

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.
Petitioners

v.

ALKERMES PHARMA IRELAND LIMITED
Patent Owner

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

**DECLARATION OF THOMAS CHARLES DOWLING, Pharm.D., Ph.D. IN
SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S.
PATENT NO. 7,919,499**

APOTEX EXHIBIT 1046
Apotex v. Alkermes
IPR2025-00514

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. BACKGROUND AND QUALIFICATIONS	2
III. INFORMATION CONSIDERED	7
IV. RELEVANT LEGAL STANDARDS	7
A. Claim Interpretation	7
B. Perspective of One of Ordinary Skill in the Art.....	7
C. Anticipation	8
D. Obviousness.....	8
V. SUMMARY OF OPINIONs	11
VI. THE CHALLENGED '499 Patent	11
VII. LEVEL OF ORDINARY SKILL IN THE ART	11
VIII. TECHNICAL BACKGROUND	13
A. The Purported Invention.....	13
B. Pertinent Prosecution History Of The '499 Patent.....	18
C. Summary of the Applied Prior Art.....	20
1. Comer (EX1004).....	20
2. Nuwayser (EX1005)	23
3. Rubio (EX1006).....	24
4. Wright (EX1007)	25
5. Kranzler (EX1008).....	25
D. State Of The Art	26

E.	The Area Under the Curve (AUC)	28
F.	AUC Does Not Meaningfully Impact Efficacy.....	31
G.	A POSITA Would Find the Claimed Comparison Inapt	33
H.	The Claimed AUC Differential is Known or Would be Apparent	36
1.	The AUC of Comer.....	36
2.	The AUC of Nuwayser	43
IX.	CLAIM CONSTRUCTION	45
A.	“the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone”	45
B.	“the serum AUC of naltrexone ... than that achieved by 50 mg/day oral administration”	46
C.	“about three”.....	48
D.	“five or more days”	49
E.	“initial oral dose”.....	50
F.	“about 35% by weight”	51
X.	THE CHALLENGED CLAIMS ARE ANTICIPATED OR OBVIOUS IN VIEW OF THE PRIOR ART	51
A.	Ground 1: Claims 1, 3-5, and 12 Are Anticipated by Comer	51
1.	Claim 1 (Preamble): A method for treating an individual in need of naltrexone comprising the step of.....	52
a.	[1.1]: parenterally administering a long acting formulation comprising	52
b.	[1.2]: about 310 mg to about 480 mg of naltrexone	54

c.	[1.3]: and a biocompatible polymer to the individual	55
d.	[1.4]: wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration	55
e.	[1.5]: and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.....	57
2.	Claim 3: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.....	57
3.	Claim 4: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.....	58
4.	Claim 5: The method of claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone wherein the serum AUC is about 3.3 times greater than that achieved by 50 mg/day oral administration.....	58
5.	Claim 12: The method of claim 1 wherein naltrexone is administered by injection.....	59
B.	Ground 2: Claims 1-13 Would Have Been Obvious Over Comer in view of Nuwayser, Rubio, and Wright	59
1.	Claim 1	62
2.	Claim 2	66
3.	Claim 3	66
4.	Claim 4	67
5.	Claim 5	67
6.	Claim 6	67
7.	Claims 7-9	68

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

8.	Claim 10.....	69
9.	Claim 11	69
10.	Claim 12	70
11.	Claim 13	70
C.	Ground 3: Claims 1-13 Would Have Been Obvious Over Nuwayser in View of Comer, Rubio, and Wright.....	71
1.	Claim 1 (Preamble): A method for treating an individual in need of naltrexone comprising the step of.....	71
a.	[1.1]: parenterally administering a long acting formulation comprising	74
b.	[1.2]: about 310 mg to about 480 mg of naltrexone	74
c.	[1.3]: and a biocompatible polymer to the individual	77
d.	[1.4]: wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration	77
e.	[1.5]: and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.....	78
2.	Claim 2	78
3.	Claim 3	79
4.	Claim 4	79
5.	Claim 5	79
6.	Claim 6	79
7.	Claims 7-9	80
8.	Claim 10	80
9.	Claim 11	80

10.	Claim 12	80
11.	Claim 13	80
D.	Ground 4: Claims 1-13 Would Have Been Obvious Over Nuwayser in view of Kranzler, Rubio, and Wright . Error! Bookmark not defined.	
XI.	OTHER CONSIDERATIONS	81
A.	Any Purported Secondary Considerations Evidence Does Not Overcome the Strong Evidence of the Obviousness of the Claims	81
XII.	CONCLUSION.....	1

EXHIBIT LIST

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

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

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

EXHIBIT	DESCRIPTION
1020	Reuning <i>et al.</i> , <i>Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems</i> , Naltrexone: Research Monograph 28 (R. E. Willette and G. Barnett, eds. National Institute on Drug Abuse 1980)
1021	Appeal Brief, Application No. 13/871,534, Oct. 19, 2015
1025	<i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , Product Details for NDA 018932, REVIA (NALTREXONE HYDROCHLORIDE) 50MG
1029	TREXAN™, <i>Physicians’ Desk Reference</i> 936-938 (46 ed. 1992) (“PDR”), at 937-939
1033	Bertil Abrahamsson and Anna-Lena Ungell, <i>Biopharmaceutical support in formulation development: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form</i> , Pharmaceutical Preformulation and Formulation (Mark Gibson ed., Interpharm/CRC) (2004), 239-291, at 262
1034	Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Products—General Considerations. FDA CDER (March 2003)
1035	Riddle <i>et al.</i> , <i>Anxiolytics, adrenergic agents, and naltrexone</i> , 38(5) J. Am. Acad. Child. Adolesc. Psychiatry, 546-556 (May 1999)
1037	Rothenberg <i>et al.</i> , <i>Behavioral naltrexone therapy: an integrated treatment for opiate dependence</i> , 23 J. of Substance Abuse Treatment (2002), at 351-360
1038	B.A. Johnson, <i>Naltrexone long-acting formulation in the treatment of alcohol dependence</i> , 3(5) Ther. Clin. Risk Manag., 741-749 (2007), at 742.
1039	Food and Drug Administration, <i>Guidance for Industry, Exposure-response relationships – study design, data analysis, and regulatory applications</i> , FDA CDER (April 2003)

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

EXHIBIT	DESCRIPTION
1040	Food and Drug Administration, Guidance for Industry, <i>Statistical approaches to establishing bioequivalence</i> , FDA CDER (April 2003)
1041	Schenker <i>et al.</i> , <i>Antecedent liver disease and drug toxicity</i> , 31 J. of Hepatology 1098-1105 (1999)
1042	U.S. Patent No. 3,332,950, issued on July 25, 1997 to H. Blumberg
1047	<i>Curriculum Vitae</i> of Thomas Dowling
1052	Resume of Mike Ramstack, as obtained from LinkedIn
1053	Resume of Richard Reuning, as obtained from LinkedIn
1054	Resume of Steve Wright, as obtained from LinkedIn
1055	Declaration Under 37 C.F.R. §1.132 of Elliot Ehrich filed in Application No. Serial No. 11/083,167
1056	S. Hamilton <i>et al.</i> , <i>Pharmacokinetics and Pharmacodynamics of Hyaluronan Infused Healthy Human Volunteers</i> , 3 The Open Drug Metabolism Journal 43-55 (2009)
1057	Trademark Registration No. 2,443,435 (Depotrex)
1058	Institution Decision entered November 7, 2018 (Paper 8) in IPR2018-00943
1060	Patent Owner's Response, filed February 7, 2019 (Paper 14) in IPR2018-00943
1061	U.S. Patent No. 5,210,083, issued on May 11, 1993 to R. Pfirrmann
1062	U.S. Patent No. 5,234,906, issued on August 10, 1993 to A. Young and G. Cooper

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

EXHIBIT	DESCRIPTION
1063	U.S. Patent No. 6,677,320, issued on January 13, 2004 to A. Diederich et al.
1064	U.S. Patent No. 6,120,787, issued on September 19, 2000 to N.O. Gustafsson et al.
1065	U.S. Patent Publication No. 2003/0211167, published on November 13, 2003
1066	U.S. Patent No. 6,455,526, issued on September 24, 2002 to R. Kohn et al.

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

I, Thomas Charles Dowling, Pharm. D., Ph.D., declare and state as follows

I. INTRODUCTION

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

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

3. I have been asked by Counsel to provide opinions regarding Claims 1-13 of United States Patent No. 7,919,499 (“the ’499 Patent”). My opinions and the bases for my opinions are set forth below.

4. This report is based on information currently available to me. I reserve the right to continue my investigation and analysis, which may include a review of documents and information not listed above. I also reserve the right to expand or otherwise modify my opinions and conclusions as my investigation and study continues, and to supplement my opinions and conclusions in response to any additional information that becomes available to me.

II. BACKGROUND AND QUALIFICATIONS

5. I am a clinical pharmacologist with over 20 years of experience in research and teaching in the areas of biopharmaceutics, advanced pharmacokinetics, and clinical pharmacokinetics. I received a Pharm.D. from Ferris State University (with high distinction) followed by a residency in pharmacy practice at the University of Maryland Medical System.

6. During my residency, I conducted research on drug pharmacokinetics, along with antibiotic surveillance in collaboration with the Centers for Disease Control, leading to a seminal publication in the *Annals of Internal Medicine*. This publication has been cited nearly 600 times since 1995.

7. I subsequently received a Ph.D. in Pharmaceutical Sciences from the University of Pittsburgh, where my research work focused upon clinical pharmacokinetics and pharmacokinetic modeling of drug elimination. Three of my dissertation chapters were published in leading scientific journals including *Pharmacotherapy*, *Journal of Chromatography B Biomedical Applications*, and *Kidney International*.

8. I was appointed as an Assistant Professor of Pharmacy in 1999 at the University of Maryland School of Pharmacy, and developed a successful research program in clinical pharmacokinetics, biopharmaceutics, and drug elimination metabolism. My research projects have been funded by organizations such as the

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

American College of Clinical Pharmacy and American Foundation for Pharmaceutical Education, with federal funding from agencies such as the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA).

9. I was the first researcher in the School of Pharmacy to conduct a clinical trial at the University of Maryland General Clinical Research Center and have subsequently served as a principal or co-principal investigator on at least 15 clinical pharmacokinetics studies evaluating blood levels of drugs or biomarkers in the body since 2000.

10. I was an original member of the University of Maryland Clinical Research Working Group and the Program in Genetics and Genomic Medicine and served as a mentor for the University of Maryland NIH K30 Clinical Research Training Program.

11. I was appointed by the Dean of the University of Maryland School of Medicine to a 3-year term as a voting member of the University of Maryland Institutional Review Board (IRB).

12. I am, or have been, a member and have held national leadership positions in many scientific and professional societies. In the American College of Clinical Pharmacy, I served as Chairman of the Research Affairs Committee and was elected to the ACCP Research Institute Board of Trustees. I am an editorial board member for the journal Pharmacotherapy and serve as a manuscript referee

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

for many leading pharmacokinetics journals such as Clinical Pharmacokinetics, Biopharmaceutics and Drug Disposition and Pharmaceutical Research. I have served as a consultant and voting member as a pharmacokinetics expert on multiple FDA advisory committees (and topics) including the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (pharmacogenomics, drug safety, pharmacokinetics, drug metabolism, transport-mediated drug interactions), the FDA Advisory Committee on Anti-Infective Drugs (PK/PD of antimicrobial agents) and FDA Advisory Committee on Pulmonary-Allergy Drugs (pharmacokinetics review of NDA 214697).

