

Case IPR2018-00943
Patent No. 7,919,499
Declaration of Kinam Park, Ph.D.
Attorney Docket No. AMNEAL 7.1R-005

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

ALKERMES PHARMA IRELAND LIMITED,
Patent Owner.

Patent No. 7,919,499 to Elliot Ehrich
Issue Date: May 19, 2015
Title: NALTREXONE LONG ACTING
FORMULATIONS AND METHODS OF USE

Inter Partes Review No. IPR2018-00943

(Exhibit 1030)

**DECLARATION OF KINAM PARK, Ph.D. IN SUPPORT
OF *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,919,499**

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I, KINAM PARK, declare and state as follows:

I. INTRODUCTION

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

2. I have been retained by Lerner, David, Littenberg, Krumholz & Mentlik, LLP (“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”) (Ex. 1001) 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. MY BACKGROUND AND QUALIFICATIONS

3. I am the Showalter Distinguished Professor of Biomedical Engineering, as well as a full Professor of Pharmaceutics at Purdue University. A copy of my CV is attached as Exhibit 1031. It contains a description of my education, academic appointments, professional activities, service on the editorial board of professional journals, books, referenced articles in scholarly journals, journal cover stories, patents, presentations, book reviews, teaching responsibilities, and thesis supervision.

4. I obtained my Ph.D. in Pharmaceutics from the University of Wisconsin in 1983, and completed a postdoctoral training in Chemical Engineering from the University of Wisconsin in 1985. I joined Purdue University as an Assistant Professor in 1986, and since 1994, I have been a Professor in the Department of Pharmaceutics at Purdue University. I also have been a Professor in the Department of Biomedical Engineering since 1998, and became the Showalter Distinguished Professor of Biomedical Engineering at Purdue University in 2006.

5. Since about 1986, I have been involved in the research, development, and manufacture of pharmaceutical formulations, and in particular controlled/sustained release drug delivery systems. I have conducted numerous research activities at Purdue University related to drug delivery technologies utilizing various polymers.

6. Since about 1994, one of my research interest has been developing long-acting microparticle formulations for oral administration. Since 2000, my research focused on injectable long-acting depot formulations based on biodegradable poly(lactide-co-glycolide) (PLGA), also known as poly(lactic-co-glycolic acid), using different manufacturing technologies, such as microenvironment-controlled encapsulation process, solvent exchange method, microfabrication, and double emulsion methods.

7. I have published 283 papers in peer reviewed journal articles, 100 book chapters, 98 conference proceedings, 22 patents, 191 journal cover stories, and 12 books, and given 294 invited lectures. Many of my publications relate directly to research, development, and design of sustained release formulations.

8. Over the years, I have received numerous honors and awards, including the Research Achievement Award (Pharmaceutics and Drug Delivery Section) (2001), the Clemson Award (basic research category) of Society for Biomaterials (2001), the Controlled Release Society Founders Award (2004), the Louis W. Busse Lectureship of School of Pharmacy at University of Wisconsin (2008), the Sigma Xi Research Award (Purdue University Chapter) (2009), Thomson Reuters' list of "The World's Most Influential Scientific Minds: 2014" (2014), Korean-American Society in Biotech and Pharmaceuticals-Daewoong Award (2014), and Controlled Release Society Distinguished Service Award (2015), Special Government Employee at FDA CDER (2016), and The University of Auckland Distinguished Visitor Award (2017).

9. I have also been on the Board of Governors of the Controlled Release Society (1993-1996), a Fellow at the American Association for Pharmaceutical Scientists (AAPS) (1993), the President of the Korean-American Pharmaceutical Scientists Association (1995-1997), a Fellow at the American Institute for Medical and Biological Engineering (1996), a Fellow at the Biomaterials Science and

Engineering of the Society for Biomaterials (2000), the President of the Controlled Release Society (2001-2002), and a Fellow of Controlled Release Society (2010).

10. I have been a member of numerous Advisory Boards, including the Advisory Panel on Polymeric Excipients, USP (1995-2005); the ACS Books Advisory Board (1997-2000); the Scientific Advisory Board, International Symposium on Recent Advances in Drug Delivery Systems (2000-2001); International Nanomedicine and Drug Delivery Symposium (2005); Board of Directors & Chairman of Fellowship Committee, CRS Foundation (2008-2013); Scientific Advisory Board, the International Conference on Biomaterials Science in Tokyo (2016), External Advisor for Internal Projects at Korea Institute of Science and Technology (KIST) (2017), and International Organizing/Advisory Committee, 5th Symposium on Innovative Polymers for Controlled Delivery, Suzhou, China (2018).

11. I am currently on editorial boards of 20 journals, including for the Journal of Biomaterials Science – Polymer Edition; the Journal of Bioactive and Compatible Polymers; Colloids and Surfaces B: Biointerfaces; Archives of Pharmacal Research; Advanced Drug Delivery Reviews; Biomaterials Research; the Journal of Pharmacy and Pharmacology; the Journal of Drug Delivery Science and Technology; Nano Reviews; Frontiers in Drug Delivery Biotechnology; and Regenerative Engineering and Translational Medicine.

12. I currently am the Editor-in-Chief for the Journal of Controlled Release. I previously have been a journal editor for several publications, including Pharmaceutical Research (Associate Editor); Pharmaceutical Research (Book Review Editor); Advanced Drug Delivery Reviews (Guest Editor); and Journal of Controlled Release (Editor, Americas).

13. Accordingly, I believe I am an expert in the field of pharmaceutical formulations, including controlled-release polymer-based pharmaceutical formulations, and I have been an expert in this field since prior to April 22, 2004. Additional details of my education, experience, and credentials are set forth in my aforementioned *curriculum vitae*. (Ex. 1031.) I also believe that, because of my education, experience, and interactions with students at all levels (undergraduate, Master, Pharm.D., and Ph.D.) and scientists, researchers, and administrators at all levels in this field, both in academia and industry, I understand who a person of ordinary skill in the art was as of April 22, 2004, and what such a person would have known. I also believe that I understand who a person of ordinary skill in the art was as of April 22, 2004, and what such a person would know from, my review of the literature in connection with my consideration of the '499 Patent.

III. THE '499 PATENT

14. I understand from the face of the '499 Patent (Ex. 1001) 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”) (Ex. 1032). I have been advised by counsel to assume that the earliest possible effective filing date for the '499 Patent is April 22, 2004.

15. The '499 Patent alleges that the “inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone.” (Exs. 1001 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

16. The specification discusses the need for improving naltrexone therapies by improving patient compliance. (Ex. 1001, 1:13-26.) Alkermes never equated its discovered difference in a pharmacokinetic property to any meaningful therapeutic difference. It is worth noting that the '499 Patent did not suggest that it provided a cure to alcoholism or drug abuse. Indeed, 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.

(Ex. 1001, 18:48-52.) In fact, it acknowledged that based on semi-quantitative comparisons of three meta-analyses, “the efficacy of Vivitex suspension compares favorably with oral naltrexone.” (*Id.* 19:30-34.) It did not, however, argue superior efficacy. I believe that a POSA would read the phrased “compares favorably” in this context as no better than oral naltrexone. What I mean by that, and what I mean when I state that there is no evidence of efficacy improvement, that there was no argument of superior efficacy, or other words to the effect, is that there is no “meaningful” evidence in the patent or raised during prosecution that would allow a POSA to draw a conclusion of improved efficacy or superiority. A POSA would note Alkermes’ acknowledgement that there were no direct studies comparing these two dosing protocols. They would know that to make any valid claim to improve efficacy would require a properly structured clinical study such as a randomized, or crossover, double-blind trial. Meta-analysis alone is of dubious weight to a POSA which is, perhaps reflected by the fact that during prosecution, Alkermes did not make more of any alleged efficacy improvements. Particularly important here is the fact 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. And Alkermes never linked any efficacy difference to a difference in AUC.

17. In some embodiments, naltrexone is combined with well-known polymers, such as PLGA, to “entrap or encapsulate” the naltrexone to form long acting formulations. (Exs. 1001, 3:14-15.) 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 that the therapy can be maintained for 24 weeks or more. (*Id.* 4:55-64.)

18. The specification also includes five examples, three of which were not present in the original provisional application to which the ’499 Patent claims priority. (Exs. 1001; 1032.) 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* Exs. 1001, 3:3-33, 5:35-8:2 and 1018, 7:48-8:60; *see* ¶ 133, *infra.*)

19. 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. (Ex. 1001, 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.

20. The '499 Patent 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. (*Id.* 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

21. I am an inventor and have been involved in patent prosecution and litigation and therefore I have a general understanding of the patent prosecution process. However, when I review a prosecution history, I do so as a technical expert.

22. I understand from 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 (Ex. 1002), which rejected the claims as allegedly being anticipated by Tice (Ex. 1015) and, in the alternative, as being obvious over the combination of Tice and Chandrashekar. I understand that Alkermes responded on October 5, 2009 (Ex. 1004) with claim amendments and a declaration under 37 CFR § 1.132 by Elliot Ehrich (the “Ehrich Declaration”) (Ex. 1003), the inventor of the ’499 Patent.

23. I understand that the Examiner issued a second non-final office action on January 6, 2010 (Ex. 1005), 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. (Ex. 1006.) A final rejection was mailed on July 20, 2010 (Ex. 1007), maintaining the enablement rejection. Alkermes filed a response after final on October 20, 2010 (Ex. 1008), 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.

24. 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. (Ex. 1009.) I understand the Examiner also included a reasons 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

25. I understand from my own experiences and from counsel that patents are read by, and are to be read in light of the knowledge of, a person of ordinary skill in the art (“POSA”) as of the earliest effective filing date of the patent. I have been told by counsel to assume that the earliest effective filing date is April 22, 2004, for purposes of this declaration. All of the prior art relied on in my declaration was filed or published more than a year before the earliest effective

filing date or was filed in the United States before the earliest effective filing date of the '499 Patent.

26. It was explained to me by counsel that a POSA is a hypothetical person who is deemed to be aware of all relevant prior art. A POSA is also a person of ordinary creativity, not an automaton.

27. I am further told by counsel that factors relevant to determining the level of skill in the art include: the educational level of the inventor(s), the types of problems encountered in the art, prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. I understand from counsel that a POSA may be a composite of different types of individuals.

28. In regards to the education levels of the inventor(s) and education level of active workers in the field, I believe one of ordinary skill in the art would have a Pharm.D. or Ph.D. degree in pharmaceutics (also known as pharmaceutical chemistry or pharmaceutical science), chemistry, chemical engineering, or biomedical engineering with two or more years of experience in in the field of controlled-release formulations, or a Master's degree in said field with five or more years of experience in the field of controlled-release formulations.

29. I note that Dr. Ehrich, the sole inventor of the '499 Patent, had a medical degree. However, the treatment steps of the claimed method are relatively

simple and very well known. Moreover, the method was not the central focus of the discussion of patentability. The central issue was the AUC and how that AUC compared to other formulations. In my experience, that is the province of a Pharm.D. or Ph.D. in a related formulation discipline, more than, typically, a medical doctor.

30. Consistent with my understanding, many of those associated with the types of solutions to those problems encountered in developing new sustained release formulations, and in particular, injectable long-acting PLGA microparticles, have a Ph.D. degree in a relevant formulation discipline. For example, according to their LinkedIn pages, Alkermes' Dr. Michael Ramstack, who is a co-inventor of Alkermes' Wright patent (Ex. 1018), has a Ph.D. in Chemical Engineering, and R. H. Reuning, author of Exhibit 1026, has a Ph.D. in Pharmacy (Exs. 1054, 1055).

31. The technology tends to be sophisticated, as it requires an interdisciplinary understanding of such diverse topics as PLGA chemistry and degradation properties, drug solubility in water and in polymers, selection of solvents, drug release kinetics, drug dose, PLGA microparticle size, etc. This also suggests that advanced degrees and practical experience are required. Indeed, even Mr. Steven Wright, first named inventor of Alkermes' Wright patent (Ex. 1018)

has an undergraduate degree in Chemical Engineering and more than 15 years of experience (Ex. 1056).

