

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.
Petitioner

v.

ALKERMES PHARMA IRELAND LIMITED
Patent Owner

Case No. IPR2025-00514
Patent 7,919,499

**DECLARATION OF JASON SCHIFFMAN, M.D. IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,919,499**

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EXHIBIT LIST

EXHIBIT	DESCRIPTION
1001	U.S. Patent No. 7,919,499, issued on April 5, 2011 to E. Ehrich (“the ’499 Patent”)
1002	File History of U.S. Patent Application No. 11/083,167, filed on March 17, 2005 (“the ’167 Application”)
1003	U.S. Provisional Application No. 60/564,542, filed on April 22, 2004
1004	Sandra D. Comer <i>et al.</i> , <i>Depot naltrexone: long-lasting antagonism of the effects of heroin in humans</i> , 159(4) <i>Psychopharmacology</i> (Feb. 2002), at 351-360
1005	U.S. Patent No. 7,157,102, issued on January 2, 2007 to E. Nuwayser (“the ’102 Patent” or “Nuwayser”)
1006	G. Rubio <i>et al.</i> , <i>Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment</i> , 36(5) <i>Alcohol & Alcoholism</i> (2001), at 419-425
1007	U.S. Patent No. 6,264,987, issued on July 24, 2001 to S. Wright <i>et al.</i> (“the ’987 Patent” or “Wright”)
1008	Henry R. Kranzler <i>et al.</i> , <i>Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study</i> , 22(5) <i>Alcoholism: Clinical and Experimental Research</i> (Aug. 1998), at 1074-79
1009	U.S. Patent No. 6,306,425, issued on October 23, 2001 to T. Tice <i>et al.</i> (“Tice”)
1010	C.N. Chiang <i>et al.</i> , <i>Clinical Evaluation of A Naltrexone Sustained-Release Preparation</i> , 16 <i>Drug & Alcohol Dependence</i> (1985), at 1-8

EXHIBIT	DESCRIPTION
1011	T.N. Alim <i>et al.</i> , <i>Tolerability Study of A Depot Form of Naltrexone Substance Abusers</i> , Problems of Drug Dependence, 1994: Proceedings of the 56th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc., Vol. II: Abstracts, National Institute on Drug Abuse Research Monograph 153 (1995), at 253
1012	U.S. Securities and Exchange Commission, <i>FORM 10-K, Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the fiscal year ended March 31, 2002</i> . Alkermes, Inc. (July 2002)
1013	U.S. Trademark Application Serial Number 76/271,990, Allegation of Use of a Mark & specimen of the mark as used in commerce, Aug. 15, 2002 (“Vivitrex Specimen” or “Specimen”)
1014	S.J. Heishman <i>et al.</i> , <i>Safety And Pharmacokinetics of a New Formulation of Depot Naltrexone</i> , Problems of Drug Dependence, 1993: Proceedings of the 55th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc., Volume II: Abstracts, National Institute on Drug Abuse Research Monograph 141 (1994)
1016	Stewart B. Leavitt, PhD, ed., <i>Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)</i> , Addition Treatment Forum Naltrexone Clinical Update (2002 Clinco Communications, Inc.), at 1-8
1017	ReVia, <i>Physicians’ Desk Reference</i> 936-938 (53rd ed. 1999) (“PDR”)
1018	U.S. Patent No. 4,882,335, issued on November 21, 1989 to J. Sinclair (“Sinclair”)
1019	Chiang <i>et al.</i> , <i>Kinetics of a naltrexone sustained-release preparation</i> , 36(5) Clin. Pharmacol. Ther. (Nov. 1984), at 704-08 “Kinetic of a naltrexone sustained-release preparation.”

EXHIBIT	DESCRIPTION
1020	Reuning <i>et al.</i> , <i>Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems</i> , Naltrexone: Research Monograph 28 (R. E. Willette and G. Barnett, eds. National Institute on Drug Abuse 1980)
1025	<i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , Product Details for NDA 018932, REVIA (NALTREXONE HYDROCHLORIDE) 50MG
1029	TREXAN™, <i>Physicians' Desk Reference</i> 936-938 (46 ed. 1992) ("PDR"), at 937-939
1031	<i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , NALTREXONE (VIVITROL) FOR SUSPENSION, EXTENDED RELEASE 380MG/VIAL
1042	U.S. Patent No. 3,332,950, issued on July 25, 1997 to H. Blumberg
1046	Declaration of Thomas Dowling
1049	<i>Curriculum Vitae</i> of Jason Schiffman
1055	Declaration Under 37 C.F.R. §1.132 of Elliot Ehrich filed in Application No. Serial No. 11/083,167
1056	S. Hamilton <i>et al.</i> , <i>Pharmacokinetics and Pharmacodynamics of Hyaluronan Infused Healthy Human Volunteers</i> , 3 The Open Drug Metabolism Journal 43-55 (2009)
1058	Institution Decision entered November 7, 2018 (Paper 8) in IPR2018-00943
1060	Patent Owner's Response, filed February 7, 2019 (Paper 14) in IPR2018-00943
1061	U.S. Patent No. 5,210,083, issued on May 11, 1993 to R. Pfirrmann

