, p. 38-42 (June 21, 2019).

On January 25, 2018, the application that ultimately issued as Avadel's U.S. Patent No. 10,272,062 ("the '062 patent") was first published. This application demonstrates Avadel's conception—and reduction to practice—of modified release formulations of oxybate and methods of using those formulations therapeutically.

A. The '079 Patent

On September 12, 2019, the application that ultimately issued as Avadel's U.S. Patent No. 10,952,986 ("the '986 patent") was first published. The final version of the claims found in the '986 patent became publicly available on October 1, 2020, and the '986 patent issued on March 23, 2021. Unlike Jazz's then-pending '598 Application, Avadel's application of the '986 patent describes a method of treatment with GHB by opening a sachet containing a GHB formulation, mixing the formulation with water, and orally administering the mixture. '321 Application File History at Claims, p. 159-162 (May 23, 2019).

A few months after the final version of the claims in Avadel's '986 patent became public, on December 10, 2020, Jazz filed U.S. Application 17/118,041 (the "'041 Application") (which

would eventually issue as the '079 patent) as a continuation of its pending '598 Application. Jazz filed a Nonpublication Request for the '041 Application, through which Jazz sought to ensure that the '041 Application would not be made public. *See* '041 Application File History, Nonpublication Request from Applicant (Dec. 10, 2020). However, by December 10, 2020, the specification of the '041 Application had already been made public, since the '662 patent—whose application the '041 Application claims priority to—had already issued on September 3, 2019. Furthermore, although Jazz added two new paragraphs to the '041 Application specification, but Jazz represented to the Examiner that the paragraphs being inserted were "material previously incorporated by reference" and so were also previously publicly available. *See* Applicant Arguments/Remarks Made in an Amendment (Dec. 21, 2020). In other words, the only truly "nonpublished" material in the '041 Application were the claims. Thus, the only reasonable inference that can be drawn from filing the Nonpublication Request and the Applicant Remarks is that Jazz was seeking to prevent others from learning what claims Jazz was pursuing in the '041 application. The following chart depicts the first seven claims in the '321 Application and the '041 Application, showing a striking similarity between the two:

Claims from Avadel's Patent Application No. 16/420,321, Amendment and Response to Non Final Office Action, filed October 1, 2020	**Claims from Jazz's Patent Application No. 17/118,041, filed December 10, 2020**
1. A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising: administering a single daily dose to said human, the single daily dose comprising an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises opening a sachet containing a gamma-hydroxybutyrate formulation, mixing the formulation with water, and orally administering the mixture.	1. A method of treating a disease or condition treatable with oxybate in a patient in need thereof, the method comprising: administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises: opening a sachet containing an oxybate formulation, mixing the formulation with water, and orally administering the mixture to the patient.
2. The method of claim 1, wherein the orally administering occurs at bedtime.	2. The method of claim 1, wherein the orally administering occurs at night.
3. The method of claim 1, wherein the mixing occurs shortly before the orally administering.	3. The method of claim 1, wherein the oxybate formulation is mixed with water immediately prior to administration.
4. The method of claim 1, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.	4. The method of claim 1, wherein the oxybate is administered with food.
5. The method of claim 1, wherein said administering results in inducing said human to sleep for 6 to 8 hours.	5. The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours.
6. The method of claim 1, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g or 9.0 g of sodium oxybate.	6. The method of claim 1, wherein the amount of oxybate administered to the human is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.
7. The method of claim 1, wherein the mixture is a suspension.	7. The method of claim 1, wherein the mixture is a suspension.

The new claims filed by Jazz in the prosecution of the '041 Application copied the claims from Avadel's application that led to the issuance of the '986 patent. Given the slavish copying, the reasonable inference is that Jazz's new claims were the result of Avadel's communication of its controlled release formulations to Jazz via its published application for the '986 patent.

Further, evidence of Jazz's reliance on Avadel's disclosure in its application for the '986 patent is reflected by the fact that in contrast to the original claims filed with the '598 Application, the new claims are not described or supported by the application's specification. In particular, the specification of the '041 Application does not disclose a method of treatment using a single daily dose of oxybate by opening a sachet containing a solid oxybate formulation, mixing that formulation with water, and orally administering the mixture to the patient. *See supra* at Section VI. Furthermore, the only oxybate compositions disclosed in the specification of the '041 Application as being within the scope of the invention are ion exchange resins. *See e.g.*, '041 Application File History at Specification, p. 9-10 (Dec. 10, 2020).

B. The '782 Patent

On June 20, 2019, the application that ultimately issued as Avadel's U.S. Patent No. 10,736,866 ("the '866 patent") was first published. The final version of the claims found in the '866 patent became publicly available when the '866 patent issued on August 11, 2020. This application demonstrates Avadel's conception—and reduction to practice—of its novel formulations. Unlike Jazz's pending '598 Application, Avadel's application of the '866 patent described detailed information regarding modified release formulations of oxybate and methods of using those formulations therapeutically.