32. As of the relevant date of April 2004, I believe I was a POSA under any plausible definition. Further, 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

33. I understand that it is often desirable to construe the meaning of claim terms to eliminate ambiguity when possible. I also understand from counsel that the claims in an IPR are to be given their broadest reasonable interpretation (“BRI”) unless they are specifically defined otherwise. My understanding of broadest reasonable interpretation is that the definition must be consistent with the understanding of a POSA in the field and with the specification and statements made during prosecution. Terms are not necessarily limited to only those examples recited in the specification. Under the BRI standard, terms can be given a more inclusive meaning.

A. “a long acting formulation”

34. Claim 1 recites “a long acting formulation.” I believe a POSA would understand this to mean a formulation that provides controlled/sustained/extended release of at least one week. A POSA would appreciate that this is distinct from immediate release. And the specification defines “long acting” as delivering

“therapeutically beneficial amounts of naltrexone to a patient for a period of at least one week.” (Ex. 1001, 3:11-13, 3:59-64.) I believe that a POSA would accept that definition.

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

35. Claim 1 recites “the serum AUC of naltrexone is about three [or 3.3] times greater than that achieved by 50 mg/day oral administration.” Interestingly, especially considering the allegedly “unexpected” discovery of this limitation, the ’499 Patent does not define this term or provide directly comparative data.

36. Although “serum AUC” is not defined by the specification, a POSA would appreciate that this refers to “area under the curve.” AUC is a pharmacokinetics concept that describes the area under the plasma concentration-time curve. The plasma concentration indicates the drug concentration in the blood, and it is also referred to as the serum concentration or plasma concentration. The pharmacokinetic profile is frequently characterized by the maximum drug concentration ($C_{\max}$), the time reaching the $C_{\max}$ ($t_{\max}$), the time period that the drug concentration in blood decreases to a half of the initial concentration ($t_{1/2}$), and the area under the curve (AUC). AUC is simply the total area defined by the plasma concentration-time profile, and thus, its unit is the plasma concentration multiplied by time. Since the plasma concentration plot is often not straight, the AUC is

calculated by integrating the drug present in each time interval either manually or using a computer program.

37. Moreover, AUC is a function of the drug dose. Alkermes appears to agree. (Ex. 1027, at 7) Integrating the AUC plot therefore allows one to calculate the extent of drug absorption which is related to the dose administered. The information on the bioavailability and clearance of a drug leads to the calculation of the dose administered. More explanation on the AUC is presented below in paragraphs 56-59.

38. AUC is not a measure of therapeutic efficacy. So long as the patient consistently has a blood concentration of the drug at or above the level needed for efficacy, the treatment should be effective. But the shape of the blood concentration plot and the AUC does not dictate efficacy. As the '499 Patent points out, "the most commonly used endpoint for oral naltrexone has been the dichotomous outcome, relapse to heavy drinking (yes/no)." (Ex. 1001, 18:30-32.)

39. The '499 Patent also lacks a definition of "about three times greater than that achieved by 50 mg/day oral administration." The problem here is not with the literal wording, but with the fact that no data is provided to establish the AUC of the claimed formulation or the AUC of 50 mg/day oral dosing. Instead, the '499 Patent merely makes unsubstantiated assertions about this relationship. (Ex. 1001, 1:36-40, 2:23-36.) It does discuss comparisons between its formulation

and oral formulations, based on “meta-analysis” of the efficacy with oral naltrexone found in the prior art (*Id.* 18:3-19:33.) But it does not provide the underlying data or provide a differential between the two dosing protocols.

40. The '499 Patent identified a number of references when discussing the differences between the pharmacokinetic profiles of a depot injection and oral dosing. (*Id.* 17:49-62). But that discussion does not reflect a comparison of the relative AUC of these two dosing protocols. Instead, the '499 Patent merely discusses peak naltrexone levels and the peaks' alleged impact on reduced tolerability of oral naltrexone including eliminating daily naltrexone peaks and decreasing the ratio of the drug to a particular metabolite. The '499 Patent does not suggest that any of these three references contain data that define the AUC of 50 mg/day oral dosing. Moreover, the references themselves do not provide AUC data. (*See* Exs. 1033; 1034; 1035.)

41. As the '499 Patent does not define the AUC of the claimed formulation or claimed oral dosing, a POSA must look to the art. They would find, that there is no single accepted data set for the AUC resulting from administering 50 mg/day orally, in the art or in the specification. Instead, the art reports varying data sets, none of which match. (*See* ¶¶ 63-86, *infra.*) Without knowing this information, it is not possible to calculate an AUC differential between these two dosing protocols—the results will vary with the data set used.

42. As noted previously, AUC is a function of dose. (Ex. 1027, at 7.) Here, the claim reflects a dosing range of 310 to 480 mg, which is a broad range. So the AUC for each of these doses will necessarily be different. And, since there is no consistent set of data provided to use for the comparative oral dosing, it is almost impossible to know if the resulting differential is accurate or meaningful.

43. As Alkermes did not provide a data set, I believe a POSA would conclude that Alkermes intended to allow a POSA to use any available data set. In other words, a POSA could use any published data for the AUC of the claimed dose compared to any data for the AUC of a 50 mg/day oral dose.

44. Regardless of the issues mentioned above, it should be noted that the AUC differential as claimed has nothing meaningful to do with efficacy. (See ¶¶ 60-62, *infra*.) As AUC is dose dependent, if the art gives the same or substantially the same dose in the same way, a POSA would reasonably expect that the AUC values would be the same. So, too, would any AUC differential.

C. “about three”

45. Claim 1 requires “about three times greater” than that achieved by oral administration of 50 mg/day. The term is not specifically defined in the ’499 Patent. I understand from counsel that dependent claims are to further narrow the claim from which they depend. Claim 5 of the ’499 Patent requires an AUC of

“about 3.3.” Thus, to a POSA, it would appear that “about three” must encompass “about 3.3” or even higher.

46. I note that the Ehrich Declaration supports this conclusion. In his declaration, Dr. Ehrich uses data indicating the AUC of 3.3 times greater than oral dosing to support patentability of claims 1, and all that depend therefrom, including claim 5.

47. I further note that since “about three” encompasses “about 3.3,” a POSA would also expect it to encompass a range of differentials, including at least about 2.7 to about 3.3, if not an even wider range. Furthermore, United States Pharmacopeia (USP) described “about” to indicate a quantity within 10%. Thus, about three indicates values ranging from, at a minimum, 2.7 to 3.3. (Ex. 1043, at 8.)

D. “five or more days”

48. Claim 2 requires that the individual not use oral naltrexone within five or more days before administration of the formulation. Because I understand the standard is the BRI, I believe a POSA would read this claim as either encompassing no prior oral naltrexone administration within five days or simply no prior oral naltrexone administration. Since the BRI standard applies, I think a POSA would choose the latter meaning.

E. “initial oral dose”

49. 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’s addiction long-term. The art, however, makes clear that there are other purposes. For example, Comer teaches the use of naltrexone as part of a detoxification process. (Ex. 1010, at 353.) There is a break between administering the detoxification doses and the treatment doses of two days. (*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. (Exs. 1015, 5:65-6:6, 6:13-17; 1011, at 1074.) Clearly the art distinguishes initial treatment doses from prior doses given for other purposes. Accordingly, I think a POSA would appreciate that “initial oral dose” as used in the ’499 Patent is an earlier treatment dose, but not a dose given for detoxification or to determine tolerance and the like.

F. “about 35% by weight”

50. 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. (Ex. 1001, 6:52-54.) A POSA would

appreciate that this term refers to the percent by weight of Naltrexone in the particle.

VII. TECHNICAL BACKGROUND AND STATE OF THE ART

51. The challenged claims are directed to treating certain conditions, such as alcoholism 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”).

52. As noted elsewhere, naltrexone as a treatment for patients suffering from alcoholism and opioid addiction dates back to the 1980s. (Exs. 1010, at 351-352; 1011, at 1075; 1012 Summary; 1013; 1014, 19:22-25; 1016, at 3; 1022 Abstract; 1023; 1024, 1:55-2:50; 1026, at 173.) Naltrexone was originally developed and patented (Ex. 1057) by Endo Laboratories in the 1960s. Naltrexone hydrochloride, originally under the tradename Trexan and later known as ReVia, received FDA approval in 1984. (Ex. 1036.) The formulation delivered 50 mg/day orally to patients for opioid and alcohol addiction. (Exs. 1023, 936-938; 1028, at 420; 1036; 1040, 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. (Exs. 1010 Abstract; 1011, at 1078; 1012, at 7; 1013; 1015, 6:19-39.)

53. Individuals in need of naltrexone include a wide variety of people suffering from a number of conditions including, for example, respiratory failure, anorexia nervosa, obesity and constipation. But, when one speaks of a patient in need of naltrexone, all too often they are addressing a patient addicted to opioids or alcohol. (Exs. 1010, at 351-352; 1011, at 1074; 1015, 1:14-2:60; 1016, at. 3; 1019; 1022 Abstract; 1024, 1:13-2:61.)

54. One of the most frequently cited problems with treating alcoholics and drug addicts is patient compliance. For a variety of reasons, addicts who start treatment with the best of intentions, sometimes discontinued taking medication, and/or going to therapy, over the weeks and months usually necessary for treatment. This can compromise the results. Using a longer term depot injection, for example, was one method already known to address such compliance issues as the addict does not have as many opportunities to avoid taking their medication. (Exs. 1010, at 351-352; 1011, at 1075; 1012, at 2; 1013; 1014, 19:21-25; 1015, 1:46-2:7; 1016, at 3; 1019, at 82; 1025, at 704.) Several depot injections were known to provide a blood concentration of 1 ng/ml/day for weeks. (Exs. 1010, at 351; 1011, at 1074, 1078; 1014, 14:25-50, 19:4-25, Fig. 7; 1015, 3:5-17, 4:35-39, 6:19-39.)

55. Some of these depot formulations included naltrexone and PLGA. (Exs. 1010, at 354; 1011, at 1075; 1012, at 2; 1014, 14:24-49, 19:4-25; 1016, at 3,

5, 20; 1017, at 5; 1018, 7:49-8:60, 12:33-40; 1025, at 704; 1026, at 173 (delivery system I).) Finally, administering naltrexone doses falling within the claimed range from PLGA-containing formulations were known. (Exs. 1010, at 351, 354; 1014, 19:4-25, Fig. 7; 1017, 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 POSA. But as will be discussed below, even that aspect was also known.

A. The Area Under The Curve (AUC)

56. When a drug (in a suitable formulation) is administered to a patient, the bioavailability of the drug is usually measured by determining the drug concentration in the blood as a function of time. The plot of the plasma drug concentration versus time is frequently characterized by the maximum drug concentration ($C_{\max}$), the time reaching the $C_{\max}$ ($t_{\max}$), the time period that the drug concentration in blood decreases to a half of the initial concentration ($t_{1/2}$), and the area under the curve (AUC). (Ex. 1044, at 261.) AUC is simply the total area defined by the plasma concentration-time profile, and thus, its unit is the plasma drug concentration multiplied by time. Since the plasma concentration profile is not straight, the AUC is calculated by integrating the drug present in each time interval either manually or using a computer program. AUC was commonly calculated by the linear trapezoidal rule. (Ex. 1044, at 262.) The AUC is divided into a series of trapezoids which are formed between the data points for two

adjacent times. The sum of the areas of individual trapezoids is the AUC. This approximate method requires that blood sampling be frequent enough to make the curvature of the plasma concentrations between two data points negligible. (Ex. 1044, at 262.) AUC can be measured faster and more accurately using a computer and various computer programs have been available since the introduction of personal computers. (Ex. 1044, at 263.)