Declaration of Jason Schiffman

EXHIBIT	DESCRIPTION
1062	U.S. Patent No. 5,234,906, issued on August 10, 1993 to A. Young and G. Cooper
1063	U.S. Patent No. 6,677,320, issued on January 13, 2004 to A. Diederich <i>et al.</i>

I, Jason Schiffman, declare and state as follows

I. INTRODUCTION

1. I am a U.S. citizen and a resident of the State of California.

2. I have been retained by Buchanan Ingersoll & Rooney PC (“counsel”) to provide my opinions in the field of pharmaceutical formulation for purposes of supporting a petition for *Inter Partes* Review (“IPR”). I have read and understand U.S. Patent No. 7,919,499 (“the ’499 Patent”) (EX1001) as well as all other references discussed in this declaration. I am being compensated for my time in an amount consistent with my customary consulting fee, and my compensation is not contingent on my opinion or the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

3. I am the founder of Camden Center, an internationally recognized center of excellence for the treatment of psychiatric, addictive, and eating disorders. A copy of my CV is attached as EX1049. It contains a description of my education, academic appointments, professional activities, and publications.

4. I am a Diplomate of the National Board of Psychiatry and Neurology and am certified in Addiction Medicine by the American Board of Preventive Medicine. I am also the founder and Medical Director of the UCLA Dual Diagnosis Program and have written extensively on the subjects of addiction, trauma, anxiety, and depression in both the academic and popular press.

5. I completed my residency in psychiatry at the UCLA Semel Institute for Neuroscience and Human Behavior.

6. I am a graduate of the MD/MBA program at the University of Southern California and received a Master of Arts degree in Linguistics from UCLA where I specialized in syntax and semantics.

7. I have extensive research experience in psychopharmacology and molecular biology and am the author of numerous scientific publications in these fields.

8. In my practice, I am familiar with various controlled release pharmaceuticals and their uses in patients. I am also aware of and have experience in administering controlled release pharmaceuticals to patients and have done so for 14 years.

9. In my clinical and research experience, I have worked on teams that include, in addition to other clinicians, research scientists experienced with pharmacokinetics as well as pharmaceutical formulations that have controlled release characteristics.

III. THE '499 PATENT

10. I understand from the face of the '499 Patent (EX1001) that it issued on April 5, 2011, from U.S. Application Serial No. 11/083,167 (“the '167 Application”), which was filed on March 17, 2005. The '499 Patent states on its face

that it claims the benefit of U.S. Provisional Application No. 60/564,542, filed April 22, 2004 (“the Provisional Application”) (EX1003). I have been advised by counsel to assume that the earliest possible effective filing date for the ’499 Patent is April 22, 2004.

11. The ’499 Patent alleges that the “inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone.” EX1001, Abstract, 1:31-33. The allegedly unexpected discovery was that the AUC from the depot formulation tested was at least three times that observed from 50 mg/day oral dosing. I note that the specification does not provide any data allowing one to review or calculate the claimed differential (“differential”) between any claimed formulation and 50 mg/day oral dosing.

12. The specification discusses the need for improving naltrexone therapies by improving patient compliance. EX1001, 1:13-26. It is my understanding that Alkermes never equated its discovered difference in a pharmacokinetic property to any meaningful therapeutic difference. I believe it is worth noting that the ’499 Patent did not suggest that it provided a cure to alcohol use disorder or any other substance use disorder. I understand that using its own data, while the claimed injection tested against a placebo did reduce the rate at which patients relapsed—11 out of 28 patients still relapsed during the 12-week test period. EX1001, 18:48-52. I understand it acknowledged that based on semi-quantitative comparisons of three

meta-analyses, “the efficacy of Vivitrex suspension compares favorably with oral naltrexone.” *Id.*, 19:30-34. I understand it did not, however, argue superior efficacy. I believe that a POSITA would read the phrase “compares favorably” in this context as no better than oral naltrexone. I understand what is meant by that is that there is no evidence of efficacy improvement and that there was no argument of superior efficacy and no “meaningful” evidence in the patent or raised during prosecution that would allow a POSITA to draw a conclusion of improved efficacy or superiority. I understand that a POSITA would note Alkermes’ acknowledgement that there were no direct studies comparing these two dosing protocols. I understand that they would know that to make any valid claim of improved efficacy would require a properly structured clinical study such as a randomized, or crossover, double-blind trial. I understand that meta-analysis alone offers uncertain weight to a POSITA, which is perhaps reflected by the fact that, during prosecution, Alkermes did not make more of any alleged efficacy improvements. I understand that Alkermes never explained why any argued improvement in efficacy over oral dosing was not completely attributable to compliance improvements which were known to result from using a long acting injection over oral dosing. I also understand that Alkermes never linked any efficacy difference to a difference in AUC.

13. From my review, I understand that naltrexone is combined with well-known polymers, such as PLGA, to “entrap or encapsulate” the naltrexone to form

long acting formulations. EX1001, 3:14-15. I saw that the specification describes its formulations as releasing naltrexone over a period of at least one week. *Id.*, 4:42-44. It then describes “Vivitrex” as a monthly administration that releases naltrexone for four weeks and states that the therapy can be maintained for 24 weeks or more. *Id.*, 4:55-64.