13. In 2004, I received the Teacher of the Year award at the University of Maryland School of Pharmacy, which was voted upon by my faculty peers. I have served as primary dissertation advisor to four Ph.D. students, who have subsequently pursued careers in the pharmaceutical industry (Abbott Laboratories, Bristol Myers Squibb), clinical research (University of Maryland, Division of Transplantation), and the FDA (Office of Clinical Pharmacology, Genomics group). In 2005, I was promoted to Associate Professor (with tenure) and was promoted to full Professor with tenure in 2014. I am currently Assistant Dean in the College of Pharmacy at Ferris State University, focusing on research and development. I also serve as the Director of the Office of Research and Sponsored Programs at Ferris State University.

14. To date, I have published over 100 works that have been cited nearly 3,000 times with an H-index of 29.¹ I have published manuscripts and have written chapters in leading clinical pharmacology and pharmacokinetics textbooks such as DiPiro's Pharmacotherapy, Winter's Basic Clinical Pharmacokinetics, and Murphy's Clinical Pharmacokinetics. I have designed and conducted many clinical trials involving the analysis of pharmacokinetic parameters and other clinical data. I have expertise in developing and validating bioanalytical assays to support pharmacokinetic studies.

15. I have expertise in evaluating biopharmaceutics and drug absorption, including transdermal absorption of ketoprofen gel and excipient-related effects on the C_{max} and AUC of single-dose formulations of cimetidine, ciprofloxacin, and acyclovir using 4-way crossover studies in healthy volunteers. I have served as the principal investigator on industry-sponsored and FDA-regulated trials evaluating bioequivalence of generic drugs and other compounds. I have served as a principal investigator on studies evaluating formulation effects on bioequivalence and other studies that were funded by the FDA's Critical Path Initiative. Along with co-investigators from the FDA, the results of these studies were published in high

¹ See Google Scholar:

<https://scholar.google.com/citations?user=L0aHm1UAAAAJ&hl=en&oi=ao>.

impact journals including the Journal of Pharmaceutical Sciences (2016), AAPS Journal (2016), and Regulatory Toxicology and Pharmacology (2013).

16. I have received nearly \$3 million in extramural funding as an investigator or project director from agencies including the NIH, FDA, and the National Institutes of Standards and Technology (NIST). My research work has been presented at major national and international scientific symposia such as the American College of Clinical Pharmacology, the American Society for Clinical Pharmacology and Therapeutics, the FDA's Office of Clinical Pharmacology Grand Rounds and the FDA's Science Day Symposium.

17. In 2009, I was elected a Fellow of the American College of Clinical Pharmacology (FCP) and in 2010 was elected a Fellow of the American College of Clinical Pharmacy (FCCP).

18. My CV, which includes a list of all my publications, is attached as EX1047. In summary, I am an expert in the areas described herein and I qualify as at least a person of ordinary skill in the art ("POSITA" or a "person of ordinary skill in the art") under the definitions previously set forth by the parties in IPR2018-00943.

III. INFORMATION CONSIDERED

19. In preparing this declaration, I have reviewed the '499 Patent and the exhibits and documents referenced herein. In addition, my opinions are further based on my education, training, experience, and knowledge in the relevant field.

IV. RELEVANT LEGAL STANDARDS

20. I am not an attorney and offer no legal opinions. For the purposes of this Declaration, I have been informed about certain aspects of the law that are relevant to my analysis, as summarized below.

A. Claim Interpretation

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

B. Perspective of One of Ordinary Skill in the Art

22. I have been informed that a patent is to be understood from the perspective of a hypothetical “person of ordinary skill in the art” (“POSITA”). Such

an individual is considered to possess normal skills and knowledge in a particular technical field (as opposed to being a genius). I have been informed that in considering what the claims of a patent require, what was known prior to that patent, what a prior art reference discloses, and whether an invention is obvious or not, one must use the perspective of such a POSITA.

C. Anticipation

23. I have been informed that a claim is not patentable if it is anticipated. I have been informed that anticipation of a claim requires that every element of a claim is disclosed expressly or inherently in a prior art reference, arranged as in the claim, when considered from the perspective of a person of ordinary skill in the relevant art. I have been informed that when the structure recited in a reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. I have been informed that extrinsic evidence may be used to explain but not expand the meaning of terms and phrases used in the reference relied upon as anticipatory of the claimed subject matter.

D. Obviousness

24. I have been informed that a patent claim is obvious under 35 U.S.C. § 103, and therefore invalid, if the claimed subject matter, as a whole, would have been obvious to a POSITA as of the priority date of the patent based on one or more prior art references and/or the knowledge of a POSITA.

25. I have been informed that an obviousness analysis must consider (1) the scope and content of the prior art, (2) the differences between the claims and the prior art, (3) the level of ordinary skill in the pertinent art, and (4) secondary considerations, if any, of non-obviousness (such as unexpected results, commercial success, long- felt but unmet need, failure of others, copying by others, and skepticism of experts).

26. I have been informed that a prior art reference may be combined with other references to disclose each element of the invention under 35 U.S.C. § 103. I have been informed that a reference may also be combined with the knowledge of a POSITA, and that this knowledge may be used to combine multiple references. I have been informed that a POSITA is presumed to know the relevant prior art. I have been informed that the obviousness analysis may take into account the inferences and creative steps that a POSITA would employ.

27. In determining whether a prior art reference would have been combined with other prior art or other information known to a POSITA, I have been informed that the following principles may be considered:

- whether the references to be combined involve non-analogous art;
- whether the references to be combined are in different fields of endeavor than the alleged invention in the patent;
- whether the references to be combined are reasonably pertinent to the problems to which the inventions of the patent are directed;

Declaration of Thomas Charles Dowling, Pharm.D., Ph.D.

- whether the combination is of familiar elements according to known methods that yields predictable results;
- whether a combination involves the substitution of one known element for another that yields predictable results;
- whether the combination involves the use of a known technique to improve similar items or methods in the same way that yields predictable results;
- whether the combination involves the application of a known technique to a prior art reference that is ready for improvement, to yield predictable results;
- whether the combination is “obvious to try”;
- whether the combination involves the known work in one field of endeavor prompting variations of it for use in either the same field or a different one based on design incentives or other market forces, where the variations are predictable to a POSITA;
- whether there is some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill in the art to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention;
- whether the combination requires modifications that render the prior art unsatisfactory for its intended use;
- whether the combination requires modifications that change the principle of operation of the reference;
- whether the combination is reasonably expected to be a success; and
- whether the combination possesses the requisite degree of predictability at the time the invention was made.

28. I have been informed that in determining whether a combination of prior art references renders a claim obvious, it is helpful to consider whether there is some teaching, suggestion, or motivation to combine the references and a reasonable

expectation of success in doing so. I have been informed, however, that a teaching, suggestion, or motivation to combine is not required.

V. SUMMARY OF OPINIONS

29. It is my opinion that Claims 1-13 of the '499 Patent would have been anticipated or obvious on the following grounds:

Ground	References	Basis	Claims Challenged
1	Comer (EX1004) as evidenced by Nuwayser (EX1005)	§102(b)	1, 3-5, 12
2	Comer in view of Nuwayser, Rubio (EX1006), and Wright (EX1007)	§103(a)	1-13
3	Nuwayser in view of Comer, Rubio, and Wright	§103(a)	1-13

VI. THE CHALLENGED '499 PATENT

30. The '499 Patent contains 15 claims. I have been asked to opine on the validity of Claims 1-13.

VII. LEVEL OF ORDINARY SKILL IN THE ART

31. I have been informed that a POSITA is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity.

32. For the purposes of this proceeding, I agree with the POSITA definition adopted by the Board in IPR2018-00943, *i.e.*, a POSITA would have had a doctorate level degree in pharmaceuticals or related formulation sciences (such as Pharm.D. or

Ph.D.) and at least two years of experience in controlled release formulation. This is consistent with my understanding, based upon my experience.

33. I understand that a POSITA definition was set forth by the Patent Owner in IPR2018-00943. That is, with respect to the technology at issue in this proceeding, a POSITA is experienced in the field of controlled-release formulations. This field often requires the collaborative teamwork among individuals with relevant experience, including pharmaceutical scientists, clinicians, and formulation scientists. Here, a POSITA would have either a Master's degree with at least two or three years' experience, or have a Ph.D. or M.D. degree with at least one or two years' experience.

34. 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 pharmacokinetic measurement of AUC and how that AUC compared to other formulations.

35. Consistent with my understanding, many of those professionals 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 (EX1007), has a Ph.D. in Chemical Engineering, and R. H. Reuning, author of Exhibit 1020, has a Ph.D. in Pharmacy. EX1052, EX1053.

36. 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 (EX1007) has an undergraduate degree in Chemical Engineering and more than 15 years of experience. EX1054.

37. As of the relevant date of April 2004, I believe I was a POSITA under any plausible definition. Further, I understand who a POSITA was as of April 22, 2004, and what such a person would know.

VIII. TECHNICAL BACKGROUND

A. The Purported Invention

38. I understand from the face of the '499 Patent (EX1001) that it issued on April 5, 2011, from U.S. Application Serial No. 11/083,167 ("the '167 Application"), which was filed on March 17, 2005. The '499 Patent states on its face that it claims the benefit of U.S. Provisional Application No. 60/564,542, filed April

22, 2004 (“the Provisional Application”) (EX1003). I have been advised by counsel to assume that the earliest possible effective filing date for the ’499 Patent is April 22, 2004.

39. The ’499 Patent describes 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 PLGA to the individual, where the serum AUC of naltrexone is about three times greater than what is achieved by administration of 50 mg/day oral administration. EX1001, 1:30-46, 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).

40. The ’499 Patent alleges that the “inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone.” EX1001, Abstract, 1:31-33. The allegedly unexpected discovery was that the AUC from the depot formulation tested was at least three times that observed from 50 mg/day oral dosing when given over a 28 day period. 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.

41. The specification discusses the need for improving naltrexone therapies by improving patient compliance. EX1001, 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. EX1001, 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 POSITA 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 POSITA to draw a conclusion of improved efficacy or superiority of the depot injection when directly compared to oral naltrexone. A POSITA 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 POSITA which is why, 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.

42. In some embodiments, naltrexone is combined with well-known polymers, such as PLGA, to “entrap or encapsulate” the naltrexone to form long acting formulations. EX1001, 3:14-15. PLGA was well-known in the art as being a copolymer used in depot injections. In fact, the best known example of PLGA use is the Lupron depot injection (approved by the FDA in 1989). 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.

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

44. The remaining examples describe various aspects of a clinical trial, none of which provide any data for AUC or the claimed AUC differential. For example, Example 2 describes screening, eligibility, and adverse events. EX1001, 8:5-18:2. Example 3 compares the “efficacy” of oral versus 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.

45. 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. EX1001, 21:2-8, 22:15-22. The amount of naltrexone in the formulations claimed varies from a range of between 190 mg to 240 mg (claim 14) and 310 mg to about 480 mg of naltrexone (claim 1).