57. AUC has been used to evaluate the extent of drug absorption, and it depends on the extent of bioavailability (F), the systemic drug clearance (Cl) and the drug dose (D) as shown below. (Ex. 1044, at 262.)

$$AUC = \frac{D \cdot F}{Cl}$$

The bioavailability (F) and the systemic drug clearance (Cl) can vary depending on individuals, and thus, the AUC value may be different depending on the individuals or a group of individuals participated in a given study. For the same group of individuals, the AUC is dependent on the drug dose (D). In fact, for many drugs, the AUC is directly proportional to dose. (*Id.*) In the above equation, the systemic drug clearance (Cl) is equal to the drug elimination constant (k) times volume of distribution (V_D) of the drug in the body. (*Id.*) Both parameters can be measured independently, and are also constants for individuals. Thus, AUC is generally directly proportional to the drug dose (D).

$$AUC = \frac{D \cdot F}{Cl} = \frac{D \cdot F}{k \cdot V_D}$$

58. AUC, along with $C_{\max}$, $C_{\min}$, C_{ss} , has been used as a measure to assess a systemic exposure of a drug, *i.e.*, dose (drug input to the body). AUC is a typical pharmacokinetic variable used to represent the average drug concentration over a time period. (Ex. 1051, at 2, 14.) AUC is also used as a measure for product quality bioavailability and bioequivalence due to its capacity to assess a systemic exposure, which in turn reflects the rate and extent of drug absorption. (Ex. 1045.) AUC is routinely used in bioequivalence studies, because AUC is directly proportional to the amount of drug being absorbed, *i.e.*, the dose. (This is of course assuming that the bioavailability and clearance of a drug remain constant for a given individual, as shown in the equation in paragraph 57.) The mean AUC values for two different products can be directly compared, and the two products are considered bioequivalent, if the AUC of the test falls within the range of 80% to 125% of the reference product. (*Id.*; Ex. 1052, at 2.)

59. The unit of AUC is the drug concentration multiplied by time. The drug concentration can be ng/mL or mg/L, or any other unit that is capable of describing the amount of drug present in the blood. Here we will use ng/mL as the concentration unit. The time can be hours (h) or days (d or day). Thus, the unit of AUC can be (ng/mL)·h or (ng/mL)·day. Usually, the unit is simplified by removing

the parenthesis, and thus, it is used as, for example, “ng·h/mL” and “ng·day/mL,” or “ng*h/mL” and “ng*day/mL.” For convenience and consistency, I will use “ng·h/mL” and “ng·day/mL” throughout this declaration. The unit “ng·days/mL” sometimes used in the prior art is the same as “ng·day/mL.”

B. AUC Does Not Meaningfully Impact Efficacy

60. AUC is a pharmacokinetic variable. But it is not, at least not in this case, a measure of efficacy. As the '499 Patent points out, “the most commonly used endpoint for oral naltrexone has been the dichotomous outcome, relapse to heavy drinking (yes/no).” (Ex. 1001, 18:30-32.) Furthermore, as noted above, it was known that naltrexone provides effective treatment as long as its blood concentration is maintained at or above 1 ng/ml. It was also known that this blood level could be achieved through oral dosing and depot injection. (See ¶¶ 52-55, *supra*.) So long as a formulation, whether oral or parenteral, provided this minimum therapeutic concentration over the desired dosing interval, the treatment should be effective no matter how much higher the blood concentration—the AUC—went. In any event, a POSA would expect it to be at least as effective as the '499 Patent, assuming the patient is compliant with their dosing regimen. Indeed, a higher AUC than therapeutically necessary could suggest exposing the patient to more of the drug than necessary. This could expose some patient to unnecessary side effects. Naltrexone was shown to cause liver toxicity to some patients

depending on the total dose. (Exs. 1053, at 1098; 1046, at 554.) As shown above in the equation in paragraph 57, a patient with reduced drug elimination rate constant may increase the naltrexone concentration to above the safe concentration. It is always good to maintain the drug concentration above the effective therapeutic level but not so high as to cause potential side effects.

61. Nothing in the specification of the '499 Patent would assure a POSA that its treatment method provided superior efficacy. Indeed, the best that can be said was that the data were comparable. Specifically, the study in the '499 Patent only compared efficacy to patients receiving a placebo. (Ex. 1001, 10:27-16:62.) The '499 Patent admits that a direct head to head comparison of efficacy between its product and oral naltrexone had not been made. (*Id.* 18:4-12.) The '499 Patent then compares its product to three meta-analyses of the efficacy of oral naltrexone found in the prior art. "Based on semi-quantitative comparisons to these 3 meta-analyses, the efficacy of Vivitrex suspension compares favorably with oral naltrexone." (Ex. 1001, 19:31-34, *see* ¶ 16, *supra*.) Clearly, despite an allegedly unexpected AUC differential, a POSA would conclude that, in terms of efficacy, oral is just as effective as their depot injection.

62. Moreover, in the Ehrich Declaration, discussed in more detail below, Dr. Ehrich never suggested that oral dosing, or the formulation of Tice, both

allegedly lower in terms of AUC and AUC differential, were in any way inferior in treating a patient's addiction. (*See* ¶ 23, *supra*.)

C. A POSA Would Find The Claimed Comparison Inapt

63. At the time that the '499 Patent was originally filed (April 22, 2004), a lot was known about the treatment of addiction with naltrexone, including the use of a long-acting depot injection. (*See* ¶¶ 51-55, *supra*.) Because of this, I do not understand why the comparison made in the claims and the Ehrich Declaration was to oral dosing. I think a POSA would have similar questions. At the time, the prior art included much closer technology. Indeed, the technology was closer than the poly(D,L-lactide) (PLA) depot injection of Tice (Ex. 1015). It would be readily apparent to a POSA that the closest technology was embodied in the depot formulations of Vivitrex or Depotrex. (Exs. 1010 Abstract, 354; 1014, 6:6-9, 14:26-49, 19:21-25, Fig. 7; 1016, at 3; 1017 at 3; 1018, 7:49-8:60, Example 3.) Both of these technologies include one-month depot injections of PLGA and about 380 mg naltrexone. Both were administered to patients fighting addiction. I think that a POSA would find data from these prior art systems far more instructive and meaningful to a consideration of the claimed invention. As noted earlier, AUC is a function of dose in this system. (Ex. 1027, at 7; *see also id.* ¶ 57.) The dosing disclosed in the art were the same, or substantially the same, as the about 380 mg dose described in the study reflected in the '499 Patent and specifically claimed in

claim 5. A POSA therefore would expect that the AUCs disclosed in the art and in the '499 Patent would be the same or substantially the same. Because the AUCs should be the same, or substantially the same, so too the relative difference between their AUCs and that of other dosing protocols, such as 50 mg/day orally, should be the same, or substantially the same, as well.

64. To the extent that there was an AUC differential, I think a POSA would not find this differential meaningful. As noted above, it does not reflect a difference in therapeutic efficacy. That said, if there was any value to be obtained by a comparison of AUC differentials, I think a POSA would only consider a differential made by comparison to the closest prior art to be helpful and would largely completely discount comparisons to oral dosing or formulations made using other polymers, such as Tice. That said, even Tice teaches that the AUC values obtained vary greatly. *See*, for example, the standard deviation in the tables of columns 15 and 16. A POSA, looking to these standard deviations, would appreciate that this provides a range. A table in Tice (Column 14) describes the AUC values of oral 50 mg table and F-1 formulation showing a wide variation.

65. Moreover, I think a POSA would be dissuaded from placing much emphasis on the claimed comparison because it is purely hypothetical. Unlike direct comparisons to other one-month depot injections, this comparison is based on the use of an arbitrary oral AUC obtained for a single day, *i.e.*, AUC_{0-1d}. To

make a comparison, one must artificially divide or average actual one-month data by 28 or 30 days, or assume that the one day's data is constant and multiply by 28 or 30 days. As shown in Comer and Nywayser, also copied below in below in paragraph 76, the naltrexone plasma concentration of long-acting PLGA microparticle formulations is not homogeneous over the 28-day period, and using an average AUC_{0-1d} by dividing AUC_{0-28d} by 28 does not provide an accurate comparison. For example, AUC_{27-28d} , or AUCs of many days near the end of the 28-day period, do not have 3 times greater AUC than the oral AUC_{0-1d} . In addition, the assumption that one-day oral AUC can be repeated exactly for 28 days is not validated. As shown by the equation in paragraph 57, AUC depends on the bioavailability (F) that can be affected by various factors. For example, AUC_{0-1d} of oral naltrexone may vary depending on the type of food present at the time of oral administration, affecting the gastric emptying, motility, and pH. Even the same person may not have exactly the same plasma concentration-time profile every day for 28 days. Thus, comparing AUC_{0-28d} of a long-acting microparticle formulation against an arbitrarily chosen AUC_{0-1d} of oral naltrexone does not provide an absolute information. This problem is eliminated by direct comparisons to other one-month depot injections, which as mentioned above were clearly available at the time. Moreover, as discussed below, the fact that the '499 Patent failed to provide standard data for comparison and the fact that the oral AUC_{0-1d} varies

depending on the study, makes it difficult for a POSA to accept the claimed comparison at face value.

**D. The Claimed AUC Differential
Is Known Or Would Be Apparent**

66. Depending on which oral AUC_{0-1d} value is used, many prior art references show that the AUC of long-acting depot formulations of the art, over a 28-day period (AUC_{0-28d}) is about three times greater than the comparable AUC derived from a 50 mg/day oral dosing.

1. The AUC Of Comer

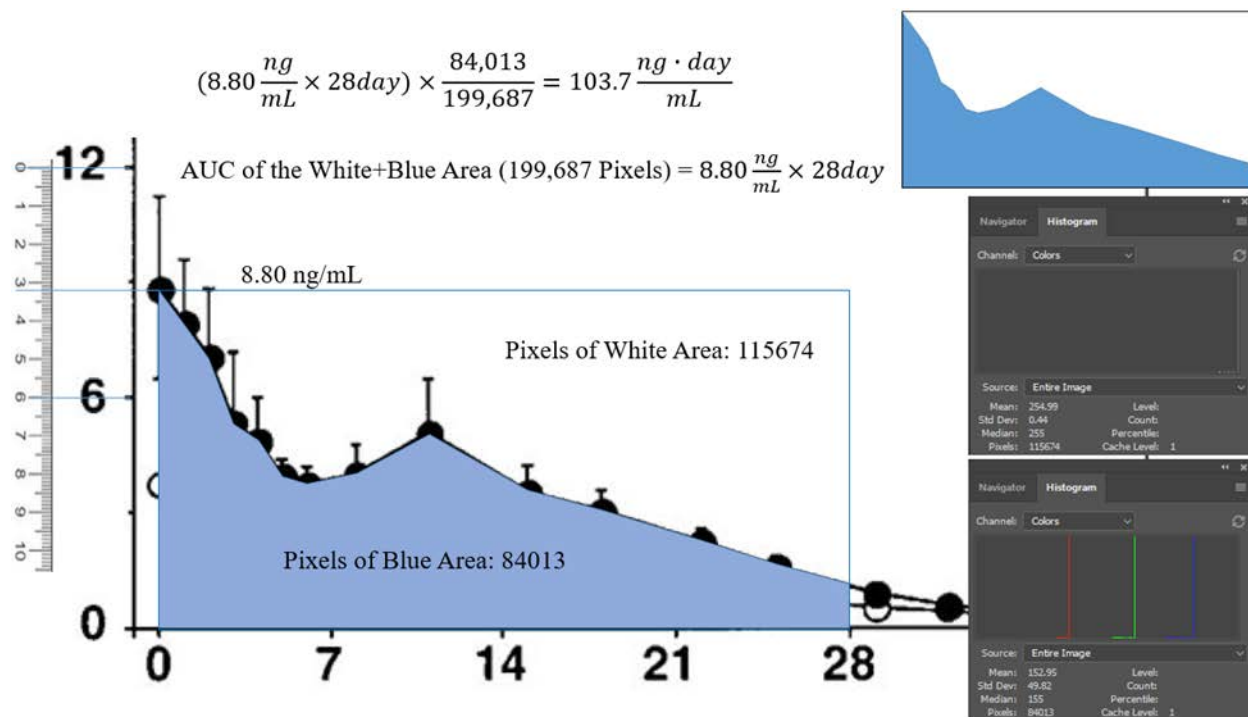
67. The AUC can be measured by using computer software that measures exact pixel numbers of an area. This allows accurate measurements of AUCs and is well known to a POSA. A POSA would have had access to various software well in advance of the filing date of the '499 Patent. However, as mentioned above in paragraph 56, older manual techniques, such as the linear trapezoidal rule, can be used for calculating AUC as well.