14. The specification further includes five examples, three of which were not present in the original provisional application to which the ’499 Patent claims priority. EX1001; EX1003. Example 1 describes how to manufacture the Vivitrex formulations. The microparticles manufacturing procedure portion of this example is virtually identical to the preparation described by Example 3 of Wright. *Compare* EX1001, 3:3-33, 5:35-8:2 *and* EX1007, 7:48-8:60; *see* ¶133, *infra*.

15. I saw that the remaining examples describe various aspects of a clinical trial, none of which provide any data for AUC or the claimed AUC differential. For example, Example 2 describes screening, eligibility, and adverse events. EX1001, 8:5-18:2. Example 3 compares the “efficacy” of oral verse injectable naltrexone, but clearly states that “a direct head-to-head comparison of efficacy has not been studied” and thus “a definitive comparison of efficacy between Vivitrex and oral naltrexone cannot be made.” *Id.*, 18:8-12. Instead, as noted above, the specification admits to using data from three non-related studies for a “semi- quantitative comparison.” *Id.*, 18:12-29, 19:30-33. Examples 4 and 5 were directed to “quality of

life” and “durability of effect and tolerability” of long acting naltrexone formulations. Again, none of the examples provided any data regarding AUC.

16. The '499 Patent then claims a method of treating an individual in need of naltrexone by parenterally administering a long acting formulation that includes 310-480 mg of naltrexone and a biocompatible polylactide-co-glycolide (“PLGA”) polymer to the individual, where the serum AUC of naltrexone is about three times greater than what is achieved by administration of 50 mg/day oral administration. EX1001, 21:2-8, 22:15-22. The amount of naltrexone in the formulations claimed varies from a range of between 190 mg to 240 mg (claim 14) and 310 mg to about 480 mg of naltrexone (claim 1).

IV. PERTINENT PROSECUTION HISTORY OF THE '499 PATENT

17. While I have been an inventor on a patent application, I do not have extensive experience in patent law. Therefore, when I review the '499 Patent prosecution history, I do so as a technical expert.

18. I understand and have been informed by counsel that the '499 Patent was filed under 37 C.F.R. §1.102(e) on March 17, 2005, as the '167 Application. I understand that a non-final rejection was mailed on May 5, 2009 (EX1002, at 333-342), which rejected the claims as allegedly being anticipated by Tice (EX1009) and, in the alternative, as being obvious over the combination of Tice and Chandrashekar. I understand that Alkermes responded on October 5, 2009 (EX1002, at 291-299)

with claim amendments and a declaration under 37 CFR §1.132 by Elliot Ehrich (the “Ehrich Declaration”) (EX1002, at 300-304; EX1055), the inventor of the ’499 Patent.

19. I understand that the Examiner issued a second non-final office action on January 6, 2010 (EX1002, at 276-286), which withdrew the anticipation and obviousness rejections over Tice in view of the Ehrich Declaration but nevertheless finally rejected the claims based on lack of enablement. Alkermes responded on April 5, 2010, by amending the claims to require a biocompatible polymer. EX1002, at 177-188. A final rejection was mailed on July 20, 2010 (EX1002, at 130-143.), maintaining the enablement rejection. Alkermes filed a response after final on October 20, 2010 (EX1002, at 121-126), amending the claims to require that the biocompatible polymer be PLGA. I note that the Ehrich Declaration did not argue that either oral dosing or Tice’s depot injection was clinically ineffective or even somehow less therapeutically effective, had fewer side effects, or was in any way an inferior treatment. The inventor did not even allege that the observed difference in AUC was somehow advantageous—just different. Nothing in the ’499 Patent or its prosecution history is more enlightening on this point. All three protocols (*i.e.*, oral naltrexone, PLA/naltrexone microspheres of Tice, and the PLGA/naltrexone microspheres of Comer and the ’499 Patent) resulted in plasma levels of 1 ng/ml or above, which had already been established as the therapeutic threshold.

20. A notice of allowance was mailed on December 1, 2010, which, I understand, acknowledged a telephone interview of November 19, 2010 where the examiner allegedly proposed to insert certain language into the claims, *e.g.*, “about 310 mg to about 480 mg” into claim 1. EX1002, at 105-114. I understand the Examiner also included a reason for allowance, which stated that “[t]here is no prior art disclosing the applicants’ [sic] composition and effect, particularly an AUC about three times greater than that achieved by 50 mg/day oral administration.” *Id.* at 4. According to the Examiner, Tice was the closest prior art and reported that its injectable formulation was comparable to taking 50 mg tablets orally. *Id.* I disagree.

V. A PERSON OF ORDINARY SKILL IN THE ART

21. It is my opinion that a POSITA, with respect to the technology at issue in this inter partes review, is experienced in the field of controlled-release formulations. This field often requires collaborative teamwork among individuals with relevant experience, including pharmaceutical scientists, clinicians, and formulation scientists. Here, a POSITA would have either a Master’s degree with at least two or three years’ experience, or have a Ph.D. or M.D. degree with at least one or two years’ experience.

22. Based on the technical and clinical nature of the subject matter of the ’499 Patent, I understand who a person of ordinary skill in the art was as of April 22, 2004, and what such a person would know.

VI. CLAIM CONSTRUCTION

23. I have been informed that during an inter partes review proceeding, claims are to be construed in light of the specification as would be read by a person of ordinary skill in the relevant art at the time the application was filed. I have been informed that claim terms are given their ordinary and customary meaning as would be understood by a person of ordinary skill in the relevant art in the context of the entire disclosure. A claim term, however, will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the claim term in the specification. In that case, the claim term will receive the definition set forth in the patent.