B. Pertinent Prosecution History Of The '499 Patent

46. I have been involved in patent 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.

47. 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 (EX1002, at 333-342), which rejected the claims as allegedly being anticipated by Tice (EX1009) and, in the alternative, as being obvious over the combination of Tice and Chandrashekar. I understand that Alkermes responded on October 5, 2009 (EX1002, at 291-299) with claim amendments and a declaration under 37 CFR §1.132 by Elliot Ehrich (the "Ehrich Declaration") (EX1055), the inventor of the '499 Patent.

48. I understand that the Examiner issued a second non-final office action on January 6, 2010 (EX1002, at 276-286), which withdrew the anticipation and obviousness rejections over Tice in view of the Ehrich Declaration but nevertheless finally rejected the claims based on lack of enablement. Alkermes responded on April 5, 2010, by amending the claims to require a biocompatible polymer. EX1002, at 177-188. A final rejection was mailed on July 20, 2010 (EX1002, at 130-143), maintaining the enablement rejection. Alkermes filed a response after final on October 20, 2010 (EX1002, at 121-126), amending the claims to require that the

biocompatible polymer be PLGA. I note that the Ehrich Declaration did not argue that either oral dosing or Tice's depot injection was clinically ineffective or even somehow less therapeutically effective, had fewer side effects, or was in any way an inferior treatment. The inventor did not even allege that the observed difference in AUC was somehow advantageous—just different. Nothing in the '499 Patent or its prosecution history is more enlightening on this point. All three protocols (*i.e.*, oral naltrexone, PLA/naltrexone microspheres of Tice, and the PLGA/naltrexone microspheres of Comer and the '499 Patent) resulted in plasma levels of 1 ng/ml or above, which had already been established as the therapeutic threshold.

49. A notice of allowance was mailed on December 1, 2010, which, I understand, acknowledged a telephone interview of November 19, 2010 where the examiner allegedly proposed to insert certain language into the claims, *e.g.*, “about 310 mg to about 480 mg” into claim 1. EX1002, at 106-114. I understand the Examiner also included a reason for allowance, which stated that “[t]here is no prior art disclosing the applicants' [sic] composition and effect, particularly an AUC about three times greater than that achieved by 50 mg/day oral administration.” EX1002, at 111-112. 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.

C. Summary of the Applied Prior Art

1. Comer (EX1004)

50. I understand that Comer was published in February 2002 and, therefore, qualifies as prior art to the '499 Patent. Comer describes a study “designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®)” in subjects dependent on heroin. Ex. 1004, 351 (Abstract). Comer states that the results of the study “suggest that th[e] depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” *Id.*

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

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

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

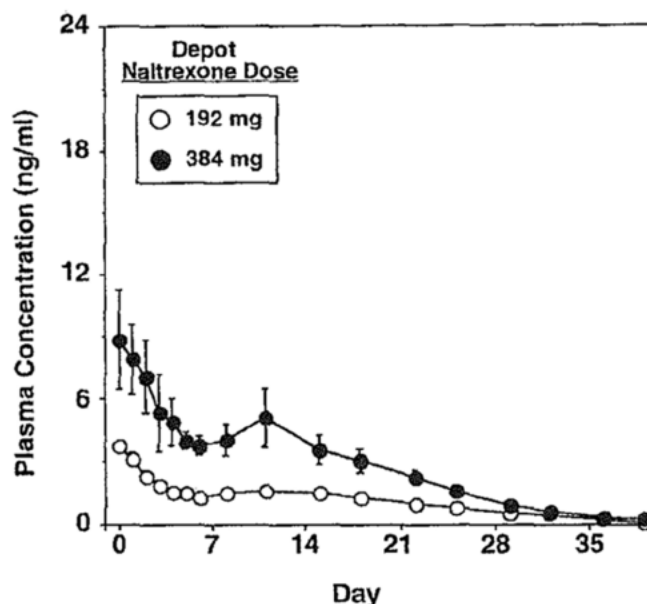


Figure 1 shows mean plasma levels of depot naltrexone over time following either a 192 mg depot dose (○) or a 384 mg depot dose (●).

Figure 1 of Comer

52. Comer states that “[a]cross the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were 3.8 (± 0.2) and 8.9 (± 1.4) ng/ml, respectively.” *Id.*, 358. Comer states that a comparative study “reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone).” *Id.* Thus, Comer states, “the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).” Even so, “antagonism of heroin’s effects occurred, despite negligible plasma levels of naltrexone.” *Id.*

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

54. I understand that the Board provided a similar summary of Comer in IPR2019-00943. EX1058, 13-16. I believe that summary to be accurate, based upon my knowledge and experience.

2. Nuwayser (EX1005)

55. I understand that Nuwayser was filed on May 31, 2002 and, therefore, qualifies as prior art to the '499 Patent. Nuwayser teaches a multi-layered microcapsule containing one or more active ingredients and a process for preparing the microcapsule. Ex. 1005, Abstract. In Example IV, Nuwayser teaches the preparation of naltrexone microcapsules by coating naltrexone microspheres with the polymer poly-L(-)-lactide-co-glycolide (PLGA). *Id.*, 19:3-25. Nuwayser teaches that the microcapsules contain a final naltrexone content of 54.4%. *Id.* “This formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days.” *Id.* Figure 7 of Nuwayser, reproduced below, provides mean plasma levels of naltrexone “after single and double [subcutaneous] injections of Depotrex™.” *Id.*

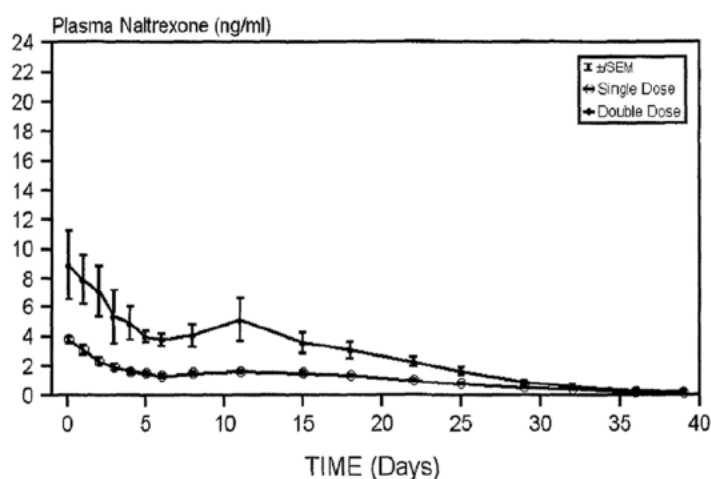


Figure 7 shows mean plasma levels of naltrexone over time following either a single dose (○) or a double dose (●) of naltrexone.

Figure 7 of Nuwayser

56. I understand that the Board provided a similar summary of Nuwayser in IPR2019-00943. EX1058, 16-17. I believe that summary to be accurate, based upon my knowledge and experience.

3. Rubio (EX1006)

57. I understand that Rubio was published in 2001 and, therefore, qualifies as prior art to the '499 Patent. Rubio states that both naltrexone and acamprosate “reduce relapse in alcohol dependence,” but they “have not yet been compared in a published trial.” Ex. 1006, 419 (Abstract). Rubio describes a study designed “to compare the efficacy of these compounds in conditions similar to those in routine clinical practice.” *Id.* Recently detoxified alcohol-dependent men were administered either one year of treatment with 50 mg/day of naltrexone (*i.e.*, one tablet per day) or 1665–1998 mg/day of acamprosate (*i.e.*, six tablets per day). *Id.*; *see also id.* at 420. Rubio found that, at the end of the year, “[n]altrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at any one time and reducing craving, compared to acamprosate.” *Id.* at 422.

58. I understand that the Board provided a similar summary of Rubio in IPR2019-00943. EX1058, 17. I believe that summary to be accurate, based upon my knowledge and experience.

4. Wright (EX1007)

59. I understand that Wright was issued on July 24, 2001 and, therefore, qualifies as prior art to the '499 Patent. Wright teaches a method for preparing microparticles having a selected polymer molecular weight. Ex. 1007, Abstract. In Example 3, Wright teaches the preparation of microparticles containing naltrexone. *Id.* at 7:50–8:60. Wright teaches that the polymers used were “MEDISORB® 7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6535 DL polymer.” *Id.* at 7:56–58.

60. I understand that the Board provided a similar summary of Wright in IPR2019-00943. EX1058, 18. I believe that summary to be accurate, based upon my knowledge and experience.

5. Kranzler (EX1008)

61. I understand that Kranzler was published in August 1998 and, therefore, qualifies as prior art to the '499 Patent. Kranzler describes a “preliminary study” of the use of sustained release naltrexone for alcoholism treatment. Ex. 1008, 1074 (Abstract). In Kranzler’s study, twenty alcohol-dependent subjects received 50 mg/day oral naltrexone for two weeks, followed by a medication-free two-week “washout period.” *Id.* at 1074–75. Fifteen of those subjects then received a single subcutaneous injection of 206 mg of a sustained-release preparation (SRP) of naltrexone, and five received placebo. *Id.* The SRP of naltrexone comprises

biodegradable, injectable microcapsules. *Id.* at 1074. Kranzler states that “[a]fter injection, [naltrexone] concentrations exceeded a mean of 1 ng/ml for 21 days,” and that “[a]dverse effects produced by the SRP of [naltrexone] were comparable with those resulting from oral [naltrexone] therapy.” *Id.* at 1074, Abstract. Kranzler concludes that “[t]he results of this preliminary study support the potential clinical utility of the SRP of [naltrexone] for treatment of alcohol dependence.” *Id.*

62. I understand that the Board provided a similar summary of Kranzler in IPR2019-00943. EX1058, 18. I believe that summary to be accurate, based upon my knowledge and experience.

D. State Of The Art

63. 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”).

64. As noted elsewhere, naltrexone as a treatment for patients suffering from alcoholism and opioid addiction dates back to the 1980s. EX1004, at 351-352; EX1008, at 1075; EX1010, Summary; EX1011; EX1005, 19:22-25; EX1012, at 3; EX1016, Abstract; EX1017; EX1018, 1:55-2:50; EX1020, at 173. Naltrexone was originally developed and patented (EX1042) by Endo Laboratories in the 1960s. Naltrexone hydrochloride, originally under the tradename Trexan and later known

as ReVia, received FDA approval in 1984. EX1025. The formulation delivered 50 mg/day orally to patients for opioid and alcohol addiction. EX1017, 936-938; EX1006, at 420; EX1025; EX1029, at 937-939.) A 50 mg daily oral dose was known to be effective and to provide serum blood levels of at least 1 ng/ml, which was recognized as necessary for efficacy. EX1004, Abstract; EX1008, at 1078; EX1010, at 7; EX1011; EX1009, 6:19-39.

65. 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. EX1004, at 351-352; EX1008, at 1074; EX1009, 1:14-2:60; EX1012, at 3; EX1014; EX1016, Abstract; EX1018, 1:13-2:61.

66. 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 desired outcome of this therapy. Using a longer acting 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. EX1004, at 351-352; EX1008, at 1075; EX1010, at 2; EX1011;

EX1005, 19:21-25; EX1009, 1:46-2:7; EX1012, at 3; EX1014, at 82; EX1019, at 704. Several depot injections were known to provide a blood concentration of 1 ng/ml/day for weeks. EX1004, at 351; EX1008, at 1074, EX1056; EX1005, 14:25-50, 19:4-25, Fig. 7; EX1009, 3:5-17, 4:35-39, 6:19-39.