68. Comer (Ex. 1010) provides the pharmacokinetic (PK) profile in Figure 1 on page 17. The plot on the left is for naltrexone. The plot on the right is for a metabolite. But I will be confining my discussion to the naltrexone plot. I have enlarged this plot below to identify accurately the time points. The AUC is indicated below in blue, and is the area below the curve, connecting each day's data points. The total pixel number is calculated by using Photoshop, which has

been available since the early 1990s, and the fraction of the blue area is calculated as well. Since we know the AUC of the total area (*i.e.*, blue area + white area in the figure), we can calculate the AUC in the blue region.

69. The AUC_{0-28d} of the Comer 384 mg dose administered (Ex. 1010 Abstract, 354) is 103.7 ng·day/mL as shown by the calculation presented in the figure below. The software I used for this calculation was Photoshop, but other software and manual methods for providing this calculation were well-known at the time of the '499 Patent. As shown in the figure below, the total area implicated by the curve is bounded by the C_{max} of 8.80 ng/ml and the duration, 28 days. This defines a box and the area can be calculated or measured by a computer in terms of the number of pixels it encompasses. Since we are only interested in the area under the curve, counting the pixels under the curve and dividing by the total number of pixels in the box gives us percentage of the total area that is under the curve. Multiplying the percentage of the total area by 8.80 ng/ml times 28 days yields the area under the curve, which in this case is 103.7 ng·day/mL. This calculation takes into account the variability in the plasma drug concentration from day to day over the 28 days that measurements were taken. As noted previously in paragraph 65, this is a more accurate measurement than taking a daily release profile, assuming it is consistent throughout 28 days, and merely multiplying the single day's profile by 28 days. For that reason alone, a POSA would consider a comparison to a more

comparable depot injection to be more appropriate and more meaningful than a comparison to once a day oral dosing.



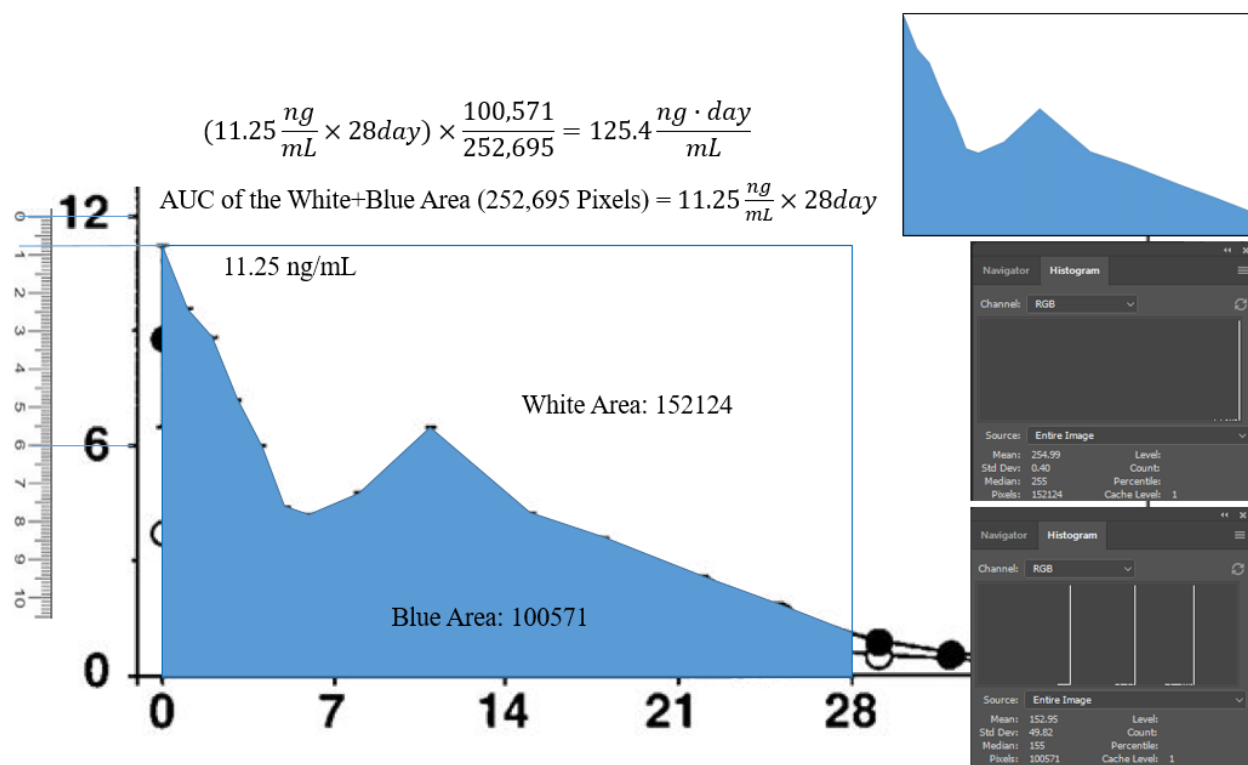
70. Alkermes acknowledged that AUC, indeed all the pharmacokinetic properties, are dose dependent (Ex. 1027, at 7), and I agree. A POSA would appreciate this as well. That being the case, the AUC for a 380 mg dose delivered from Alkermes' vehicle should provide the AUC illustrated above or something substantially similar to that. And a POSA would expect that as well. The data presented in the Ehrich Declaration tends to bear out this relationship. For example, in Table 8 of Exhibit A, the AUC_{0-t} is 120.6. However, the mean has a standard deviation of 19.6. (Ex. 1003, at 6.) A POSA would find these quite comparable. In fact, as shown by the equation in paragraph 57, different groups of

individuals participated in different studies may have had slightly different bioavailability (F) and systemic drug clearance (*i.e.*, elimination constant (k) and volume of distribution (V_D)), and it is common to see minor differences in the pharmacokinetic properties depending on the studies. The important point here is that the two AUC values are statistically the same. For a given cohort, the AUC will be dose dependent as long as the same formulation is administered the same way.

71. To a POSA, the comparability of these AUC measurements between two 28-day depot injections of about 380 mg of naltrexone in a PLGA particle would be the most meaningful. This is, of course, subject to the fact that neither appears to have a direct impact on therapeutic efficacy. A POSA would want to know that each day the patient has sufficient minimum blood levels for efficacy. They would want to know if at any point during the period of treatment blood levels dipped below a therapeutic value. They might also be interested in any spike in blood concentration as that might indicate an exposure to drug levels that could be accompanied by side effects. Other than ensuring that dosing each day is within this therapeutic window, a POSA would appreciate that the AUC alone is not particularly therapeutically meaningful. Accordingly, how the AUCs compare to some other administration technique, *e.g.*, oral dosing, is even less meaningful.

72. Even though a comparison to oral dosing would not be very meaningful to a POSA, it is nonetheless reflected in the claims of the '499 Patent. Because the patent provides no data, a POSA would look at the Ehrich Declaration, which provides the only AUC data presented during prosecution. The oral AUC provided for Cohort A of Exhibit A, labeled Table 8 is 1.278 ng·day/mL. Over a 28-day interval, this equates to 35.78 ng·day/mL. Dividing the AUC_{0-28d} of Comer, which is 103.7 ng·day/mL, by the 35.78 ng·day/mL from oral dosing, as reflected in Cohort A, yields a differential of 2.90. A POSA would conclude that this is about three.

73. Looking at the actual Figure in Comer, a POSA would see each data point at the center of a standard deviation, indicated by a vertical bar through its center. If instead of using the location of the actual data point, one were to use the upper end of the standard deviation, the AUC of the Comer increases from 103.7 ng·day/mL to 125.4 ng·day/mL, as shown in the figures and calculations below.



Now, comparing the AUC of Comer (*i.e.*, 125.7) with that of the injectable dose reflected in Table 8 of the Ehrlich Declaration (*i.e.*, 120.6) shows them to be even more comparable. Moreover, using Comer's AUC in comparison to the oral dosing provided by the Ehrlich Declaration for Cohort A, the differential becomes 3.5.

(*e.g.*, $(\frac{125.4}{1.278 \times 28} = 3.5).$)

74. Now, if instead of using the oral data provided by the Ehrlich Declaration, the oral AUC_{0-28d} data found in Tice (Ex. 1015, 14:34-58) is used, the mean AUC_{0-28d} of Comer is 3.2 times greater than the oral AUC_{0-28d}.

($\frac{103.7}{(27.8 \div 24) \times 28} = 3.2$). And if the higher end of the standard deviation of Comer is

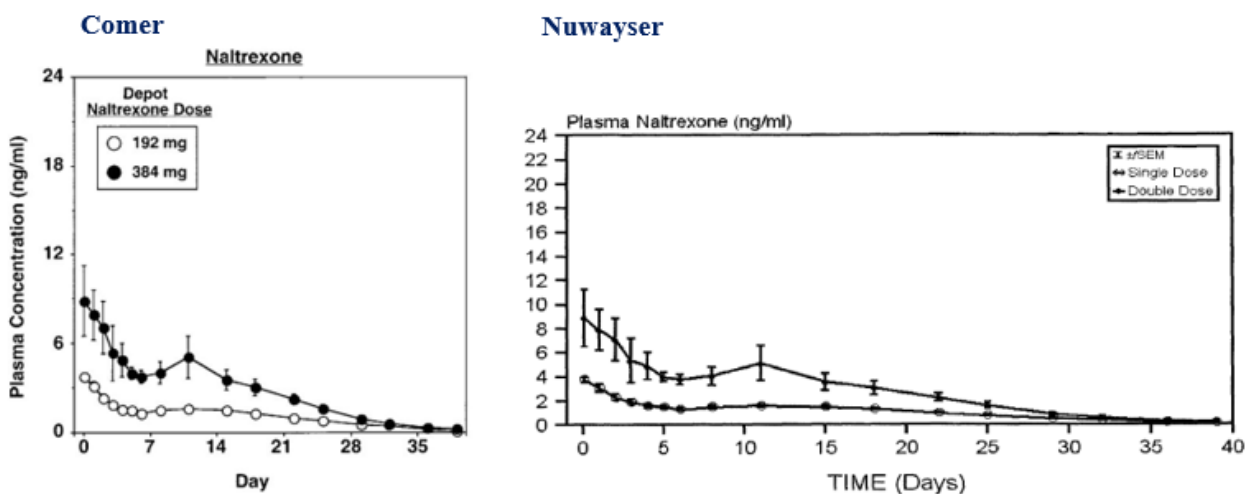
used, then the AUC differential is 3.9 times greater than the oral AUC_{0-28d} used in the Tice patent ($\frac{125.4}{(27.8 \div 24) \times 28} = 3.9$). Note, I have rounded to a single decimal place.

2. The AUC Of Nuwayser

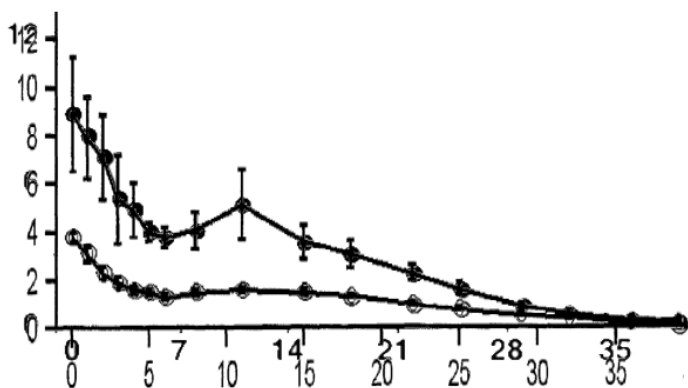
75. Nuwayser (Ex. 1014), like Comer (Ex. 1010), teaches administering a naltrexone/PLGA microparticle to six heroin dependent patients over a period of 28 days. Nuwayser explains in Examples II and IV (Ex. 1014, 6:6-9, 14:25-49, 19:4-25) how the particles are made and the exact proportion of naltrexone in the particles. It identifies this formulation as a “Depotrex” formulation available from Biotek, Inc. of Woburn, MA. (*Id.* cover sheet, Fig. 7.) Comer, similarly, identifies its formulation with the trademark Depotrex manufactured by the same company. (Ex. 1010, at 354.)