A. “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone”

24. In the '943 IPR, Patent Owner asserted that the phrase “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone” should be construed as “a single injection of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” EX1060, 5-7 (emphasis added). The “single injection” language appears nowhere in the claims or specification, and nothing supports so limiting the claims.

25. Patent Owner pointed to the use of “the step” and “a long acting formulation” in the claims as meaning “singular.” The '499 Patent does focus on the difference between an injectable formulation given once every 28 days and once-a-

day oral dosing for 28 days. In this context, clearly the '499 Patent is claiming the number of doses used during the claimed period rather than how many shots, or how many pills, were needed to administer the claimed dose.

26. Further, Patent Owner's construction requiring a "single injection" cannot be correct given that "parenteral" administration is not limited to injection but also encompasses infusion. *See, e.g.*, EX1061, claim 1 ("composition for parenteral infusion or injection"), EX1062, 12:18-20 ("parenteral compositions for injection or infusion"), EX1063, 7:55-62 ("the parenteral route comprises subcutaneous, intramuscular and intravenous injection or infusion"). This is further apparent from claim 12 which depends from claim 1 and recites "naltrexone is administered by injection".

27. In view of the foregoing and in view of my analysis of the specification, it is my opinion that the term "the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone" should be given its plain meaning which does not exclude multiple injections for the reasons explained above.

B. "the serum AUC of naltrexone ... than that achieved by 50 mg/day oral administration"

28. The '499 Patent does not define "the serum AUC of naltrexone ... than that achieved by 50 mg/day oral administration."

29. The claims require a “serum AUC” but “serum AUC” is not defined by the specification. A POSITA would appreciate that this refers to serum “area under the curve.” AUC is merely the area under a curve created by plotting plasma drug concentration versus time. In other words, the area under the curve is a plot of plasma concentration of a drug versus time after dosage and gives insight into the extent of exposure to a drug and its clearance rate from the body. The area under the curve or AUC has a long history of use in pharmacology and pharmacokinetics, As Dr. Dowling explains in his declaration, a POSITA would clearly know the meaning of AUC and how it is determined. EX1046, ¶¶98-99.

30. I am also aware that in IPR2018-00943, the Board also confirmed that “AUC is a well-known pharmacokinetic parameter referring to area under the curve.” EX1058, 9. The Board determined that “serum AUC is represented by a plasma concentration-time curve.” *Id.* The Board also determined that “[b]y its plain terms, claim 1 requires that the serum AUC achieved by parenterally administering the long-acting formulation of naltrexone (i.e., a long-acting formulation comprising about 310 mg to about 480 mg naltrexone and a polylactide-co-glycolide polymer as a biocompatible polymer) is about three times the serum AUC achieved by administration of a 50 mg/day oral naltrexone formulation.” EX1001, 21:3–9. I have adopted this understanding of the term “the serum AUC”

for purposes of this proceeding, and I believe it to be an accurate understanding based upon my knowledge and experience.

31. The '499 Patent does not define or specify the AUC of the claimed formulation or oral dosing. However, during prosecution of the '499 Patent, Patent Owner filed a Declaration under 37 C.F.R. §1.132 (“the Ehrlich Declaration”) purporting to show unexpected results for the serum AUC of the claimed long-acting naltrexone formulation over that of a 50 mg/day oral formulation (i.e., an unexpected serum AUC differential). EX1055, 1–18.

32. The Ehrlich Declaration provides two data sets (Cohort A and Cohort B) for the serum AUCs of the claimed long-acting naltrexone formulation and the 50 mg/day oral naltrexone. *See id.* at 6 (Table 8). For Cohort A, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.307,2 which is 3.37 times the serum AUC value of 1.278 for the 50 mg oral naltrexone dose. *Id.* at 2. Similarly, for Cohort B, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.921, which is 3.35 times the 1.468 serum AUC value for the 50 mg oral naltrexone dose. *Id.*

33. In the Examiner’s Statement of Reasons for Allowance, the Examiner referenced this data as showing “an AUC about three times greater than that achieved by 50 mg/day oral administration,” and explained that “no prior art disclos[es]” this effect. EX1055, 4. Because these serum AUC data points were presented during

prosecution and were relied on by the Examiner in allowing the application issuing as the '499 Patent, a POSITA would understand that the serum AUC achieved by 50 mg/day oral administration encompasses these data points. Accordingly, I agree with the Board's determination in IPR2018-00943 that "the reference to a '50 mg/day' AUC in 'than that achieved by 50 mg/day oral administration' as encompassing at least serum AUCs of 1.278 ng·day/ml and 1.468 ng·day/ml." EX1058, 11-12.

C. "about three"

34. The '499 Patent does not define "about three." However, Claim 5 (which depends from claim 1) specifies an AUC of about 3.3 times greater than oral dosing. Thus, "about three" necessarily encompasses at least 3.3. A POSITA would thus appreciate that "about three" also encompasses at least "about 2.7." As explained by Dr. Dowling, this term could encompass a wider range. (EX1046, ¶102.) I agree with the Board's determination in IPR2018-00943 that "about three necessarily encompasses at least 3.3" and "at least about 2.7." EX1058, 13. During prosecution, Patent Owner submitted the Ehrlich Declaration which provides data of a serum AUC for long-acting naltrexone formulation that is 3.3 times greater than that achieved by oral dosing. EX1055, 2. Additionally, Dr. Dowling testifies, and supports with evidence, that the term "about" as used in the art encompasses "a quantity within 10%." EX1046, ¶¶102-103.