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

E. The Area Under the Curve (AUC)

68. 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). EX1033, at 261. AUC is simply the total area calculated from 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 is most commonly calculated by the linear trapezoidal rule. EX1033, 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. EX1033, at 262. I performed AUC calculations using this linear trapezoidal rule.

69. AUC can also be measured faster and just as accurately using a computer and various computer programs that have been available since the introduction of personal computers. EX1033, at 263. I understand that the Petitioner's expert, Dr. Kinam Park, in IPR2018-00943, used such a methodology. I reviewed his calculations and approve of both the methodology and his AUC determinations.

70. 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. EX1033, 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 most 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).

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

71. 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 quantify systemic drug exposure over a specified time period. EX1039, at 2, 14. AUC is also used as a measure for product quality, including bioavailability and bioequivalence, due to its capacity to assess systemic exposure, which in turn reflects the rate and extent of drug absorption. EX1034. 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.*; EX1040, at 2.)

72. 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 is often measured in 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.”

F. AUC Does Not Meaningfully Impact Efficacy

73. AUC is a pharmacokinetic measure of total drug exposure over a period of time after a dose or series of doses are administered. 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).” EX1001, 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. 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 POSITA 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 could suggest exposing the patient to more of the drug than necessary thereby leading to unwanted (toxic) side effects. Naltrexone was shown to cause liver toxicity to some patients depending on the total dose. EX1041, at 1098; EX1035, at 554. As shown above in the equation in paragraph 68, a patient with reduced drug elimination may have increased naltrexone exposure that could exceed the safe concentration. It is most desirable to maintain the drug concentration within a therapeutic range that is above the minimum effective concentration but not so high as to cause potential side effects.

74. Nothing in the specification of the ’499 Patent would assure a POSITA 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. EX1001, 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.” EX1001, 19:31-34. Clearly, despite an allegedly unexpected AUC differential, a POSITA would conclude that, in terms of efficacy, oral is just as effective as their depot injection.

75. 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.

G. A POSITA Would Find the Claimed Comparison Inapt

76. 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. Because of this, I do not understand why the comparison made in the claims and the Ehrich Declaration was to oral non-sustained release dosing—because much closer prior art was available. I think a POSITA 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. EX1009. It would be readily apparent to a POSITA that the

closest technology was embodied in the depot formulations of Vivitrex or Depotrex. EX1004, Abstract, 354; EX1005, 6:6-9, 14:26-49, 19:21-25, Fig. 7; 1016, at 3; EX1013 at 3; EX1007, 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 POSITA 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. EX1021, at 7. 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 POSITA 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.

77. To the extent that there was an AUC differential, I think a POSITA 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 POSITA 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 POSITA, 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.

78. Moreover, I think a POSITA would be dissuaded from placing much emphasis on the claimed comparison because it is purely hypothetical. Unlike direct comparisons to other long acting depot injections administered on a monthly basis, 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 to 28 or 30 day AUC values, one must estimate, by extrapolation, the 28 or 30 day AUC using one day's AUC data from a single oral dose, and multiplying by 28 or 30. As shown in Comer and Nywayser below, 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 68, 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 provides limited useful information. This problem is avoided 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 POSITA to accept the claimed comparison at face value.

H. The Claimed AUC Differential is Known or Would be Apparent

79. 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

80. As I mentioned above, the AUC can be measured using the linear trapezoid rule. That is,

$$\text{AUC}_{1-n} = \sum \left\{ \frac{Cp_1 + Cp_2}{2} \cdot (t_2 - t_1) \right\} + \left\{ \frac{Cp_2 + Cp_3}{2} \cdot (t_3 - t_2) \right\} + \dots$$

81. Comer (EX1004) 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. When each of the plasma concentrations are determined from Figure 1, AUC can be determined over the course of 28 days as follows:

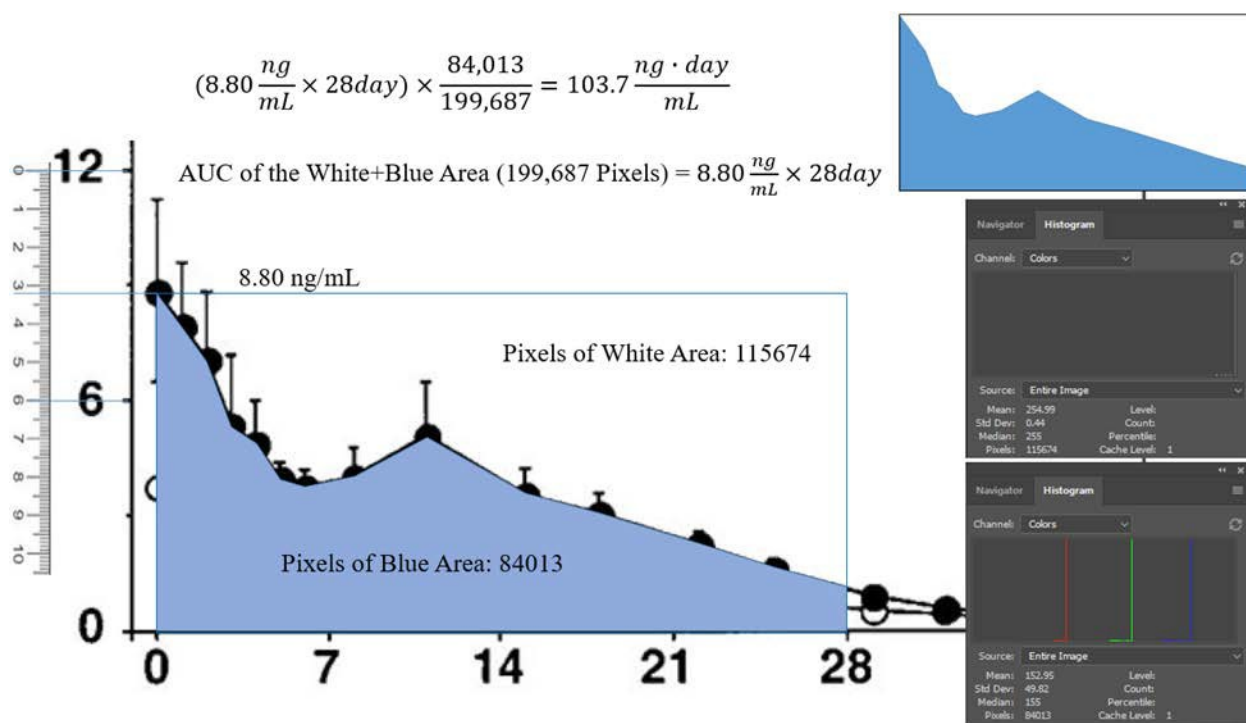
Time (Day)	Measured from Y axis (mm)	Mean Conc from plot (Cp, ng/mL)	AUC* (ng·day/mL)	(interval, in days)
0	0	0		
0.083333333 (2 hours)	43	8.9	0.37	0-0.083
1	38	7.9	7.68	0.083-1
2	34	7.0	7.45	1-2
3	26	5.4	6.21	2-3
4	24	5.0	5.17	3-4
5	19	3.9	4.45	4-5
6	18	3.7	3.83	5-6
8	19	3.9	7.66	6-8
11	25	5.2	13.66	8-11
15	17	3.5	17.39	11-15
18	15	3.1	9.93	15-18
22	11	2.3	10.76	18-22
25	7.5	1.6	5.74	22-25
28	5	1.0	3.88	25-28
Total			104.20	0-28

82. The AUC_{0-28d} of the Comer 384 mg dose administered (EX1004 Abstract, 354) is 104.20 ng·day/mL as shown by the calculation presented above.

83. I understand that Dr. Kinam Park in IPR2018-00943 measured AUC by using computer software that measures exact pixel numbers of an area. This allows accurate measurements of AUCs and is well known to a POSITA. A POSITA would have had access to various software well in advance of the filing date of the '499 Patent. I am also in agreement with his methodology. Dr. Park's AUC is indicated below in blue, and is the area below the curve, connecting each day's data points. The total pixel number was 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.

84. The AUC_{0-28d} of the Comer 384 mg dose administered (EX1004 Abstract, 354) is 103.7 ng·day/mL as shown by the calculation presented in the figure below. The software he 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, 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 POSITA 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.



85. Alkermes acknowledged that AUC, indeed all the pharmacokinetic properties, are dose dependent (EX1021, at 7), and I agree. A POSITA 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 POSITA 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. EX1055, at 6. A POSITA would find these quite comparable. In fact, as shown by the equation in paragraph 68, 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.

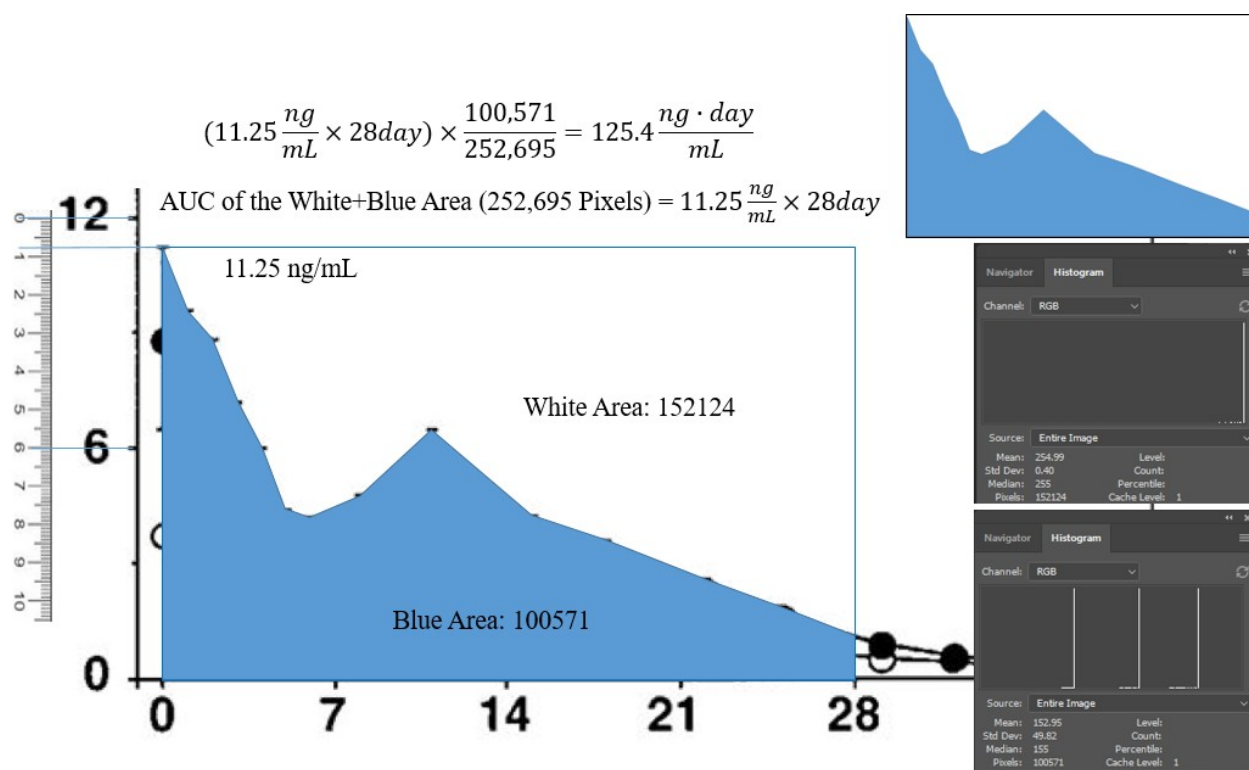
86. To a POSITA, the comparability of these AUC measurements between two 28-day depot injections of about 380 mg of naltrexone in a PLGA particle would be the most meaningful. This is, of course, subject to the fact that neither appears to have a direct impact on therapeutic efficacy. A POSITA would 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 POSITA 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.