76. Moreover, Dr. Nuwayser, the inventor of Nuwayser, is one of the authors of Comer. Comer does not specifically identify the makeup of the Depotrex particles, but Nuwayser provides those details. (Ex. 1014, 6:6-9, 14:25-49, 19:4-25.) Similarly, Nuwayser does not identify a specific dose, but one would expect that dose to be the dose of Comer, looking at their pharmacokinetic plots. (*Compare* Exs. 1010 Fig. 1 *with* 1014 Fig. 7.) As shown below, a POSA would recognize that the Nuwayser AUC is exactly the same as the Comer AUC,

as they are two figures drawn from the same data. The figure below on the left is the data from Figure 1 of Comer and the figure on the right is from Figure 7 of Nuwayser.



77. If the above two figures are overlapped, the two pharmacokinetic profiles match exactly. One figure was adjusted in the X and Y dimensions to match the size. As shown below, the two are exactly the same data.



Since the plots are the same, so too must their AUCs and their differentials over oral dosing as discussed above in connection with Comer.

3. The AUC Of Vivitrex

78. Vivitrex, currently known as Vivitrol¹, is an Alkermes depot injection that includes 380 mg naltrexone in PLGA. (Exs. 1016, at 3; 1017, at 5; 1018 Example 3, 7:49-8:60.) It was to be administered monthly to patients suffering from alcoholism and/or opioid dependence. (Ex. 1016, at 3.) Alkermes has acknowledged that pharmacokinetics, which include AUC, is dose dependent. (Ex. 1027, at 7.) Since the dose of Vivitrex is 380 mg of naltrexone (Ex. 1017, at 5) the AUC resulting from its use must be the same as that claimed, as well as Comer and Nuwayser. This product reflected in the 10-K is the same as that tested in the '499 Patent so its properties should be the same. As described above in paragraphs 57 and 70, the exact AUC values may be different due to the differences in the cohort participated in each study. But in the same cohort, the AUC is directly dependent on the dose. This means that to compare the AUCs of two different formulations, they have to be tested in the same cohort. Otherwise,

¹ Vivitrol and Vivitrex appear to be the same product. Vivitrex was renamed Vivitrol sometime after the Vivitrex trademark was granted. (Ex. 1050, at 742.) Therefore, any data discussed relating to Vivitrex should apply equally to Vivitrol, and vice versa.

differences in the absolute AUC values are unavoidable. This further highlights that the comparison of AUCs of oral and long-acting formulations depends on which data is used.

79. AUC data was provided for Vivitrol in one of the FDA documents titled (FDA PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING VIVITROL[®] (naltrexone for extended-release injectable suspension) NDA 21-897. 16 September 2010). Table 3, as shown below, shows the C_{max} and AUC_{0-28d} values of Vivitrol and oral 50 mg naltrexone from the FDA submission. (Ex. 1047, at 23.)

Table 3: Steady State Pharmacokinetic Parameters of Naltrexone and 6 β -naltrexol following VIVITROL (380 mg) and Oral Naltrexone (50 mg) Administration

		VIVITROL	Oral Naltrexone
Dose / # of Subjects		380 mg every 28 days; Dose 4 of 4 / n=10	50 mg daily ^a ; Dose 5 of 5 / n=14
Naltrexone	C_{max} (ng/mL)	28.0 (12.2)	13.7 (10.6)
	AUC_{0-28} (ng•day/mL)	160 (24.2)	41.2 ^b
	$t_{1/2}$ (days)	4.7 (1.3)	0.17 (0.07)
6 β -naltrexol	C_{max} (ng/mL)	34.2 (12.9)	139 (36.0)
	AUC_{0-28} (ng•day/mL)	294 (70.4)	1002 ^c
	$t_{1/2}$ (days)	5.1 (1.1)	0.57 (0.08)

^a 50 mg/day $\times$ 28 days = 1400 mg total equivalent monthly dose

^b Calculated as ($AUC_{0-1} \times 28$), where $AUC_{0-1} = 1.47$ ng•day/mL following the 5th oral dose

^c Calculated as ($AUC_{0-1} \times 28$), where $AUC_{0-1} = 35.8$ ng•day/mL following the 5th oral dose

80. The data in the Vivitrol column appears to match the data in the Ehrich Declaration for Cohort B. (*Compare* Ex. 1003 Exhibit A (Table 8) *and* Table 3 above (Ex. 1047).) $C_{\max}$, AUC_{0-28} , and $t_{1/2}$ in Table 3 above are 28.0, 160, and 4.7, respectively, while they are 27.96, 159.9, and 4.732, respectively for Cohort B in Table 8 of the Ehrich Declaration. In addition, the $C_{\max}$, AUC_{0-28} , and $t_{1/2}$ values for oral naltrexone are exactly the same, too. Accordingly, the AUC and the AUC differential between Vivitrex/Vivitrol and the oral data of the Ehrich Declaration must be identical to the data resulting from the study reflected in the '499 Patent—indeed, it is the same data. While neither the '499 Patent nor Exhibits 1016-1018 provide AUC data, since the products described in these publications are identical, so too must their AUC and AUC differential. And the above-data bears this out. By placing the information contained in Exhibits 1016-1018 in the public domain, a POSA would have reason to believe that producing a product as disclosed in those exhibits would necessarily provide these same properties.

81. If a POSA were to use either the Ehrich or Tice data to determine the differential between the AUC resulting from the formulations described by Comer, Nuwayser, or Vivitrex and a 50 mg/day oral dosing, the resulting AUC differential would be about three, indeed about 3.3. As this AUC differential was known, or would at least be readily apparent to a POSA, this was not an unexpected result.

E. AUC Differential Varies With The Data Used

82. As noted above, the AUC differential can vary depending on whether the oral data from Tice or the Ehrich Declaration is used. However, in the Comer, Nuwayser, and Vivitrex examples above, the result was still a differential of about three times greater than oral dosing. But that is not always the case. There is a considerable amount of publicly known 50 mg/day oral naltrexone data and the differential can vary widely, depending on which data set is used. I have reviewed the following three references: Baek, Alza, Eon. (Exs. 1037; 1038; 1039.) The $C_{\max}$ and AUC values described therein are summarized in the following table. The AUC values are also described in two different units, ng·h/mL and ng·day/mL. As shown in the table, $C_{\max}$ and AUC values vary widely depending on the study.

Table. Examples of $C_{\max}$ and AUC values of oral 50 mg naltrexone dose.

Study	$C_{\max}$ (ng/mL)	AUC _{0-24h} / AUC _{0-1d}	AUC _{0-∞h} / AUC _{0-∞d}	AUC _{0-28d}
Eon Labs (Ex. 1037)	6.812	21.773 ng·h/mL / 0.907 ng·day/mL	24.229 ng·h/mL / 1.009 ng·day/mL	25.4 ng·day/mL
ALZA (Ex. 1038)	8.82	20.36 ng·h/mL / 0.848 ng·day/mL	20.61 ng·h/mL / 0.859 ng·day/mL	23.8 ng·day/mL
Baek (Levia) (Ex. 1039)	12.27	(AUC _{0-12h}) 43.31 ng·h/mL / 1.80 ng·day/mL	(AUC _{0-12h}) 67.68 ng·h/mL / 2.82 ng·day/mL	50.5 ng·day/mL
Baek	12.01	(AUC _{0-12h})	(AUC _{0-12h})	50.7 ng·day/mL

(Traxone) (Ex. 1039)		43.45 ng·h/mL / 1.810 ng·day/mL	70.15 ng·h/mL / 1.923 ng·day/mL	
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83. Using the AUC data for Comer (103.7 and 125.4 ng·day/mL), and the AUC data for the claimed invention as reflected in the Ehrich Declaration (120.6 ng·day/mL), and calculating the AUC differential for ALZA, the differentials are, respectively, 4.4, 5.3, and 5.1. These have been rounded to one decimal place. In contrast, using the Baek (Traxone) data, the differentials are, respectively, 2.1, 2.5, and 2.4. None of the differentials resulting from this data are closer than 2.5. The Eon Labs data results in a differential of 4 or greater.

84. I think a POSA would take away three points from reviewing these materials. First, in view of this data, it should be readily apparent to a POSA that a differential of about three, or even higher, could be expected. And based on the arguments made in the Ehrich Declaration and Tice, a POSA may even expect a range of one to five times.

85. Second, what should not get lost in this discussion of AUC, and what I believe a POSA would find most relevant to the claims, which are to a method of medical treatment, is that no matter which data set is used, or which differential results, there has been no change in efficacy. As shown above, the AUC based on oral dosing projected over 28 days can vary widely. But in each case, the patients

received 50 mg of naltrexone a day, which would have treated their alcohol or opioid addictions. And as admitted in the '499 Patent, the efficacy of the Vivitrex suspension (covered by the claims) “compares favorably with oral naltrexone.” (Ex. 1001, 19:30-33.)

86. And finally, given its sensitivity to mathematical manipulation and its lack of any impact on therapeutic efficacy, a POSA would realize that a differential of the AUC of a depot injection, which is about three times that of a 50 mg/day oral dose, is not a superior result.

VIII. THE CHALLENGED CLAIMS WERE TAUGHT BY COMER AND NUWAYSER

A. Comer Discloses The Subject Matter Of Claims 1, 3-5, And 10-12

87. Comer describes the testing in human patients of a depot injection made from 384 mg of naltrexone (Depotrex[®]), specifically the Comer 384 mg dose comprised two 192 mg naltrexone injections. (Ex. 1010, at 354.) “[F]or the high dose, participants received two naltrexone injections (384 [sic] mg naltrexone base).” (*Id.*) I note that in the quote, the reference says “394.” However, that is the only occurrence of that number. Through the rest of the paper it is “384,” which happens to be two times the 192 dose given.

88. Comer’s depot formulation was injected into the buttocks of the patients using an 18 gauge needle—*i.e.*, parenteral administration. (*Id.*) This 384 mg dose of depot naltrexone antagonized heroin-induced subjective ratings for

five weeks and plasma levels remained above the therapeutic level of 1 ng/ml for 28 days. (*Id.* Abstract, 351, 354-355.) “These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” (*Id.* Abstract, 351.)

89. Comer therefore teaches the method of claim 1—treating patients in need of naltrexone (*i.e.*, patients that are dependent on heroin) by parenterally administering (*i.e.*, depot injection into the buttocks) a long acting (*i.e.*, 1 ng/ml blood levels for four weeks) formulation of about 310 mg to about 480 mg (384 mg) and PLGA. The only remaining element of the claim is the observed AUC differential when compared to a 50 mg/day oral dose. However, as discussed previously in paragraphs 67-74, *supra*, the differential between the AUC of Comer and 50 mg/day oral dosing is at least three, and, indeed, at least 3.3. (*See* ¶ 72 (differential of 2.9 when comparing Comer to Ehrich oral data, ¶ 73 (differential of 3.5 comparing Comer’s highest point of standard deviation to Ehrich oral data), and ¶ 74 (differential of 3.2 and 3.9, respectively when comparing Comer data to the oral data of Tice.) So Comer’s AUC differential is about three compared to 50 mg/day oral dosing of naltrexone.

90. I realize that Comer cites to, but does not describe, Depotrex[®]. Nevertheless, this material was known to a POSA at the time of the ’499 Patent to be an extended release microcapsule comprising naltrexone and a PLGA polymer.

Nuwayser, for example, specifically, describes a formulation of PLGA (65% LA: 35% GA) and 54.4% naltrexone which, when administered subcutaneously, delivered therapeutic levels in six heroin addicts for 30 days. (Ex. 1014, 19:4-25.) Figure 7 of Nuwayser, entitled “Naltrexone Plasma Level in Six Human Subjects After Single and Double SC Injections of Depotrex™,” links the formulation of its Examples II and IV to “Depotrex.” Indeed, a POSA would have more confidence that the materials are the same in view of the similarities between the protocols used in both and the identity of results. The protocol briefly described in Nuwayser is the same as that found in Comer, and the data in Figure 7 of Nuwayser matches that of Figure 1 of Comer. (See ¶¶ 75-77, 81, 89, *supra*.) And as I mentioned previously, Dr. Nuwayser is both the inventor of Nuwayser and an author of Comer. It would be clear to a POSA that “Depotrex” as used in Comer refers to a PLGA /naltrexone microcapsule as disclosed in Nuwayser. (Exs. 1010, at 354, Fig. 1; 1014, 19:4-25, Figure 7.)