D. “five or more days”

35. Claim 2 requires that the individual not use oral naltrexone within five or more days before administration of the formulation. This was not the original language of the claim, as filed. The original language mirrors the language used in the specification, namely “has not used oral naltrexone within five days, such as within ten days, before said administration.” EX1001, 2:1-2. Putting aside the fact that within five days entails within 10 days, the claim can either be read to encompass no prior oral naltrexone administration within five days or simply no prior oral naltrexone administration ever. The use of the phrase “or more” in the claim, and the attempt to define the concept as encompassing ten days, manifests an intention to cover a range greater than five days. Thus, the term “five or more days” encompasses no prior oral naltrexone administration, ever.

E. “initial oral dose”

36. Claim 11 requires the individual not receive an “initial oral dose” of naltrexone. The ’499 Patent does not define this term. The only reference to dosing in the ’499 Patent is to the administration of naltrexone to treat a patient to overcome his or her addiction. The art, however, makes clear that there are other purposes. For example, Comer teaches the use of naltrexone as part of a detoxification process prior to treatment. EX1004, at 353. There is a break of two days between administering the detoxification doses and the treatment doses. *Id.* Similarly, a small

percentage of the patient population can have serious adverse reactions to naltrexone. Naltrexone has been given orally to test for this prior to giving a depot injection for treatment. EX1009, 5:65-6:6, 6:13-17; EX1008, 1074. Clearly the art distinguishes initial treatment doses from prior doses given for other purposes. Accordingly, “initial oral dose” as used in the ’499 Patent is an earlier treatment dose, not a dose provided for other purposes.

F. “about 35% by weight”

37. Claim 13 requires the long acting formulation be present at a concentration of about 35% by weight. The specification does not specifically define what is meant by “formulation,” but does describe how to produce the microparticles, i.e., 30-75% drug loading. EX1001, 6:52-54. A POSITA would appreciate that this term refers to the percent by weight of the particle.

VII. TECHNICAL BACKGROUND AND STATE OF THE ART

38. The challenged claims are directed to treating certain conditions, such as alcohol use disorder (historically also referred to as “alcohol dependence” and “alcoholism”) and opioid use disorder (historically also referred to as “opioid dependence” and “opioid addiction”), by parenterally administering about 310-480 mg of naltrexone to a patient via a “long acting” depot injection that includes a biodegradable polymer polylactide-co-glycolide (“PLGA”).

39. As noted elsewhere, naltrexone as a treatment for patients suffering from alcohol use disorder and opioid use disorder dates back to the 1980s. EX1004, at 351-352; EX1008, at 1075; EX1010, Summary; EX1011; EX1005, 19:22-25; EX1012, at 3; EX1016, Abstract; EX1017; EX1018, 1:55-2:50; EX1020, at 173. Naltrexone was originally developed and patented (EX1042) by Endo Laboratories in the 1960s. Naltrexone hydrochloride, originally under the tradename Trexan and later known as ReVia, received FDA approval in 1984. EX1031. The formulation delivered 50 mg/day orally to patients for opioid and alcohol use disorder. EX1017, 936-938; EX1006, at 420; EX1025; EX1029, at 937-939.) A 50 mg daily oral dose was known to be effective and to provide serum blood levels of at least 1 ng/ml, which was recognized as necessary for efficacy. EX1004, Abstract; EX1008, at 1078; EX1010, at 7; EX1011; EX1009, 6:19-39.

40. Individuals that may benefit from naltrexone include a wide variety of people suffering from a number of conditions including, for example, opioid-induced respiratory failure, anorexia nervosa, bulimia, obesity, self-injury, and opioid-induced constipation. But, when one speaks of a patient in need of naltrexone, they are typically referring to a patient with opioid or alcohol use disorder. EX1004, at 351-352; EX1008, at 1074; EX1009, 1:14-2:60; EX1012, at 3; EX1014; EX1016, Abstract; EX1018, 1:13-2:61.

41. One of the most frequently cited problems in treating opioid and alcohol use disorder is patient compliance. For a variety of reasons, individuals who start treatment for these conditions often discontinue taking medication and/or participating in other aspects of their care over the many months usually necessary for recovery. Failure to retain patients in treatment is the primary reason for treatment failure in substance use disorders. Using a longer term depot injection, for example, was one method already known to address such compliance issues as the addict has fewer opportunities to avoid taking their medication. EX1004, at 351-352; EX1008, at 1075; EX1010, at 2; EX1011; EX1005, 19:21-25; EX1009, 1:46-2:7; EX1012, at 3; EX1014, at 82; EX1019, at 704. Several depot injections were known to provide a blood concentration of 1 ng/ml/day for weeks. EX1004, at 351; EX1008, at 1074, EX1056; EX1005, 14:25-50, 19:4-25, Fig. 7; EX1009, 3:5-17, 4:35-39, 6:19-39.