87. Even though a comparison to oral dosing would not be very meaningful to a POSITA, it is nonetheless reflected in the claims of the '499 Patent. Because the patent provides no data, a POSITA 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.

88. Dividing the AUC_{0-28d} of Comer using the linear trapezoid rule, which is 104.2 ng·day/mL, by the 35.78 ng·day/mL from oral dosing, as reflected in Cohort A, yields a differential of 2.9. A POSITA would conclude that this is about three. Using Dr. Park's AUC_{0-28d} determination from Comer, which is 103.7 ng·day/mL, by the 35.78 ng·day/mL from oral dosing, as reflected in Cohort A, also yields a differential of 2.9.

89. Looking at the actual Figure in Comer, a POSITA 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 Ehrich 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 Ehrich Declaration for Cohort A, the differential becomes 3.5.

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

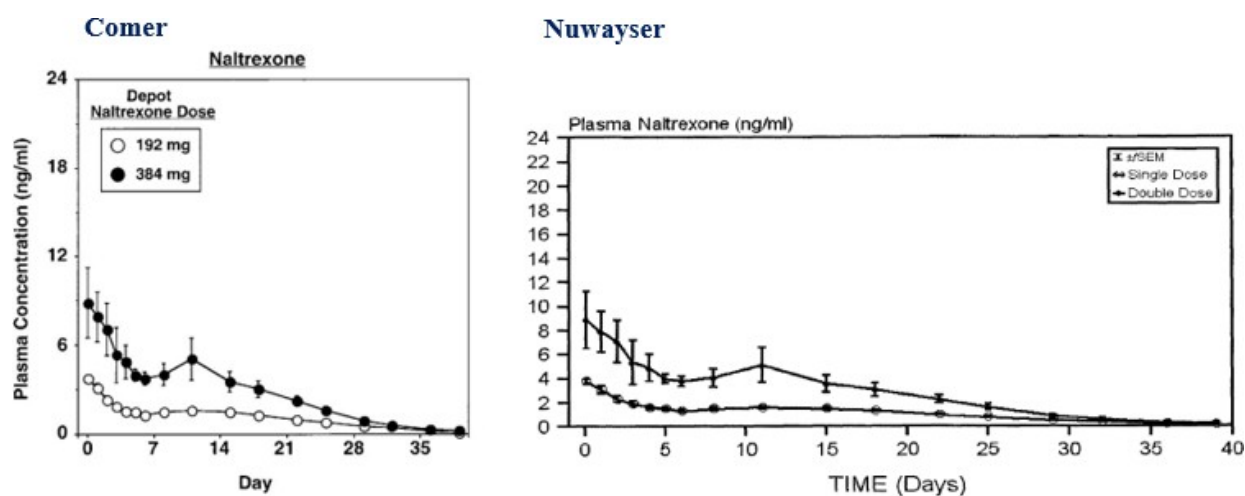
90. Now, if instead of using the oral data provided by the Ehrich Declaration, the oral AUC_{0-28d} data found in Tice (EX1009, 14:34-58) is used, the mean AUC_{0-28d} of Comer is 3.2 times greater than the oral AUC_{0-28d}. $(\frac{103.7}{(27.8 \div 24) \times 28} = 3.2)$. And if the higher end of the 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 for clarity.

2. The AUC of Nuwayser

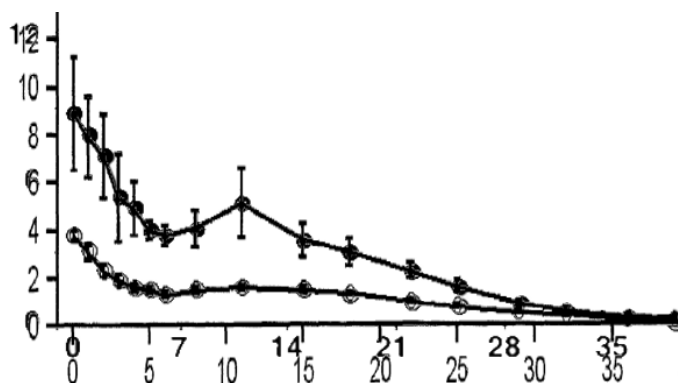
91. Nuwayser (EX1005), like Comer (EX1004), teaches administering a naltrexone/PLGA microparticle to six heroin dependent patients over a period of 28 days. Nuwayser explains in Examples II and IV (EX1005, 6:6-9, 14:25-49, 19:4-25) how the particles are made and the exact proportion of naltrexone in 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. EX1004, at 354. In fact, Biotek Inc. had also registered Depotrex as a trademark and identified it as a “pharmaceutical preparation[], namely, long-term delivery systems comprised of microcapsules of naltrexone and biodegradable polymers for the treatment of drug addiction, alcoholism and other disease.” EX1057.

92. 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. EX1005, 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* EX1004, Fig. 1 *with* EX1005, Fig. 7. As shown below, a POSITA 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.



93. 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.

IX. CLAIM CONSTRUCTION

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

94. In IPR2018-00943, the Patent Owner asserted that the phrase “the step of parenterally administering a long-acting formulation comprising about 310 mg to about 480 mg of naltrexone” should be construed as “a *single injection* of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” 943POR, 5-7 (emphasis added). The “single injection” language appears nowhere in the claims or specification, and nothing supports so limiting the claims.

95. The Patent Owner pointed to the use of “*the* step” and “*a* long acting formulation” in the claims as meaning “singular.” The ’499 Patent does focus on the difference between an injectable formulation given *once* every 28 days and *once-a-day* oral dosing for 28 days. In this context, clearly the ’499 Patent is claiming the

number of *doses used* during the claimed period rather than how many shots, or how many pills, were needed to administer the claimed dose.

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

97. In view of the foregoing and in view of my analysis of the specification, it is my opinion that the term "the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone" should be given its plain meaning which does not exclude multiple injections, *e.g.*, administration using two injections (as disclosed in Comer, see below) for the reasons explained above.

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

98. The '499 Patent does not define "the serum AUC of naltrexone ... than that achieved by 50 mg/day oral administration." The claims require a "serum AUC" but "serum AUC" is not defined by the specification. A POSITA would appreciate

that this refers to serum “area under the curve.” AUC is merely the area under a curve created by plotting plasma drug concentration versus time.

99. In IPR2018-00943, the Board determined that “AUC is a well-known pharmacokinetic parameter referring to area under the curve.” EX1058, 9. The Board determined that “serum AUC is represented by a plasma concentration-time curve.” *Id.* The Board also determined that “[b]y its plain terms, claim 1 requires that the serum AUC achieved by parenterally administering the long-acting formulation of naltrexone (i.e., a long-acting formulation comprising about 310 mg to about 480 mg naltrexone and a polylactide-co-glycolide polymer as a biocompatible polymer) is about three times the serum AUC achieved by administration of a 50 mg/day oral naltrexone formulation.” Ex. 1001, 21:3–9. I agree with the Board’s understanding of the term.

100. While the ’499 Patent does not define or specify the AUC of the claimed formulation or oral dosing, during prosecution of the ’499 Patent, the Patent Owner filed a Declaration under 37 C.F.R. § 1.132 (“the Ehrich Declaration”) purporting to show unexpected results for the serum AUC of the claimed long-acting naltrexone formulation over that of a 50 mg/day oral formulation (*i.e.*, an unexpected serum AUC differential). Ex. 1055, 1–18.

101. The Ehrich Declaration provides two data sets (Cohort A and Cohort B) for the serum AUCs of the claimed long-acting naltrexone formulation and the

50 mg/day oral naltrexone. *See id.* at 6 (Table 8). For Cohort A, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.307, which is 3.37 times the serum AUC value of 1.278 for the 50 mg oral naltrexone dose. *Id.* at 2. Similarly, for Cohort B, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.921, which is 3.35 times the 1.468 serum AUC value for the 50 mg oral naltrexone dose. *Id.* In the Examiner's Statement of Reasons for Allowance, the Examiner referenced this data as showing "an AUC about three times greater than that achieved by 50 mg/day oral administration," and explained that "no prior art disclos[es]" this effect. Ex. 1002, at 111-112. Because these serum AUC data points were presented during prosecution and were relied on by the Examiner in allowing the application issuing as the '499 Patent, a POSITA would understand that the serum AUC achieved by 50 mg/day oral administration encompasses these data points. Accordingly, I agree with the Board's determination in IPR2019-00943 that "the reference to a '50 mg/day' AUC in 'than that achieved by 50 mg/day oral administration' as encompassing at least serum AUCs of 1.278 ng·day/ml and 1.468 ng·day/ml." EX1058, 11-12.

C. "about three"

102. The '499 Patent does not define "about three." However, Claim 5 (which depends from Claim 1) specifies an AUC of about 3.3 times greater than oral dosing. Thus, it is my opinion that "about three" encompasses at least 3.3.

Additionally, it is my opinion that a POSITA would thus appreciate that “about three” also encompasses at least “about 2.7” because this constitutes a quantity within 10% of 3.0. However, one of ordinary skill in the art would appreciate that this term could encompass an even wider range. For example, I note that in the Ehrich Declaration, the inventor equated “the per day 380 mg MEDISORB® Naltrexone AUC_{0-t} [of] 4.307 [to be] about 3.3 time greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.278.” EX1055, 12. Likewise, for a second patient cohort, Dr. Ehrich equated “the per day 380 mg MEDISORB® Naltrexone AUC_{0-t} [of] 4.921 [to be] about 3.3 time greater than the per day AUC_{0-t} of oral Naltrexone 50 mg which is 1.468.” *Id.*

103. I also agree with the Board’s determination in IPR2019-00943 that “about three necessarily encompasses at least 3.3” and “at least about 2.7.” EX1058, 13. During prosecution, the Patent Owner submitted the Ehrich Declaration which provides data of a serum AUC for long-acting naltrexone formulation that is 3.3 times greater than that achieved by oral dosing. EX1055, 2.

D. “five or more days”

104. Claim 2 requires that the individual not use oral naltrexone within five or more days before administration of the formulation. This was not the original language of the claim, as filed. The original language mirrors the language used in the specification, namely “has not used oral naltrexone within five days, such as

within ten days, before said administration.” EX1001, 2:1-2. Putting aside the fact that ten days is not within five days, the claim can either be read to encompass no prior oral naltrexone administration within five days or simply no prior oral naltrexone administration *ever*. The use of the phrase “or more” in the claim, and the attempt to define the concept as encompassing ten days, manifests an intention to cover a range greater than five days. Thus, it is my opinion that the term “five or more days” encompasses no prior oral naltrexone administration, *ever*.