91. In terms of the dependent claims 3 and 4, Comer’s teaches release for a month (28 days), so it directly teaches the subject of these claims. Claim 5 specifies that the dose is 380 mg and that the differential be about 3.3 times the AUC of oral dosing. As just noted above, Comer teaches a differential that is about 3.3 (*e.g.*, 2.9, 3.5, 3.2, and 3.9, depending on the comparison). (See ¶ 89, *supra*.) And that AUC differential was based on a comparison of about a 380 mg

depot injection and 50 mg/day oral dosing of naltrexone. Moreover, Alkermes admitted that, *inter alia*, AUC is dose dependent. Comer administers the same dose (384 mg, which is about 380 mg), and therefore it must result in the same AUC, and would also provide the claimed AUC differential.

92. Claim 10 specifies that the patient being treated is alcohol dependent. Although the patients in the Comer study were opioid dependent, Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. (Ex. 1010, at 352.)

93. Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. In Comer, patients did get oral naltrexone. But they did not get the depot injection until two days after the last oral dose and a POSA would not consider this an “initial oral dose.” (*Id.* 353.) In this instance, Comer provided the oral naltrexone as part of a detoxification process to ensure that the “participants were willing and able to tolerate [naltrexone’s] effects.” (*Id.*) A POSA would not consider this a part of the dosing administered to the patient to treat them, a process that begins following detoxification. Indeed, Comer clearly contemplated administering the depot injection in “settings where oral naltrexone may not be given prior to depot naltrexone.” (*Id.* 359)

94. As mentioned above, Comer teaches injection into the buttocks, so teaches the subject matter of claim 12.

**B. Nuwayser Discloses The Subject
Matter Of Claims 1, 3-5, And 11-12**

95. Nuwayser describes formulations of extended release microcapsules of naltrexone (65:35 PLGA and 54.4% naltrexone by weight) and explains that they can be subcutaneously implanted in heroin dependent patients to provide therapeutic levels of naltrexone for a period of 30 days. (Ex. 1014, 6:6-9; 14:25-49, 19:4-25, Figure 7). Nuwayser provides a graph of the AUC resulting from the use of the microcapsules of Example IV. (*Id.* Figure 7.) Nuwayser does not expressly disclose the amount of its microcapsules administered to the heroin dependent patients that generated the observed AUC in Figure 7.

96. Knowing the exact composition of the microcapsules and that they were therapeutically effective (so they must have delivered at least about 1 ng/ml—long known to be the therapeutic threshold), over 28 days, and knowing the observed AUC, a POSA could readily determine the therapeutic dose by integration of the plot in Figure 7, sometimes referred to as “back calculating.” And as discussed previously, the pharmacokinetic plots of Figure 1 of Comer and Figure 7 of Nuwayser are identical. (*See* ¶¶ 75-77, *supra*.) Therefore, the AUCs and the AUC differential, identified previously for Comer (*see* ¶¶ 67-74, 81, 89, *supra*) are the same for Nuwayser. So too must the doses be the same.

97. A POSA reading Nuwayser has the means, the protocol, and the endpoint. The dose is disclosed as well to a POSA from back calculating the information provided. Moreover, as discussed later, determining the dose, or using the dose of Comer in combination would be a normal exercise of ordinary skill.

98. Challenged claims 3-5, 11, and 12 are specifically taught by Nuwayser as well. Claims 3 and 4 are taught by Nuwayser's delivery of a therapeutic dose for 28 days. As for claim 5, Nuwayser's dose is about 380 mg as just discussed. Since the dose is the same as that disclosed and claimed in the '499 Patent, the AUC and differential must be the same also. As previously discussed, this includes a differential of about 3.3. (*See* ¶ 89, *supra.*) Nuwayser's AUC and differential should be the same as Comer's.

99. Claim 11 requires that the patient not receive an "initial" dose of naltrexone orally. Nothing in Nuwayser discloses giving any prior dose of naltrexone. Claim 12 requires that the parenteral administration be an injection. Nuwayser teaches subcutaneous injection ("SC") so teaches the subject matter of claim 12. (Ex. 1014 Figure 7.)

**IX. THE CHALLENGED CLAIMS
WERE READILY APPARENT TO A POSA**

**A. Comer In View Of Nuwayser And/Or Nuwayser In
View Of Comer And Either In View Of Wright And Rubio**

100. Even if Comer and/or Nuwayser did not teach all of the elements of the claims, such as the specific formulation of Depotrex[®] or the dose, what is missing would be readily apparent to a POSA from Comer, in view of Nuwayser and/or Nuwayser in view of Comer.

101. Comer discloses the method of claim 1—treating patients in need of naltrexone (heroin dependent patients) by parenterally administering (depot injection into the buttocks) a long acting (1 ng/ml blood levels for four weeks) formulation of about 310 mg to about 480 mg (384 mg) and a biocompatible (Depotrex[™].) As noted before, I believe a POSA would know from Nuwayser what Depotrex was and how to make and use it such that the disclosure of Depotrex in Comer is sufficient. I've been asked by counsel to assume, just for the sake of argument, that one would not read the discussion of Depotrex from Nuwayser as the meaning of the term Depotrex used in Comer. In that case, I think that a POSA would be motivated to use the Nuwayser naltrexone formulation of Examples II and IV in the method taught by Comer. And I think that they would have a reasonable expectation of success in doing so.

102. Specifically, to the extent that Comer does not describe the specific formulations that should be used, a POSA would seek out acceptable formulations capable of providing Comer's results. That POSA would find Nuwayser. Comer teaches a method of treating heroin addicts by using 384 mg naltrexone in naltrexone/PLGA microcapsules by parenterally injecting a depot formulation into a patient to provide therapeutic treatment for about 28 days or more. (Ex. 1010, at 351, 354, 358-359, Fig. 1.) But for the dose, Nuwayser teaches the same thing. (Ex. 1014, 19:4-25.) And, both provide data on the pharmacokinetic profile of their formulations, which a POSA would recognize to be the same, or nearly so. (Exs. 1010 Fig. 1; 1014 Figure 7; *see* ¶¶ 75-77, *supra*.) A POSA would therefore reasonably expect that using sufficient microparticles produced in accordance with Nuwayser to provide 384 mg of naltrexone, would achieve the AUC results of Comer.

103. Because the 384 mg/dose of Comer is about 380 mg and falls within the claimed range of 310-480 mg taught by the '499 Patent and AUC is dose dependent, both the AUC and the AUC differential for Comer should be the same as that claimed. Indeed, the calculations provided herein support the same. (*See* ¶ 89, *supra*.) To the extent that the result of the dose did not provide the plot of Figure 7 of Nuwayser, a POSA could clearly adjust the dose to arrive at that plot, if

indeed a POSA felt doing so was significant. (*See supra* ¶¶ 60-66, 82-86, *infra* ¶¶ 106-107.)

104. This combination of references can be looked at in the opposite order as well. Nuwayser describes formulations of extended release microcapsules of naltrexone (65:35 PLGA and 54.4% naltrexone by weight) and explains that the microcapsules can be subcutaneously implanted in heroin dependent patients to provide therapeutic levels of naltrexone for a period of 30 days. (Ex. 1014, 14:26-49, 19:4-25, Figure 7.) Nuwayser provides a plot of the pharmacokinetics of the AUC resulting from the use of the microcapsules of Examples II and IV. (*Id.*) The only thing that Nuwayser arguably does not explicitly disclose is dose—how much of the formulation made in accordance with its Examples II and IV are needed to provide the plot in Fig. 7. (*Id.*) A POSA seeking to find that answer could generate a standard curve without unreasonable experimentation. But a POSA would also be motivated to look to other known parenteral doses of naltrexone and would find Comer.

105. Like Nuwayser, Comer describes giving long acting PLGA naltrexone parenterally to six heroin dependent patients and a therapeutic level was delivered for about a month. Indeed, both reference administered “Depotrex” produced by the same manufacturer. And, Dr. Nuwayser is an author of Comer and was an employee of Biotek Inc. Finally, in both, the pharmacokinetic curves were reported

and are close to superimposable. (*Compare* Exs. 1010 Fig. 1 *with* 1014 Figure 7; *see* ¶¶ 75-77, *supra*.) That would motivate a POSA looking for an appropriate dose to use that recited in Comer.

106. And as before with Comer in view of Nuwayser, a POSA would have a reasonable expectation of success given the success reported by both Comer and Nuwayser. Indeed, one would have a reasonable expectation that the AUC results of the combination would be those reported in the figures of both Nuwayser and Comer. The differential between this AUC and 50 mg/day oral doses should be the same as well. (*See* ¶¶ 81, 89, *supra*.) To the extent that the AUC results were not that reflected in Nuwayser, using 384 mg of Comer as a starting point, a POSA would reasonably expect to be able to adjust the dose to achieve the disclosed pharmacokinetic properties shown in Figure 7 of Nuwayser. Moreover, any difference in AUC and especially AUC differential would be discounted by a POSA, particularly since they would not consider the differential to be very meaningful as discussed earlier. (*See supra* ¶¶ 60-66, 82-86, 106, *infra* ¶ 107.)

107. Here, the closest prior art, Nuwayser and Comer actually teach or suggest the *same dose*, of the *same drug*, from the *same particle*, on the *same protocol*. In view of the lack of impact of the AUC, and particularly, the AUC differential when compared to oral dosing, on efficacy, and the failure to compare other depot injections instead focusing on oral dosing, at the very least, the

emphasis that a POSA would give to this difference in AUC between those of Comer and Nuwayser and that claimed is minimal. (See ¶¶ 82-86, *supra*.) And since the AUC resulting from Comer and/or Nuwayser should be the same as or very similar to that claimed, the claimed AUC would be readily apparent to a POSA based on the AUC teachings of Comer and/or Nuwayser.

108. In regards to the dependent claims, claim 2 requires that treatment last for at least 24 weeks and that there be no prior oral dose of naltrexone. Treating patients for 24 weeks or more was known. Comer teaches that naltrexone had already been used for “chronic administration of over 1 year.” (Ex. 1010, at 351.) While I’m not a medical doctor, there are a number of references, in addition to Comer, teaching long term treatment of six months or more. (Exs. 1028, at 419, 420, 421, 423; 1049 Abstract; 1050 Abstract.) Rubio, for example, is a 12-month study in which alcoholic patients were given naltrexone (50 mg/day oral). (Ex. 1028, at 419-420.) Moreover, drug and alcohol addiction affect numerous families and is well known to be chronic. In fact, addictions often persist throughout a patient’s life. Accordingly, I think a POSA would expect, that for at least some patients, a treatment of 24 weeks or longer would be required. As to not providing prior oral dosing, as discussed above, the BRI encompasses no prior oral administration of naltrexone. Comer contemplated treating with the depot injection without a prior oral dose of naltrexone. (Ex. 1010, at 359 (“In a treatment setting

where oral naltrexone may not be given prior to depot naltrexone”).) Similarly, Nuwayser has no disclosure of providing its patients with oral doses of naltrexone. So claim 2 is at least suggested to a POSA.

109. Claim 3, requires at least two weeks of naltrexone release, and claim 4 requires release for four weeks. Four-week release is taught by both Comer and Nuwayser as noted in connection with claim 1 above. These claims are readily apparent to a POSA as well. Claim 5 requires that the dose be 380 mg and that the AUC be about 3.3 times that of 50 mg/day oral dosing. As to the dose, for the reasons discussed above, both Comer and Nuwayser teach a dose that is about 380 mg. As to the AUC differential, Comer and Nuwayser actually provide an AUC differential of about three, and indeed about 3.3, when compared to the 50 mg/day oral dosing data of the Ehrich declaration (Ex. 1003) and Tice (Ex. 1015). (*See* ¶¶ 67-77, 81, 89, *supra*.) Even if that were not the case, a POSA would be motivated to adjust the dose to an amount within the range claimed in claim 1, and in particular, about 380 mg, to achieve the desired release profile throughout the intended period, as illustrated in Figures 1 and 7 of Comer and Nuwayser, respectively. Alternatively, to the extent that the dose was the same, but the AUC and/or differential were/was different, a POSA, knowing all they would know about AUC in this system, would likely discount that differential. (*See* ¶¶ 81-86, 106-107, *supra*.)