42. Some of these depot formulations included naltrexone and PLGA. EX1004, at 354; EX1008, at 1075; EX1010, at 2; EX1005, 14:24-49, 19:4-25; EX1012, at 3, 5, 20; EX1013, at 5; EX1007, 7:49-8:60, 12:33-40; EX1019, at 704; EX1020, at 173 (delivery system I.) Finally, administering naltrexone doses falling within the claimed range from PLGA-containing formulations were known. EX1004, at 351, 354; EX1005, 19:4-25, Fig. 7; EX1013, at 4-5. So, other than the claimed AUC differential, every element of the '499 Patent's claimed method was

well within the knowledge of a POSITA. But as will be discussed below, even that aspect was also known.

VIII. SUMMARY OF THE PRIOR ART

A. Comer (EX1004)

43. Comer describes a study “designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®)” in subjects dependent on heroin. EX1004, 351 (Abstract). Comer states that the results of the study “suggest that th[e] depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” *Id.*

44. As background, Comer states that, although approved as a treatment for heroin dependence, “naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment.” *Id.*, 351 (Abstract). Comer states, however, that “[s]ustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness.” *Id.*, 352. In particular, “[a] new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, longlasting elevation in plasma naltrexone levels with either no or minimal side effects.” *Id.* Comer states that “[a]lthough this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin.” *Id.* Thus, “[t]he purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the

effects of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone.”

Id.

45. Comer states that naltrexone microcapsules were reconstituted in a suspending medium and 2.4 ml of the suspension was injected into study participants. *Id.*, 354. Participants given a “low dose” received one placebo injection and one naltrexone injection (192 mg naltrexone base) subcutaneously into the buttocks using an 18 gauge needle. *Id.* Participants given a “high dose” received two naltrexone injections (384 naltrexone base). *Id.* Figure 1 of Comer, reproduced below, provides mean plasma levels of naltrexone as a function of depot naltrexone dosage and dates after administration of depot naltrexone. *Id.*

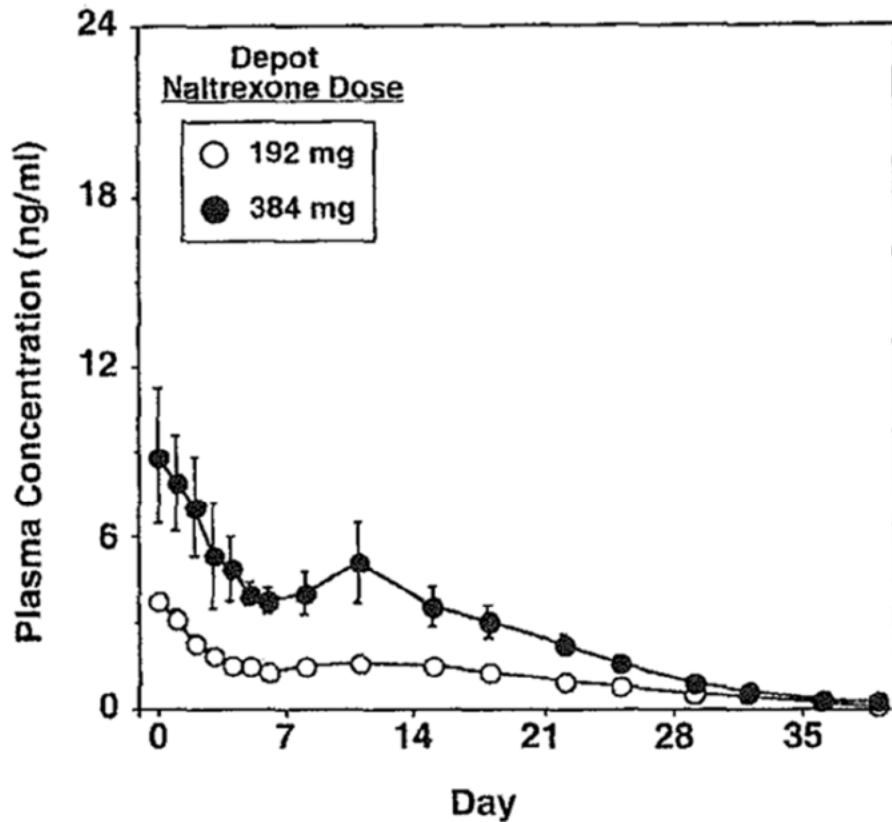


Figure 1 shows mean plasma levels of depot naltrexone over time following either a 192 mg depot dose (○) or a 384 mg depot dose (●).

Figure 1 of Comer (EX1004)

46. Comer states that “[a]cross the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were 3.8 (± 0.2) and 8.9 (± 1.4) ng/ml, respectively.” *Id.*, 358. Comer states that a comparative study “reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone

plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone).” *Id.* Thus, Comer states, “the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).” Even so, “antagonism of heroin’s effects occurred, despite negligible plasma levels of naltrexone.” *Id.*

47. Comer summarizes that “the data presented in the current study demonstrate that this formulation of naltrexone produced a long-lasting antagonism of the effects of intravenous heroin, with minimal side-effects.” *Id.*, 359. And thus, “a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications.” *Id.*