E. “initial oral dose”

105. Claim 11 requires the individual not receive an “initial oral dose” of naltrexone. The ’499 Patent does not define this term. The only reference to dosing in the ’499 Patent is to the administration of naltrexone to treat a patient to overcome his or her addiction. The art, however, makes clear that there are other purposes. For example, Comer teaches the use of naltrexone as part of a detoxification process prior to treatment. EX1004, at 353. There is a break of two days between administering the detoxification doses and the treatment doses. *Id.* Similarly, a small percentage of the patient population can have serious adverse reactions to naltrexone. Naltrexone has been given orally to test for this prior to giving a depot injection for treatment. EX1009, 5:65-6:6, 6:13-17; EX1008, 1074. Clearly the art distinguishes initial treatment doses from prior doses given for other purposes. Accordingly, it is my

opinion that the “initial oral dose” as used in the ’499 Patent is an earlier *treatment* dose, not a dose provided for other purposes.

F. “about 35% by weight”

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

107. And finally, given its lack of any impact on therapeutic efficacy, a POSITA 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.

X. THE CHALLENGED CLAIMS ARE ANTICIPATED OR OBVIOUS IN VIEW OF THE PRIOR ART

108. In the following paragraphs, I explain why Claims 1-13 of the ’499 Patent are unpatentable over the prior art asserted in Grounds 1-5.

A. Ground 1: Claims 1, 3-5, and 12 Are Anticipated by Comer

109. In my opinion, Claims 1, 3-5, and 10-12 are anticipated by Comer. As I explain below, Comer describes each element claimed, including the allegedly unexpected AUC. Nuwayser evidences what a POSITA would understand from Comer’s reference to “Depotrex,” *e.g.*, Depotrex contains the claimed PLGA.

1. Claim 1 (Preamble): A method for treating an individual in need of naltrexone comprising the step of

110. In my opinion, Comer as evidenced by Nuwayser discloses the preamble of Claim 1. Comer describes testing in human opioid-dependent patients of a depot injection made from 384 mg of naltrexone (Depotrex®). EX1004, at 351-354. “The active formulation contained drug equivalent to 192 mg naltrexone base...and for the high dose, participants received two naltrexone injections (384 [sic] mg naltrexone base).” *Id.* at 354.

a. [1.1]: parenterally administering a long acting formulation comprising

111. In my opinion, Comer discloses Element [1.1] as evidenced by Nuwayser (EX1005). This is because Comer seeks to provide a “sustained-release form of naltrexone” in order to “improve compliance” with patients. EX1004, 351. *See also id.*, 352.

112. The '499 Patent states that “long acting” may also be referred to as “extended, sustained, or controlled release” preparations and defines “long acting” as delivering “therapeutically beneficial amounts of naltrexone to a patient for a period of at least one week.” EX1001, 3:11-13, 3:59-64. Comer discloses a “sustained-release form of naltrexone” that is “long-lasting” and thus discloses a long acting formulation. EX1004, 351-352, Fig. 1.

113. Comer discloses “a depot formulation of naltrexone (Depotrex[®])” (EX1004, 351) and while not stated in Comer, *per se*, a POSITA would understand from, for example, Nuwayser, that Depotrex[®] is an extended release microcapsule comprising naltrexone and PLGA. Specifically, in Example IV, Nuwayser describes a formulation containing 54.4% naltrexone in PLGA (65% lactide: 35% glycolide, or 65% LA: 35% GA), identified as “Depotrex.” When administered subcutaneously, Depotrex delivered therapeutic levels in six heroin addicts for 30 days. EX1005, 14:26-50, 19:4-25, Fig. 7. In addition, a POSITA would note the superimposable nature of the AUC plots provided in Figure 1 of Comer and Figure 7 of Nuwayser, which would only serve to underscore the identity of Depotrex referenced in Comer. EX1004, at 354, Fig. 1; 1014, 19:4-25, Fig. 7.

114. Accordingly a POSITA would know that “Depotrex” as referenced in Comer refers to PLGA/naltrexone microcapsules used for depot injection as described in Nuwayser. Indeed, PLGA is a well-known polymer used in sustained release drug products. *See, e.g.*, EX1064, 1:41-44, EX1065, [0003]-[0004], EX1066, 9:7-35.

115. Comer’s depot formulation was injected into the buttocks of the patients using an 18 gauge needle—*i.e.*, satisfying the claimed parenteral administration. EX1004, at 354. Comer determined that 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 approximately four weeks. (*Id.* at 351.) “These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” *Id.*

116. Thus, it is my opinion that Comer teaches 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 PLGA (evidenced by Nuwayser). The advantages of such administration are, in my view, disclosed and myriad.

b. [1.2]: about 310 mg to about 480 mg of naltrexone

117. In my opinion, Comer as evidenced by Nuwayser discloses Element [1.2]. As I discussed above with respect to the preamble, Comer describes testing in human opioid-dependent patients of a depot parenteral administration made from 384 mg of naltrexone (Depotrex®). EX1004, at 351-354. Comer discloses that “[t]he active formulation contained drug equivalent to 192 mg naltrexone base...and for the high dose, participants received two naltrexone injections”, *i.e.*, “384 mg depot naltrexone”. EX1004, 354, Fig. 1. Thus, Comer discloses Element [1.2].

118. Also, as I explained above, the phrase “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone” does not exclude the two injections of Comer. Comer’s administering

of the “high dose” constituting two 192 mg naltrexone injections (total=384 mg) satisfies the claimed step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone. Indeed, Comer itself refers an “administration of ... 384 mg depot naltrexone” (EX1004, 354) recognizing that the two 192 mg naltrexone injections constitute a single “high dose” administration of naltrexone.

c. [1.3]: and a biocompatible polymer to the individual

119. In my opinion, Comer as evidenced by Nuwayser discloses Element [1.3]. As I discussed above with respect to Element [1.1], Comer as evidenced by Nuwayser discloses a formulation comprising PLGA (65% lactide: 35% glycolide, or 65% LA: 35% GA), identified as “Depotrex.” EX1004; EX1005, 14:26-50, 19:4-25, Fig. 7. Thus, Comer as interpreted by Nuwayser discloses Element [1.3].

d. [1.4]: wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration

120. In my opinion, Comer as evidenced by Nuwayser discloses Element [1.4]. This is because the plot of Figure 1 of Comer discloses an AUC that is about three times greater than that achieved by 50 mg/day oral administration to the same extent as the '499 Patent.

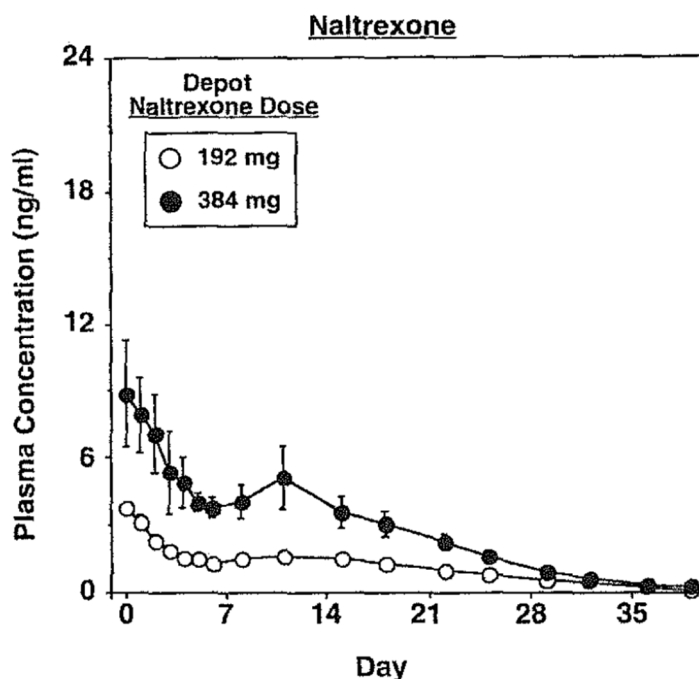


Figure 1 of Comer

121. This differential results from comparing the AUC of Comer to the oral data presented in the Ehrich Declaration, the same oral data used by Patent Owner when making its comparison. So, Comer's AUC differential over 50 mg/day oral dosing is about 3, indeed about 2.9. *See calculations under linear trapezoidal rule and plotting area using Photoshop above.*

122. Moreover, during an appeal filed in the '499 Patent's grandchild, Application No. 13/871,534, filed April 26, 2013 (now abandoned), the Patent Owner admitted that "[t]he Examiner appears to ignore the fact that the result (superior efficacy and pharmacokinetic profile) is dose dependent...." EX1021, at 7. The dose of Comer is 384 mg, which is the same dose (about 380 mg) as that

given in the clinical study reported in the '499 Patent and the Ehrich Declaration, and upon which the Patent Owner relied for their observation of alleged unexpected results. EX1001, 1:30-40, 8:32-4, 17:49-62. Since the doses are the same and the Patent Owner has admitted that AUC is dose dependent, Comer must also have the disclosed AUC differential if compared to the same oral dosing data.

e. [1.5]: and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

123. In my opinion, Comer as evidenced by Nuwayser discloses Element [1.5]. As I discussed above with respect to Elements [1.1] and [1.3], Comer as interpreted by Nuwayser discloses a formulation comprising PLGA (65% lactide: 35% glycolide, or 65% LA: 35% GA), identified as “Depotrex.” EX1004; EX1005, 14:26-50, 19:4-25, Fig. 7. Thus, Comer as evidenced by Nuwayser discloses Element [1.5].

124. Thus, for all of the foregoing reasons, it is my opinion that Comer as evidenced by Nuwayser anticipates Claim 1.

2. Claim 3: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.

125. It is my opinion that Comer discloses the subject matter of Claim 3. Comer’s release for a month meets the limitation of Claim 3, requiring at least two weeks of naltrexone release. *See, e.g.*, EX1004, Figure 1, 359 (“formulation of

naltrexone that requires only once-a-month administration has important and exciting treatment implications”).

3. Claim 4: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.

126. It is my opinion that Comer discloses the subject matter of Claim 4. Comer’s release for a month meets the limitation of Claim 4, requiring release for four weeks. *See, e.g.*, EX1004, Figure 1, 359 (“formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications”).

4. Claim 5: The method of claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone wherein the serum AUC is about 3.3 times greater than that achieved by 50 mg/day oral administration.

127. It is my opinion that Comer discloses the subject matter of Claim 5. The AUC differential resulting from the comparison of Comer to the Ehrich Declaration, as previously discussed, shows a differential of about three, indeed about 2.9. However, if instead of using the oral data provided by the Ehrich Declaration, the oral AUC_{0-28d} data found in Tice (EX1009, 14:34-58) is used, the mean AUC_{0-28d} of Comer is 3.2 times greater than the oral AUC_{0-28d}. ($\frac{103.7}{(27.8+24) \times 28} = 3.2$). 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 ($\frac{125.4}{(27.8+24) \times 28} = 3.9$).

128. Thus, Comer discloses a serum AUC that is about 3.3 times greater than that achieved by 50 mg/day oral administration.

5. Claim 12: The method of claim 1 wherein naltrexone is administered by injection.

129. It is my opinion that Comer discloses the subject matter of Claim 12. As I noted in connection with Claim 1, Comer discloses administering two naltrexone injections into the buttocks. EX1004, at 354. Comer discloses that the two naltrexone injections constitute a single “administration”, *i.e.*, a “high dose” of naltrexone as explained above. EX1004, at 354.