110. Claim 6 requires that the treatment last at least 24 weeks. That claim would be readily apparent to a POSA for the reasons described in connection with claim 2, which includes the same limitation. (Ex. 1028, at 419-420.)

111. Claims 7-9 require a second dose be given 7 days or more after the first one is given and that the subsequent dose be substantially similar to (claim 8) or the same as (claim 9) to the first dose. In my opinion, this would be readily apparent to a POSA. Since Comer and Nuwayser both teach four-week dosing, a POSA would not consider a second dose earlier than seven days. Moreover, if a single 7, 14, or even 30-day period were all that was needed for alcohol or opioid treatment, the compliance problem that drives the reasoning for a depot injection might not be as compelling. A POSA would expect that more than one dose would be needed. Comer, for example, taught that chronic treatment could continue for a year. (Ex. 1010, at 351.) Moreover, I can see no reason why a POSA would consider using anything other than identical doses for successive doses. Anything else would be out of the ordinary.

112. Claim 10 specifies that the patient is alcohol dependent. Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. (Ex. 1010, at 352.) Rubio also teaches the use of an equivalent dose, 50 mg/day oral dosing, to treat alcoholics. (Ex. 1028, at 420.)

113. Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. As discussed in Grounds 1 and 2, the oral dosing in Comer was not an “initial” dose, and there is no oral dosing suggested in Nuwayser. Comer also taught administration without an earlier dose of naltrexone. Claim 12 requires that the parenteral administration be an injection. Comer teaches injection into the buttocks. (Ex. 1010, at 354.) Nuwayser teaches subcutaneous (“SC”) injection. (Ex. 1014 Figure 7.)

114. As to claim 13, Nuwayser specifically teaches that its microparticles include naltrexone in the amount of 54.4% by weight. And, Wright² (Ex. 1018) discloses that it was well known that drug loading could be in the range of 30-70% by weight of the formulation. (Ex. 1018, 8:14-18.) So loading a microparticle with 35% naltrexone would be readily apparent to a POSA.

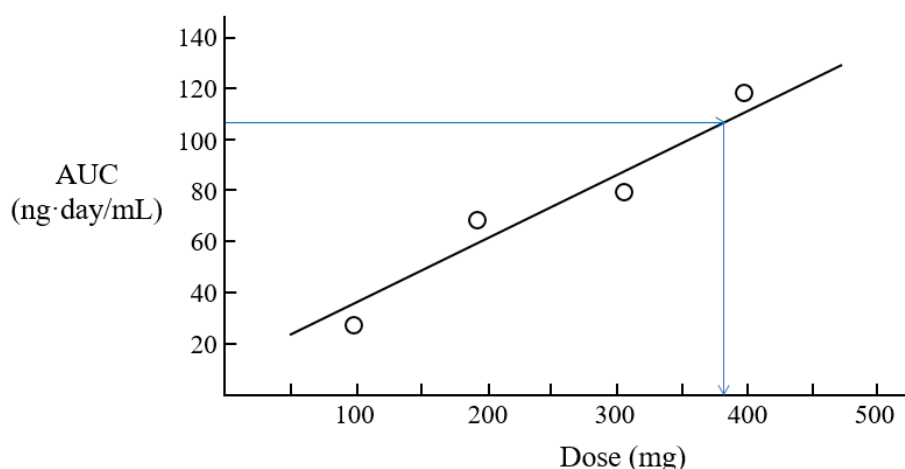
B. Nuwayser In View Of Kranzler, Wright, And Rubio

115. Nuwayser describes formulations of extended-release microcapsules of naltrexone (65:35 PLGA and 54.4% naltrexone by weight) and explains that the microcapsules can be subcutaneously implanted in heroin dependent patients to provide therapeutic levels of naltrexone for a period of 30 days. (Ex. 1014, 14:26-49, 19:4-25, Figure 7.) Nuwayser provides a graph of the AUC resulting

² Wright published on July 24, 2001. It is prior art under 35 U.S.C. § 102(e). It was of record, but not discussed during prosecution.

from the use of these microcapsules of Examples II and IV. (*Id.*) Even if one were to assume that Nuwayser does not expressly disclose the amount of microcapsules used and that a POSA does not look to Comer for a dose as I discussed earlier, a POSA could determine the dose that resulted in the disclosed AUC without undue experimentation.

116. A POSA knows from Nuwayser the exact composition of the microcapsules, that they were therapeutically effective (*i.e.*, delivered at least about 1 ng/ml), over at least 28 days. And a POSA knows how to confirm that they have arrived at the correct dose—it will result in the pharmacokinetic plot of Figure 7. As shown in the figure below, POSA can easily conduct an experiment to establish a standard curve (or calibration curve) correlating the AUC as a function of dose. A POSA can administer several doses of naltrexone in microparticles (*e.g.*, 100, 200, 300, and 400 mg naltrexone) to a group of individuals and measure the resultant AUCs, and plot them to find the best fit through linear regression. Once the standard curve is established, the dose for a given AUC can be easily found out. For example, if the AUC of a sample with an unknown naltrexone dose is measured, that value can be used to find the naltrexone dose, as indicated by blue arrows.



117. And Kranzler established that 206 mg naltrexone delivered by a depot injection provided 3 weeks of 1 ng/ml blood levels. This would also suggest to a POSA that more would be needed for longer duration of action and would further motivate a POSA to experiment with higher doses until the pharmacokinetic profile at Figure 7 of Nuwayser was met. (Exs. 1011, at 1074; 1014 Figure 7.)

118. As to the AUC being three times that of oral dosing, as described earlier, the AUC of Nuwayser would be the same or substantially the same as that resulting from the 380 mg depot injection of the '499 Patent. Thus, the AUC differential when compared to 50 mg/day and dosing would be about three. (See ¶¶ 75-77, 81, 89, *supra*.) Moreover, Nuwayser resulted in an effective method. (Ex. 1014, 19:23-25 (“This formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (*see* FIG. 7).”).) Since AUC is dose dependent and it is readily within the level of skill of a POSA to determine the claimed dose for the reasons just given, the resulting AUC differential should be

readily apparent as well. A POSA could readily adjust the dose to arrive at the plot of Figure 7, if indeed a POSA felt it necessary to do so. And given the lack of consequence of this comparison as previously discussed, any difference in AUC differential would not be considered significant by a POSA. (*See* ¶¶ 60-66, 82-86, 106-107, *supra*.)

119. In regards to the dependent claims, claim 2 requires that treatment last for at least 24 weeks and that there be no prior oral dose of naltrexone. Treating patients for 24 weeks or more was known. While I'm not a medical doctor, there are a number of references teaching long term treatment of six months or more. (Exs. 1028, at 419, 421, 423; 1022, at 6; 1049 Abstract; 1050 Abstract.) Moreover, drug and alcohol addiction affect numerous families and is well known to be a chronic condition in many addicts. In fact, addictions often persist throughout a patient's life. *See* also the references teaching treating patients for extended periods of time, such as Rubio (Ex. 1028) discussed in paragraphs 108 and 110. Accordingly, I think a POSA would expect, that for at least some patients, a treatment of 24 weeks or longer would be required. As to not providing prior oral dosing, as discussed above, the BRI encompasses no prior oral administration of naltrexone. Nuwayser has no disclosure of providing its patients with oral doses of naltrexone. So claim 2 is at least suggested to a POSA.

120. Claim 3, requires at least two weeks of naltrexone release, and claim 4 requires release for four weeks. Four-week release is taught by Nuwayser as noted in connection with claim 1 above. These claims are readily apparent to a POSA as well. Claim 5 requires that the dose be 380 mg and that the AUC be about 3.3 times that of 50 mg/day oral dosing. As to the dose, for the reasons discussed above in connection with Nuwayser, Nuwayser teaches a dose that is about 380 mg. If not, that dose could be determined by standard techniques. As to the AUC differential, Nuwayser actually provides an AUC differential of about three, and indeed about 3.3, when compared to the 50 mg/day oral dosing data of the Ehrich declaration (Ex. 1003) and Tice (Ex. 1015). (*See* ¶¶ 75-77, 81, 89, *supra*.) Even if that were not the case, a POSA would be motivated to adjust the dose to an amount within the range claimed in claim 1, and in particular, about 380 mg, to achieve the desired release profile throughout the intended period, as illustrated in Figure 7 of Nuwayser, respectively. As is true for all of the combinations described herein, to the extent that there were differences in the AUC or AUC differential, since Nuwayser (and Comer) provides a pharmacokinetic plot, which establishes a successful endpoint, a POSA could adjust the dose so as to arrive at the claimed AUC differential. Alternatively, to the extent that the dose was the same, but AUC differential different, a POSA, knowing all they would know about AUC in this system, would likely discount that differential. (*See* ¶¶ 81-86, 106, 107, *supra*.)

121. Claim 6 is obvious for the reasons previously discussed in connection with claim 2. Claims 7-9 require a second dose be given seven days or more after the first one is given and that the subsequent dose be substantially similar to (claim 8) or the same as (claim 9) to the first dose. It would be readily apparent to a POSA to administer the formulation in this manner. Nuwayser teaches a four-week dosing, so a POSA would not consider a second dose earlier than seven days. Moreover, if a single 7, 14, or even 30-day period were all that was needed for alcohol or opioid treatment, the compliance problem that drives the reasoning for a depot injection might not be as compelling. A POSA would expect that more than one dose would be needed. And there would be no reason not to administer the same depot injection each month until treatment is completed.

122. Claim 10 specifies that the patient is alcohol dependent. The patients in the Nuwayser study were opioid dependent. But POSAs knew that the receptors, and the plasma blood levels for treating alcoholics and opioid abusers, is the same—about 1 ng/ml. (Ex. 1024, 1:55-2:41.) Kranzler also taught that high dose depot injections of naltrexone were safe and effective in treating alcohol, at least for 21 days. (Ex. 1011, at 1074, 1077-78.)

123. Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. There is no oral dosing suggested in Nuwayser. Kranzler discloses oral naltrexone as part of the detoxification protocol. But there is a 2-

week drug free interval before the depot is given. (Ex. 1011, at 1074-75.) I think it would be apparent to a POSA that prior oral dosing of naltrexone is not necessary.

124. Claim 12 requires that the parenteral administration be an injection. Nuwayser teaches subcutaneous (“SC”) injection. (Ex. 1014 Figure 7.) Kranzler teaches injection of either naltrexone or placebo depots. (Ex. 1011, at 1074.) This would be apparent to a POSA as well.

125. Claim 13 requires that the naltrexone be present in the amount of about 35% by weight of the formulation. Nuwayser specifically teaches that the microparticles include naltrexone in the amount of 54.4% by weight. Wright teaches that it was well-known that drug loading could be in the range of 30-70% by weight of the formulation. (Exs. 1018, 8:14-18.) So loading a microparticle with this amount of drug would be readily apparent to a POSA, with a reasonable likelihood of success.

**C. Alkermes’ 10-K In View Of The
Vivitrex Specimen, Wright, And Rubio**

126. It would be readily apparent to a POSA to arrive at the challenged claims based on the combination of the Alkermes’ July 1, 2002 Form 10-K (“Alkeremes’ 10-K”) (Ex. 1016) in view of Alkermes’ specimen submitted to support its trademark application (“Vivitrex Specimen”) (Ex. 1017) and Alkermes’ U.S. Patent No. 6,264,987 to Wright *et al.* (“Wright”) (Ex. 1018).

1. Alkermes' 10-K

127. A POSA working in the pharmaceutical industry, research institute, or in academia is always looking for the newest information relevant to their research. This is to make sure that a POSA is not left behind others, improves its own research outcome, and does not repeat the same experiment that others have done. A POSA usually attends national and international conferences related to its own research, as well as reads scientific and technical journals in the field. In a competitive environment like research and development of pharmaceutical formulations, introduction of a better product faster than others is critical for the success of the product.

128. Alkermes' 10-K discloses that “we are developing VivitrexTM, a Medisorb formulation of naltrexone, for the treatment of alcoholism and opiate dependence. (Ex. 1016, at 3.) Alkermes' 10-K does not disclose the dose, but does state that Vivitrex is an “injectable extended-release technology and is designed to provide once-a-month dosing to enhance patient adherence by removing the need for daily dosing.” (*Id.* 5.)