48. The Board provided a similar summary of Comer in IPR2018-00943. EX1058, 13-16.

B. Nuwayser (EX1005)

49. Nuwayser teaches a multi-layered microcapsule containing one or more active ingredients and a process for preparing the microcapsule. EX1005, Abstract. In Example IV, Nuwayser teaches the preparation of naltrexone microcapsules by coating naltrexone microspheres with the polymer poly-L-(–)-lactide-co-glycolide (PLGA). *Id.*, 19:3-25. Nuwayser teaches that the microcapsules contain a final naltrexone content of 54.4%. *Id.* “This formulation delivered a therapeutic level of

naltrexone in six heroin addicts for a period of 30 days.” *Id.* Figure 7 of Nuwayser, reproduced below, provides mean plasma levels of naltrexone “after single and double [subcutaneous] injections of Depotrex™.” *Id.*

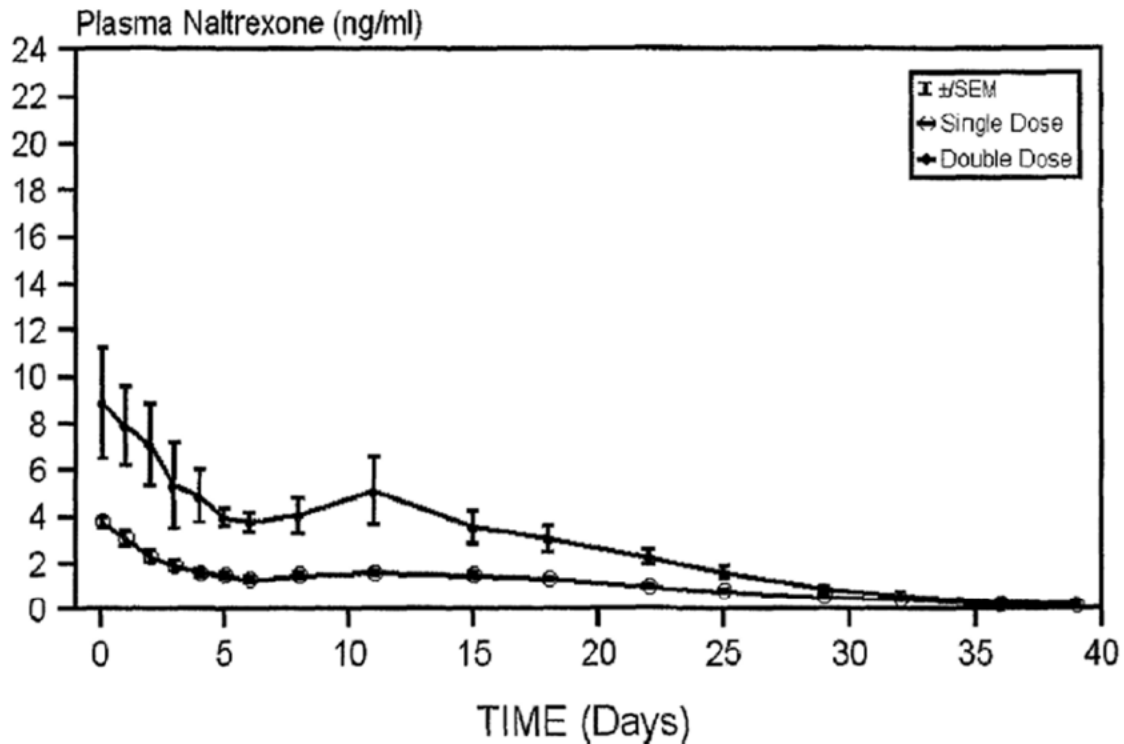


Figure 7 shows mean plasma levels of naltrexone over time following either a single dose (○) or a double dose (●) of naltrexone.

Figure 7 of Nuwayser (EX1005)

50. The Board provided a similar summary of Nuwayser in IPR2018-00943. EX1058, 16-17.

C. Rubio (EX1006)

51. Rubio states that both naltrexone and acamprosate “reduce relapse in alcohol dependence,” but they “have not yet been compared in a published trial.”

EX1006, 419 (Abstract). Rubio describes a study designed “to compare the efficacy of these compounds in conditions similar to those in routine clinical practice.” *Id.* Recently detoxified alcohol-dependent men were administered either one year of treatment with 50 mg/day of naltrexone (*i.e.*, one tablet per day) or 1665–1998 mg/day of acamprosate (*i.e.*, six tablets per day). *Id.*; *see also id.* at 420. Rubio found that, at the end of the year, “[n]altrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at any one time and reducing craving, compared to acamprosate.” *Id.* at 422.

52. The Board provided a similar summary of Rubio in IPR2018-00943. EX1058, 17.

D. Wright (EX1007)

53. Wright teaches a method for preparing microparticles having a selected polymer molecular weight. EX1007, Abstract. In Example 3, Wright teaches the preparation of microparticles containing naltrexone. *Id.* at 7:50–8:60. Wright teaches that the polymers used were “MEDISORB® 7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6535 DL polymer.” *Id.* at 7:56–58.

IX. THE CHALLENGED CLAIMS WERE READILY APPARENT TO A POSITA

A. A Single Injection Would be Obvious Based on Comer in View of Nuwayser and/or Nuwayser in view of Comer and Either in View of Wright and Rubio

54. In the '943 IPR, Patent Owner asserted that claim 1 should be construed to require a single injection of naltrexone, excluding the two injections disclosed by Comer. As explained in my discussion of claim construction, the “single injection” language of Patent Owner’s construction appears nowhere in the claims or specification, and nothing supports so limiting the claims. Nonetheless, it is my opinion that it would have been obvious to modify Comer to administer the 384 mg naltrexone with a single injection. This is true for a number of reasons.