B. Ground 2: Claims 1-13 Would Have Been Obvious Over Comer in view of Nuwayser, Rubio, and Wright

130. It is my opinion that the Challenged Claims are also obvious over Comer in view of Nuwayser, Rubio and Wright. Comer and Nuwayser are described in above Ground 1. As I explain below, Comer does not expressly discuss that Depotrex formulation contains PLGA. But, it is my opinion that a POSITA interested in Depotrex would find Nuwayser, which describes Depotrex fully.

131. In IPR2018-00943 IPR, the Patent Owner asserted that Claim 1 should be construed to require a single injection of naltrexone, excluding the two naltrexone injections of Comer’s “high dose” administration. EX1060, 5-7,13-14. As I explained above the “single injection” language of the Patent Owner’s construction appears nowhere in the claims or specification, and nothing supports so limiting the

claims. Nonetheless, a POSITA would have modified Comer to administer the 384 mg naltrexone with a single injection. This is true for a number of reasons.

132. The efficacy of naltrexone in treating drug dependencies was known to be limited by poor patient compliance or adherence to the prescribed daily dosing. EX1004, 351. A POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer. For example, patients receiving a drug treatment via intramuscularly injection may have a wound at the injection site and develop inflammation. In addition, intramuscular injections allow for the potential introduction of bacteria and other pathogens into the patient. These intramuscular injections can have commonly known complications such as muscle damage, nerve damage, potential for injecting into a blood vessel (which can result in a hematoma), and the potential for the abscess formation. More serious complications from intramuscular injections can result in tissue necrosis, granulomas, muscle fibrosis as well as other complications. Patients receiving intramuscular injections often experience significant pain with these injections thereby decreasing their motivation to receive these injections. Additional effects of intramuscular injections can result in the liquid formulation of the drug being administered leaking out of the injection site thereby reducing the dosage amount that patient actually receives. Requiring a patient to receive more

than one of these injections at a single time doubles the chance of this complication, is excessive for a patient to have to endure and further decreases their motivation to continue receiving these intramuscular injections. Therefore, it logically makes sense that decreasing the number of intramuscular injections would reduce the likelihood of these complications and reduce the likelihood that a patient will avoid treatment becoming noncompliant.

133. In addition, Comer, itself, provides motivation for a POSITA to reduce the number of depot injections of a long-acting naltrexone formulation. For example, Comer describes “[e]leven of 12 participants report[ing] pain during administration of the depot injections.” EX1004, 357. Indeed, the “discomfort associated with the actual injections of depot naltrexone and mild soreness at the injection site [continued] for 2-3 days following the injections.” *Id.*, 359. Thus, for example, a POSITA would have been motivated to reduce pain associated with multiple injections by reducing two injections to just one.

134. In my opinion, a POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer, and would have had reason and been motivated to modify Comer to employ a single 384 mg naltrexone injection as opposed to two separate 192 mg injections with a reasonable expectation of success. Such a modification would have merely

constituted combining prior art elements (two injections) according to known methods to yield predictable results. While Comer employed a single concentration of naltrexone for both the low and high doses and increased the dose by employing two injections, a POSITA would have recognized that employing a single injection containing the total 384 mg naltrexone would have been a desirable alternative to avoid the above potential drawbacks of multiple injections, yielding only predictable results.

1. Claim 1

135. It is my opinion that Comer in view of Nuwayser disclose 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 PLGA polymer (Depotrex).

136. If one did not accept that Nuwayser defined Depotrex used in Comer to a POSITA as explained in Ground 1, a POSITA would nonetheless have had reason and been motivated to use the Nuwayser naltrexone formulation in the method taught by Comer with a reasonable expectation of success. Assuming Comer does not specifically describe the specific naltrexone formulation that should be used, a POSITA would seek out acceptable formulations. Comer teaches a method of treating heroin addicts by using 384 mg naltrexone in parentally injectable

naltrexone-containing microcapsules. EX1004, at 351, 354, 358-359, Fig. 1. But except for the dose, Nuwayser teaches the same thing. EX1005, 19:4-25. And both provide data on the release profile of their formulations, which a POSITA would recognize to be the same, or nearly so. EX1004, Fig. 1; EX1005, Fig. 7.

137. Thus, it is my opinion that a POSITA would have reasonably expected that using sufficient PLGA microparticles produced in accordance with Nuwayser to provide 384 mg dose of naltrexone called for in Comer would achieve the results of Comer, *i.e.*, a 28-day release of a therapeutic dose of naltrexone having a similar release profile and AUC. And, as AUC is dose dependent and Comer teaches giving the claimed dose, the claimed AUC differential, or one rendering it obvious, would reasonably be expected if the same oral data used by Alkermes was used to calculate the differential. In fact, when the AUCs of Comer and Nuwayser are compared to the oral data in the Ehrich Declaration, the AUC differential is about three, indeed about 2.9.

138. Given the sameness of the AUC plots of Comer and Nuwayser and that both stated that they provided therapeutic doses for about a month, it is my opinion that a POSITA would also have had a reasonable expectation that their combined teachings would be successful. EX1004, at 351, 359 (“These results suggest that this depot formulation of naltrexone provides a safe, effective long-lasting antagonism of the effects of heroin.”); EX1005, 19:23-25 (“This formulation delivered a

therapeutic level of naltrexone in six heroin addicts for a period of 30 days (*see* FIG. 7).”).

139. But even if the claimed AUC differential did not result from this combination, the claims would still be obvious because this limitation should be given little weight. First, it is my opinion that a POSITA would realize that the AUC and AUC differential between a depot injection and oral dosing of naltrexone would not be expected to have a meaningful impact on efficacy. So long as therapeutic blood levels were maintained, which was known in the art to result from oral dosing and depot injections, the treatment should be equally effective no matter how much higher the blood concentration, *i.e.*, the AUC (assuming compliant use). In fact, it is even possible that an enhanced AUC above levels necessary to minimally maintain therapeutic blood levels could raise the risk of toxicity.

140. Nothing in the specification would suggest to a POSITA that using a naltrexone depot injection (whether it is that described by the '499 Patent, in Comer, or Nuwayser) would provide meaningfully different therapeutic effects than oral dosing 50 mg/day. A depot injection might provide better compliance, but that was known. EX1004, 351-352. Indeed, when distinguishing oral dosing and other depot injections during prosecution, Alkermes noted that Tice (EX1009) resulted in an AUC that was roughly the same as oral dosing—not three times that level as claimed.

EX1002; EX1055, at 4. Alkermes did not argue, however, that either was less effective.

141. Moreover, it is my opinion that a POSITA would discount any AUC differential because it did not result from a comparison made to the closest prior art. Here the closest prior art is not oral dosing or Tice, as the Examiner suggested. Instead, it is my opinion that a POSITA would look to Comer and Nuwayser, alone or in combination, both of which involved administering about 380 mg naltrexone in a PGLA-containing formulation as once-a-month depot injections. Since the dose, formulation, and manner of administration were exactly the same as that claimed, and the pharmacokinetic plots of each can be superimposed, it is my opinion that a POSITA would understand that the AUC and differential should all be the same or not patentably different.

142. It is also my opinion that a POSITA would be concerned that the AUC comparisons made in the '499 Patent are hypothetical. Unlike direct comparisons to one-month depot injections, this comparison is based on the use of oral AUC data obtained for a single day. To make a comparison, one must artificially divide or average the one-month data or assume that the one-day's data is consistent and multiply it by 28 days. Accordingly, it is my opinion that a POSITA would not consider any difference in AUC differential to be significant for all the reasons discussed herein.

2. Claim 2

143. Claim 2 recites “The method of claim 1 comprising administering the long acting formulation comprising naltrexone every four weeks for a period of about 24 weeks or more wherein the individual has not used oral naltrexone within five or more days before said administration”.

144. Claim 2 requires that treatment occur every 4 weeks and last for at least 24 weeks and that there be no prior oral dose of naltrexone. As to the former, Comer teaches treating patients every 4 weeks for 24 weeks because Comer teaches that naltrexone had already been used for “chronic administration of over 1 year.” EX1004, at 351. Moreover, Rubio teaches that treatment protocols of 12 months in alcoholics were known. EX1006, at 419-420. Long term treatment of six months or more was known. *See, e.g.*, EX1037 Abstract; EX1038 Abstract. As to the latter limitation, Comer contemplated treating with the depot injection without a prior oral dose of naltrexone. EX1004, 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. Therefore, it is my opinion that Claim 2 is obvious.

3. Claim 3

145. It is my opinion that Comer discloses the subject matter of Claim 3 as I explained above in Ground 1. Claim 3 requires at least two weeks of naltrexone

release, while claim 4 requires about four weeks. Four-week release is taught by both Comer and Nuwayser as noted in connection with claim 1 above. Accordingly, these claims are obvious as well.

4. Claim 4

146. It is my opinion that Comer discloses the subject matter of Claim 4 as I explained above in Ground 1.

5. Claim 5

147. It is my opinion that Comer discloses the subject matter of Claim 5 as I explained above in Ground 1. Claim 5 requires that the AUC be about 3.3 times that of 50 mg/day oral dosing. Comer and Nuwayser both disclose this. Moreover, as just discussed any difference in AUC differential would not carry patentable weight, as the difference is not meaningful in terms of therapeutic efficacy, the differential was not determined by a comparison to the closest art, and it falls within the margin of error in measurement.

6. Claim 6

148. Claim 6 recites “The method of claim 1 wherein the long acting formulation is administered over a period of about 24 week period or longer.” It is my opinion that Comer discloses and suggests the subject matter of Claim 6. This is obvious for the reasons I described in connection with Claim 2, which includes the same limitation.

7. Claims 7-9

149. Claim 7 recites “The method of claim 1 further comprising a second administration of a long acting formulation comprising naltrexone at least about 7 days after the first administration.” Claim 8 recites “The method of claim 7 wherein the second long acting formulation is substantially similar to the first long acting formulation.” Claim 9 recites “The method of claim 7 wherein the second long acting formulation is the same as the first long acting formulation.”

150. 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. This protocol would have been obvious to a POSITA for the following reasons. Since Comer and Nuwayser both teach four-week dosing, it is my opinion that a POSITA would not consider a second dose earlier than seven days. (*Id.* ¶ 111.) Moreover, if a single 7, 14, or even 30-day period were all that was needed for alcohol or opioid treatment, the very compliance problem that drives the reasoning for a depot injection would not be as compelling. Therefore, it is my opinion that a POSITA would expect that more than one four-week dose would be needed. And there is no reason to use different formulations than the one already established as successful.

8. Claim 10

151. Claim 10 recites “The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency.” The patients in the Comer study were opioid dependent. But Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. EX1004, at 352. So, to a POSITA, Comer’s result also places the art in possession of treating an alcoholic with a 384 mg depot injection as claimed. Rubio teaches treating alcoholics as well. EX1006, at 419-420. Thus, it is my opinion that Comer teaches the additional limitations of Claim 10.