A few months later, on March 23, 2021, Jazz filed U.S. Application 17/210,064 (the "'064 Application") (which would eventually issue as the '782 patent) as a continuation of Jazz's '041 Application. As it did with the '041 Application, Jazz filed a Nonpublication Request for the '064 Application, even though the only "nonpublished" information in the application was the claims. *See* '064 Application File History, Nonpublication Request from Applicant (Mar. 23, 2021). The only reasonable inference that can be drawn from this is that Jazz wanted to ensure that no one

was aware of the claims in the application. Once again, when comparing the first four claims in the '064 Application with those in the '866 patent, there is a striking similarity:

Jazz '782 Claims (as first filed in '064 app)	**Avadel '866 Patent**
1. A formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; A modified release portion comprising gamma-hydroxybutyrate; a viscosity enhancing agent; and an acid; Wherein the viscosity enhancing agent and the acid are separate from the immediate release portion and the modified release portion.	1. A formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; A modified release portion comprising gamma-hydroxybutyrate; A suspending or viscosifying agent selected from…; An acidifying agent selected from…; Wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion; and Wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.
2. The formulation of claim 1, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropymethyl cellulose carboxymethyl cellulose sodium, hydroxypropyl cellulose and mixtures thereof.	*See Claim 1:* a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof…
3. The formulation of claim 1, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.	*See Claim 1:* an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprlic acid, and benzoic acid…
4. The formulation of claim 1, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol,	4. The formulation of claim 1, wherein the formulation further comprises a lubricant or glidant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate,

sodium benzoate, sodium stearyl fumarate, and zinc stearate.	glycerol benzoate, sodium stearyl fumarate, talc, or colloidal silicon dioxide.

The new claims filed by Jazz in the prosecution of the '064 Application copied the claims from Avadel's application that led to the issuance of the '866 patent. Given the slavish copying, the reasonable inference is that Jazz's new claims were the result of Avadel's communication of its controlled release formulations to Jazz via its published application for the '866 patent.

Further, evidence of Jazz's reliance on Avadel's disclosure in its application for the '866 patent is reflected by the fact that in contrast to the original claims filed with the '598 Application, the new claims are not described or supported by the application's specification. In particular, the specification of the '064 Application does not disclose the use of a viscosity-enhancing agent or an acid that is separate from the immediate release portion and modified release portion of the formulation. *See supra* at Section VI.C.

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Because the issued claims of the Jazz Resinate Patents lack written description support, they are not entitled to the priority date of February 18, 2015. Indeed, they are invalid for lack of written description. *See supra* at Section VI. Even were one to credit the '079 patent with the date of the earliest recitation a method of treatment using a single daily dose of oxybate by opening a sachet containing a solid oxybate formulation, mixing that formulation with water, and orally administering the mixture to the patient, that would only get to Jazz's December 10, 2020 filing of the claims in the '041 Application.

Similarly, even if one were to credit the '782 patent with the date of the earliest recitation of the use of a viscosity enhancing agent or a viscosity enhancing agent and acid that are separate

from the immediate release portion and modified release portion, that would only get to Jazz's March 23, 2021 filing of the claims in the '064 Application.[9]

Because Avadel's application for the '062 patent published on January 25, 2018, it is prior art to the claims of the Jazz Resinate Patents, and those claims are therefore anticipated. Further, as demonstrated by the disclosures in the '062 patent, the inventors of the Avadel application had fully conceived of (and reduced to practice) the subject matter claimed in the Jazz Resinate Patents prior to communicating their invention to Jazz by way of the published application for the '062 patent. The claims of the Jazz Resinate Patents are therefore invalid for lack of inventorship.

VIII. THE '079 AND '782 PATENTS ARE UNENFORCEABLE FOR INEQUITABLE CONDUCT AND/OR UNCLEAN HANDS

For the reasons discussed in Defendant's Answer & Counterclaims in both actions, the '079 and '782 patent are unenforceable for inequitable conduct and/or unclean hands. *See* Counterclaims Counts III-IV, C.A. No. 21-1138-MN (Dkt. 12) at ¶¶ 18-62; Counterclaims Counts III-IV, C.A. No. 21-1594-MN (Dkt. 25) at ¶¶ 41-89.

[9] To the extent that the Court finds that the '782 patent is entitled to an earlier priority date than the March 23, 2021 filing of the claims in the '064 Application, the "modified" limitation in the claims is not entitled to a date earlier than February 18, 2016. During prosecution, in the Non-Final Rejection of June 18, 2021 of the '782 patent, the Examiner noted the word "modified" in the claims of the '782 patent did not have support in the '889 application. Thus, the Examiner found the earliest potential priority date for the claimed subject matter in of "a formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; a modified release portion comprising gamma-hydroxybutyrate," is February 18, 2016, the effective filing date of U.S. Application No. 15/047,586 (the "'586 application").

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Respectfully submitted,

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