55. The efficacy of naltrexone in treating substance use disorders was known to be limited by poor patient compliance or adherence to the prescribed daily dosing. EX1004, 352. A POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer.

56. Patients having opioid use disorder and alcohol use disorder have been known to have difficulties complying with naltrexone treatment for a number of reasons. By 2003, the efficacy of naltrexone in treating alcohol and opioid use disorders was known to be limited by poor patient compliance or adherence to the prescribed daily dosing. Patient adherence is particularly important in treating

alcohol and opiate dependence because the compulsion to self-administer drugs directly conflicts with the need to remain abstinent. This daily conflict further exacerbates problems of poor adherence, contributing to the spiral towards relapse common to both maladies.

57. Factors affecting a patient's drug compliance or adherence to prescribed treatment may be categorized to patient-centered factors, therapy-related factors, social and economic factors, healthcare system factors, and disease factors. Patient-centered factors include psychological factors (e.g., beliefs, motivation, and attitude), physical impairments, and effects of substance use. Therapy-related factors include route of administration, dosing frequency, treatment complexity, frequency of office visits, and duration of the treatment period.

58. It has been well-established that reducing the number of injections administered to patients would offer benefits for the patient's health outcomes and adherence to the prescribed treatment. For example, increasing the number of injections administered to patients has been long recognized as a factor contributing to noncompliance. Extended-release formulations have been widely used to allow reduction of the number of injections administered to patients, which may enhance convenience and thereby improve adherence.

59. Patients receiving a drug treatment via intramuscularly injection may have a wound at the injection site and develop inflammation. In addition,

intramuscular injections allow for the potential introduction of bacteria and other pathogens into the patient. Intramuscular injections can have commonly known complications such as tissue necrosis, granulomas, muscle damage, nerve damage, accidental intravenous or intraarterial injection (which can cause significant morbidity), and the potential for abscess formation. Patients receiving intramuscular injections often experience significant pain with these injections thereby decreasing their motivation to receive treatment.

60. An additional potential complication of intramuscular injections is sub-therapeutic dosing due to leakage of the liquid formulation of the drug being administered out of the injection site.

61. Administering an amount of medication to a patient as two separate intramuscular injections each containing half the dose rather than as a single intramuscular injection containing the entire dose doubles the risk of these complication and the discomfort that the patient must endure and further decreases their motivation to continue treatment.

62. As a practical matter, administering two doses of a medication doubles the operational burden on a medical practice, doubles the administrative costs with administering such injections, and as I mention above, also doubles the risk of adverse events with no additional benefit.

63. Therefore, it would be self-evident to a POSITA that administration of a dose of a drug as a single intramuscular injection is superior to administration of that same dose as two separate intramuscular injections as the latter increases the risk of adverse events, increases patient discomfort, and increases administrative burden on the medical practice, all without providing any increase in benefit.

64. A POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer, and would have had reason and been motivated to modify Comer to employ a single 384 mg naltrexone injection as opposed to two separate 192 mg injections with a reasonable expectation of success. A POSITA would deem the two naltrexone low dose injections (192 mg) separated by an hour as taught by Comer as a single naltrexone high dose injection (384 mg) when assessing their effect on naltrexone plasma concentration over a long period of, for example, 4 weeks. Such a modification would have merely constituted combining prior art elements (two injections) according to known methods to yield predictable results. While Comer employed a single concentration of naltrexone for both the low and high doses and increased the dose by employing two injections, a POSITA would have recognized that employing a single injection containing the total 384 mg naltrexone would have been a desirable

alternative to avoid the above potential drawbacks of multiple injections, yielding only predictable results. EX1046, ¶¶134, 160.

65. A POSITA would have had a reasonable expectation of success to employ a single 384 mg naltrexone injection as opposed to two separate 192 mg injections for the reasons discussed above. Further, Comer states that “after reconstituting in suspending medium, 2.4 ml of the suspension was injected. The active formulation contained drug equivalent to 192 mg naltrexone base.” EX1004, 354. This equates to a dosage concentration of 80 mg/mL, and the volume of a single injection at this concentration would be 4.8 mL, which a POSITA would consider to be an acceptable volume for intramuscular injection.

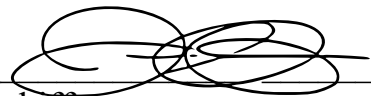
66. A POSITA would have also recognized that naltrexone would be reconstituted at higher concentrations if a smaller volume was desired. *See, e.g.*, EX1008, 1075 (206 mg naltrexone in 2.4 ml). Optimization of the concentration and volume of the injectable composition would have been well within the skill of a POSITA. Indeed, the '499 Patent does not specify any volume requirements of the injectable and itself employed larger injection volumes (*e.g.*, 4 mL) without concern. EX1001, 5:10-12.

X. CONCLUSION

67. In signing this Declaration, I understand that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

68. I hereby declare that all statements made herein 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 Section 1001 of Title 18 of the United States Code.

Date 1/23/25



Jason Schiffman