129. Alkermes' 10-K indicates that the name “Vivitrex” is pending trademark approval at the time of filing. Accordingly, a next step a POSA would take is to determine what type of trademark was pending, what useful information was provided about the covered product, and if it was approved.

2. Vivitrex Specimen

130. I understand from counsel that USPTO records are public and that the trademark specimen for Vivitrex is part of the prior art. Those records indicate that the Vivitrex Specimen was deposited with the United States Postal Service on August 15, 2002, and was submitted to the USPTO to support Alkermes' trademark filing. (Ex. 1017, at 5.) In its trademark file, Alkermes stated that the mark was being used "in connection with Polymer-based Drug Delivery Formulations for Clinical Use and Pharmaceutical Products, namely, Injectable Drug Delivery Formulations." (*Id.* 4.) Most relevant to a POSA would be the statement that Vivitrex Specimen states "CONTENTS: Medisorb[®] Naltrexone (190 mg or 380 mg) for injectable suspension." (*Id.*) This tells a POSA that a dose of 190 mg or 380 mg may be used and confirms the use of Medisorb.

131. Medisorb was a family of polymers used in extended-release formulations known and commercially available at the time. Accordingly, a POSA would look to other references to determine how the formulation was made.

3. Wright

132. Specifically, Alkermes' own Wright (Ex. 1018) teaches a method of preparing microparticles having particular weight ratios of biodegradable PGLA polymers. Wright even refers to these polymers by the MEDISORB trademark. Wright states that the molecular weight of the polymer affects drug release

characteristics and influences the biodegradation rate of the polymer. (Ex. 1018, 1:33-38.) But that generally will not dramatically impact the AUC, as the AUC is dependent on the total dose administered for a cohort participated in the study. Thus, the plasma concentration-time profile may change, but the AUC remains the same. Wright specifically exemplifies naltrexone microparticles that include three types of Medisorb, *e.g.*, 75:25, 85:15, and 65:35. (*Id.* Example 3, 7:65-8:8.) A POSA would have reason to look to Wright to identify the Medisorb reference in the 10-K and Vivitrex Specimen.

133. As shown in the below table, the methods of making the microparticles of Wright and the '499 Patent are virtually identical.

'499 Patent (Ex. 1001, 6:44-7:17)	Wright (Ex. 1018, 7:50-8:34)
Preparation of Naltrexone Base Microparticles.	The starting molecular weight of the polymer (kD) and the final molecular weight of the polymer in a finished microparticle product (kD) was determined for microparticles containing the nucleophilic compound naltrexone. The starting polymer lactide:glycolide ratio was 75:25, 85:15,

'499 Patent (Ex. 1001, 6:44-7:17)	Wright (Ex. 1018, 7:50-8:34)
	and 65:35. The polymers used were MEDISORB [®] 7525 DL polymer, MEDISORB [®] 8515 DL polymer and MEDISORB [®] 6535 DL polymer, all available from Alkermes, Inc., Blue Ash, Ohio.
The naltrexone base microparticles were produced using a co-solvent extraction process. The theoretical batch size was 15 to 20 grams.	The naltrexone base microparticles were produced using a co-solvent extraction process. The theoretical batch size was 15 to 20 grams.
The polymer (MEDISORB [®] 7525 DL polymer, MEDISORB [®] 8515 DL polymer and MEDISORB [®] 6536 ³ DL polymer, all available from Alkermes, Inc., Blue Ash, Ohio) was dissolved in ethyl acetate to produce a 16.7% w/w	The polymer was dissolved in ethyl acetate to produce a 16.7% w/w polymer solution.

³ As mentioned above, a POSA would appreciate that the 6536 is a typographical error and that the proper name is MEDISORB[®] 6535.

'499 Patent (Ex. 1001, 6:44-7:17)	Wright (Ex. 1018, 7:50-8:34)
polymer solution.	
The naltrexone base anhydrous was dissolved in benzyl alcohol to produce a 30.0% w/w solution. In various batches, the amount of drug and polymer used was varied to produce microparticles with different theoretical drug loading ranging from 30%-75%.	The naltrexone base anhydrous was dissolved in benzyl alcohol to produce a 30.0% w/w solution. In various batches, the amount of drug and polymer used was varied to produce microparticles with different theoretical drug loading ranging from 30%-75%.
The ambient polymer and drug solutions were mixed together until a single homogeneous solution (organic phase) was produced. The aqueous phase was at ambient conditions and contained 1% w/w polyvinyl alcohol and a saturating amount of ethyl acetate. These two solutions were pumped via positive displacement pumps at a ratio of 3:1 (aqueous:organic) through a ¼' in-line	The ambient polymer and drug solutions were mixed together until a single homogeneous solution (organic phase) was produced. The aqueous phase was at ambient conditions and contained 1% w/w polyvinyl alcohol and a saturating amount of ethyl acetate. These two solutions were pumped via positive displacement pumps at a ratio of 3:1 (aqueous:organic) through a ¼" in-line

'499 Patent (Ex. 1001, 6:44-7:17)	Wright (Ex. 1018, 7:50-8:34)
mixer to form an emulsion.	mixer to form an emulsion.
The emulsion was transferred to a stirring solvent extraction solution consisting of 2.5% w/w of ethyl acetate dissolved in distilled water at 5-10° C., at a volume of 0.5 L of extraction solution per-theoretical gram of microparticles.	The emulsion was transferred to a stirring solvent extraction solution consisting of 2.5% w/w of ethyl acetate dissolved in distilled water at 5-10° C. and at a volume of 0.5L of extraction solution per theoretical gram of microparticles.
Both the polymer and drug solvents were extracted into the extraction solution from the emulsion droplets to produce microparticles.	Both the polymer and drug solvents were extracted into the extraction solution from the emulsion droplets to produce microparticles.
The initial extraction process ranged from two to four hours.	The initial extraction process ranged from two to four hours.
The microparticles were collected on a 25 µm sieve and rinsed with a cold (<5° C.) 25% w/w ethanol solution.	The microparticles were collected on a 25 µm sieve and rinsed with a cold (<5° C.) 25% w/w ethanol solution.
The microparticles were dried cold	The microparticles were dried cold

'499 Patent (Ex. 1001, 6:44-7:17)	Wright (Ex. 1018, 7:50-8:34)
overnight (approximately 17 hours) using nitrogen. The microparticles were then transferred to the reslurry solution, which consisted of a vigorously stirring 25% w/w ethanol solution at 5-10° C.	overnight (approximately 17 hours) using nitrogen. The microparticles were then transferred to the reslurry solution, which consisted of a vigorously stirring 25% w/w ethanol solution at 5-10C.
After a short mixing time (five to fifteen minutes), the reslurry solution and the microparticles were transferred to a stirring 25% w/w ethanol secondary extraction solution (approximately 25° C. at a volume of 0.2 L of secondary extraction solution per theoretical gram of microparticles).	After a short mixing time (five to fifteen minutes), the reslurry solution and the microparticles were transferred to a stirring 25% w/w ethanol secondary extraction solution (approximately 25° C. at a volume of 0.2 L of secondary extraction solution per theoretical gram of microparticles).
The microparticles stirred for six hours enabling additional solvent removal from the microparticles to take place.	The microparticles stirred for six hours enabling additional solvent removal from the microparticles to take place.
The microparticles were then collected on a 25 µm sieve and rinsed with a 25%	The microparticles were then collected on a 25 µm sieve and rinsed with a 25%

'499 Patent (Ex. 1001, 6:44-7:17)	Wright (Ex. 1018, 7:50-8:34)
w/w ethanol solution at ambient temperature.	w/w ethanol solution at ambient temperature.
These microparticles dried in a hood under ambient conditions overnight (approximately 17 hours), were sieved to remove agglomerated microparticles and then placed into a freezer for storage.	These microparticles dried in a hood under ambient conditions overnight (approximately 17 hours), were sieved to remove agglomerated microparticles and then placed into a freezer for storage.

134. The only remaining element of the challenged claims is the recited serum AUC differential of naltrexone when compared to a 50 mg/day oral dose. Based on Wright, a POSA could make the three different types of naltrexone microparticles. As discussed in the context of Comer and Nuwayser, the AUC is dose dependent and here the art teaches using a dose that is the same as that claimed in claims 1 and 5. The AUC and AUC differential should therefore meet the claims as well. (See ¶¶ 78-81, *supra*.) The '499 Patent refers to "Vivitrex," as do the Alkermes' 10-K and the Vivitrex Specimen. And the '499 Patent itself confirms that the particles made in Wright are Vivitrex. (Exs. 1018, Example 3; 1001, 6:44-7:18.) A POSA would expect that their pharmacokinetic properties,

such as AUC and AUC differential and their therapeutic efficacy, would be identical. This would appear to be an inherent property of Vivitrex, or at the very least, a consequence of its formulation. If not, any variation would be minor and well within a POSAs reasonable expectation.

135. As described above in paragraph 57, AUC is dependent on the drug dose. For a given cohort of patients or volunteers, the bioavailability and clearance remain constant, and thus, AUC is merely a consequence of administering a certain amount of drug. Thus, for the same microparticle formulations, AUC depends on the dose of naltrexone administered.

136. Turning to the dependent claims, claim 2 requires that treatment last for at least 24 weeks and that there be no prior oral dose of naltrexone. Claim 6 requires that the treatment last at least 24 weeks. The 10-K teaches that the clinical trial included repeat doses of Vivitrex. As discussed previously, treating patients for 24 weeks or more was known or would be readily apparent to a POSA. (*See* ¶ 119, *supra*; Ex. 1028, at 419-420; 1022, at 6; 1049; 1050.) This applies to claim 6 as well. As to the requirement in claim 2 that there be no prior oral dosing, none of Exhibits 1016, 1017, or 1018 suggest prior oral dosing is necessary or appropriate.

137. Claim 3, requires at least two weeks of naltrexone release, and claim 4 requires release for four weeks. The 10-K states that the Vivitrex is administered monthly. (Ex. 1016, at 5.)

138. Claim 5 requires a dose of 380 mg and that the AUC be about 3.3 times that of 50 mg/day oral dosing. This was discussed above in paragraph 120.

139. Claims 7-9 require that a second dose be given 7 days or more after the first dose and that the subsequent dose be substantially similar to (claim 8) or the same as (claim 9) to the first dose. This would be readily apparent to a POSA because a POSA would expect that more than one dose would be needed. Having developed a first depot formulation that is safe and effective, it is obvious that that dose would be used again. (*Id.*) In addition, the 10-K states that the clinical trial tested “repeated doses of Vivitrex administered monthly to alcohol-dependent patients.” (Ex. 1016, at 5-6.)

140. Claim 10 specifies that the patient is alcohol dependent. The 10-K states that Vivitrex is used “for the treatment of alcoholism” and was administered to “alcohol-dependent patients.” (Ex. 1016, at 3, 5-6.)

141. Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. As noted in the context of claim 2, none of the art relied upon references in this ground teach or suggest using an initial dose.

142. Claim 12 requires that the parenteral administration be an injection. As noted in connection with claim 1, the 10-K teaches “injectable extended-release technology” and the Specimen states “injectable drug delivery formulations” and “injectable suspension.” (Exs. 1016, at 3; 1017, at 4-5.)

143. Claim 13 requires that the naltrexone be present in the amount of about 35% by weight of the formulation. Wright teaches drug loadings of 30-75%. (Ex. 1018, 8:14-18.)

X. CONCLUSION

144. For the reasons described herein, I believe that it was known or would be apparent to a POSA to provide a method of treatment for parenterally administering the claimed amount of naltrexone and PLGA, and achieve a serum AUC that is about three (or 3.3) times greater than that achieved by an oral formulation. I believe a POSA would appreciate that the claimed formulation was known and also know how to administer the claimed formulation. A POSA would also know that the AUC differential is entitled to minimal weight for all the reasons discussed herein.

Case IPR2018-00943 (Patent No. 7,919,499)
Declaration of Kinam Park, Ph.D.

I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001).

Executed on: April 19, 2018

Kinam Park
Kinam Park

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