9. Claim 11

152. Claim 11 recites “The method of claim 1 wherein the individual does not receive an initial oral dose of naltrexone.” In Comer, patients did get oral naltrexone, but they did not get the depot injection until two days later. EX1004, at 353. Oral naltrexone was administered “to ensure that participants were willing and able to tolerate its effects”—not as part of the same “method for treating an individual in need of naltrexone”, as required in claim 11. EX1004, 353. That oral dosing in Comer was not an “initial” treatment dose, as it was given for other purposes. *See also* EX1004, at 359 (“In a treatment setting where oral naltrexone may not be given prior to depot naltrexone....”). Moreover, there is no oral dosing

suggested in Nuwayser. Therefore, it is my opinion that Claim 11 is obvious in view of Comer.

10. Claim 12

153. Claim 12 requires that the parenteral administration be an injection. Comer teaches injection into the buttocks. EX1004, at 354. Nuwayser teaches subcutaneous (“SC”) injection. EX1005, Fig. 7. Therefore, it is my opinion that Claim 12 is therefore obvious in view of Nuwayser.

11. Claim 13

154. Claim 13 recites “The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35% by weight.” While Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight (EX1005, 19:22-23), Wright demonstrates that it was well-known to employ naltrexone drug loading in the range of 30-75% by weight of the formulation. EX1007, 7:63-8:1. *See also id.*, 12:8-32 (disclosing the use PLGA microparticles). Therefore, it is my opinion that Claim 13 would have been obvious because the claimed naltrexone concentration is encompassed by the range contemplated by the prior art and is not patentable, e.g., given that a POSITA would have had reason to optimize the concentration of the naltrexone formulation in view of the fact that the prior art teaches the general conditions of the Challenged Claims.

C. Ground 3: Claims 1-13 Would Have Been Obvious Over Nuwayser in View of Comer, Rubio, and Wright

155. It is my opinion that Claims 1-13 would have been obvious over Nuwayser in view of Comer, Rubio, and Wright. As I discuss below, Nuwayser identifies a naltrexone/PLGA depot injection formulation, a treatment protocol, and the pharmacokinetic plot that results from its administration. Nuwayser is not explicit as to the dose providing that plot. But in seeking to determine that dose, it is my opinion that a POSITA would find Comer, which used the same protocol, resulting in an identical plasma level plot, and used about 380 mg of naltrexone to do so.

1. Claim 1 (Preamble): A method for treating an individual in need of naltrexone comprising the step of

156. It is my opinion that Nuwayser discloses the preamble of Claim 1. In Example IV, Nuwayser describes a formulation of PLGA (65% LA: 35% GA) and 54.4% naltrexone, described as Depotrex, which, when administered subcutaneously, delivered therapeutic levels in six heroin addicts for 30 days. EX1005, 14:26-50, 19:4-25.

157. As I noted above, in IPR2018-00943, the Patent Owner asserted that Claim 1 should be construed to require a single injection of naltrexone, excluding the two naltrexone injections of Comer's "high dose" administration. EX1060, 5-7, 13-14. As I explained above, the "single injection" language of Patent Owner's

construction appears nowhere in the claims or specification, and nothing supports so limiting the claims. Further, as I noted above, Comer discloses that the two 192 mg naltrexone injections constitute a single “administration” of 384 mg naltrexone, *i.e.*, a single “high dose” of naltrexone, satisfying Claim 1. Nonetheless, it would have been obvious to modify Nuwayser and Comer to administer the 384 mg naltrexone with a single injection. This is true for a number of reasons detailed below.

158. The efficacy of naltrexone in treating drug dependencies was known to be limited by poor patient compliance or adherence to the prescribed daily dosing. EX1004, 351. It is my opinion that a POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer. For example, patients receiving a drug treatment via intramuscularly injection may have a wound at the injection site and develop inflammation. In addition, intramuscular injections allow for the potential introduction of bacteria and other pathogens into the patient. These intramuscular injections can have commonly known complications such as muscle damage, nerve damage, potential for injecting into a blood vessel (which can result in a hematoma), and the potential for the abscess formation. More serious complications from intramuscular injections can result in tissue necrosis, granulomas, muscle fibrosis as well as other complications. Patients receiving intramuscular injections often experience significant pain with

these injections thereby decreasing their motivation to receive these injections. Additional effects of intramuscular injections can result in the liquid formulation of the drug being administered leaking out of the injection site thereby reducing the dosage amount that patient actually receives. Requiring patient to receive more than one of these injections at a single time doubles the chance of this of these complication, is an additional burden for the patient to endure, and further decreases their motivation to continue receiving these intramuscular injections. Therefore, it logically makes sense that decreasing the number of intramuscular injections would reduce the likelihood that these complications and reduce the likelihood that a patient will avoid treatment becoming noncompliant.

159. In addition, Comer, itself, provides motivation for a POSITA to reduce the number of depot injections of a long-acting naltrexone formulation. For example, Comer describes “[e]leven of 12 participants report[ing] pain during administration of the depot injections.” EX1004, 357. Indeed, the “discomfort associated with the actual injections of depot naltrexone and mild soreness at the injection site [continued] for 2-3 days following the injections.” *Id.*, 359. Thus, for example, a POSITA would have been motivated to reduce pain associated with multiple injections by reducing two injections to just one.

160. Further, it is my opinion that a POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for

the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer, and would have had reason and been motivated to modify Comer to employ a single 384 mg naltrexone injection as opposed to two separate 192 mg injections with a reasonable expectation of success. Such a modification would have merely constituted combining prior art elements (two injections) according to known methods to yield predictable results. While Comer employed a single concentration of naltrexone for both the low and high doses and increased the dose by employing two injections, a POSITA would have recognized that employing a single injection containing the total 384 mg naltrexone would have been a desirable alternative to avoid the above potential drawbacks of multiple injections, yielding only predictable results.

a. [1.1]: parenterally administering a long acting formulation comprising

161. It is my opinion that Nuwayser discloses Element [1.1]. As I discussed above, Nuwayser discloses that Depotrex—a long acting formulation—was administered subcutaneously, *i.e.*, thus satisfying “parenterally”. Thus, Nuwayser discloses Element [1.1].

b. [1.2]: about 310 mg to about 480 mg of naltrexone

162. It is my opinion that Nuwayser discloses Element [1.2]. For example, in Figure 7, Nuwayser shows the naltrexone plasma level of the six human heroin addicts described in Example IV after single and double SC injections of Depotrex.

Figure 7. Naltrexone Plasma Level in Six Human Subjects After Single and Double SC Injections of Depotrex™

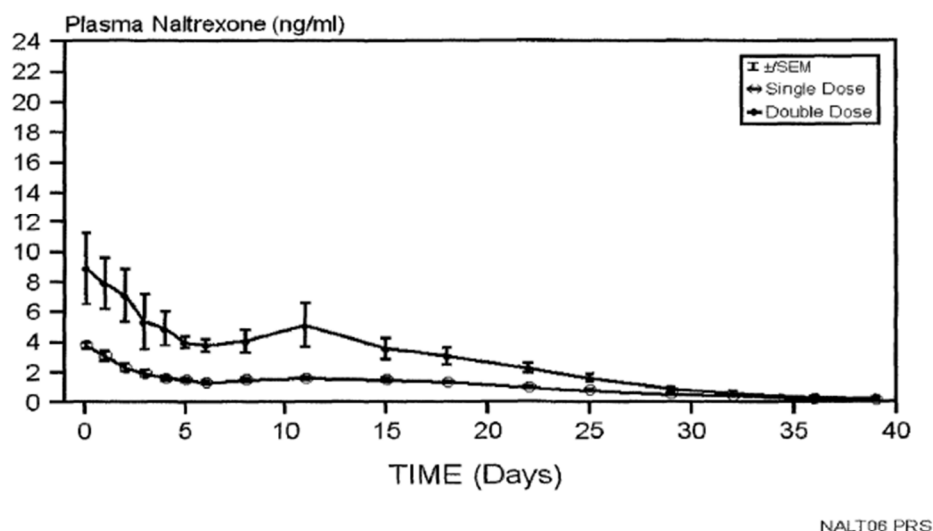


Figure 7 of Nuwayser

163. The data in that figure demonstrates that the total AUC discloses a dose of about 380 mg by integration of the plot of Figure 7. This falls within the claimed range of 310-480 mg. EX1005, 19:4-25, Fig. 7.

164. 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. EX1005, 14:26-49, 19:4-25, Fig. 7. Nuwayser provides a plot of the pharmacokinetics, including the AUC resulting from the use of these microcapsules. The only thing that Nuwayser arguably does not explicitly disclose is the dose—how much of the formulation

made in accordance with its Examples II and IV is needed to provide the AUC plot in Fig. 7.

165. However, like Nuwayser, Comer describes giving long-acting PLGA naltrexone parenterally to six heroin dependent patients where a therapeutic level was delivered for about a month. Indeed, both references administered “Depotrex” produced by the same manufacturer, Biotek Inc. In addition, Dr. Nuwayser is both an author of Comer and an employee of Biotek. Finally, in both, the pharmacokinetic plots were reported and are superimposable. *Compare* EX1004, Fig. 1 *with* EX1005, Fig. 7. All of this would have motivated a POSITA looking for an appropriate dose to use that disclosed in Comer, namely 384 mg (about 380 mg).

166. And a POSITA would have had a reasonable expectation of success given the success reported by both Nuwayser and Comer and the near identity of their disclosed protocols and pharmacokinetic plots. 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. Moreover, as described previously, since the doses of Comer and Nuwayser are about 380 mg, and since AUC is dose-dependent, the AUC should be the same, and the same as that resulting from the formulation claimed in the '499 Patent (380 mg).

167. The AUC differential resulting from the combination should be the same as that claimed as well, assuming that the same oral dose data is used. the

inventor's data and/or that of Tice, the AUC differential would be about three, indeed about 3.3.

168. To the extent that the dose did not provide the AUC of Nuwayser's Figure 7, as the claimed AUC differential, it is my opinion that a POSITA could adjust the dose to arrive at that disclosed AUC endpoint of Figure 7. Further, it is my opinion that a POSITA could do so assuming that a POSITA considered the AUC differential to be significant, which, as discussed in connection with Claim 1 of Ground 3, a POSITA would not.

c. [1.3]: and a biocompatible polymer to the individual

169. It is my opinion that Nuwayser discloses Element [1.3]. As discussed above, Nuwayser discloses that Depotrex—a formulation comprising biocompatible polymer, PLGA—was administered to six heroin addicts. Thus, Nuwayser discloses Element [1.3].

d. [1.4]: wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration

170. It is my opinion that Nuwayser discloses Element [1.4]. For example, in Figure 7, Nuwayser shows the naltrexone plasma level of the six human heroin addicts described in Example IV after single and double SC injections of Depotrex. The data in that figure demonstrates that plasma levels of 1 ng/ml could be obtained for at least 28 days. EX1005, 19:4-25, Fig. 7.

171. Further, since the plot of Nuwayser is superimposable with that of Comer, the AUC and the AUC differential for Nuwayser must be the same as for Comer, assuming again that the same comparison is made. Moreover, since “superior efficacy and pharmacokinetic profile” are dose dependent EX1021, at 7, the dose disclosed by Nuwayser must be substantially the same as that given in the clinical study (380 mg) described in the '499 patent and the Ehrich Declaration and disclosed in Comer. Since the doses must be the same, the AUC and differential (based on the oral data used by Alkermes) must be the same.

e. [1.5]: and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

172. As I discussed above, it is my opinion that Nuwayser discloses that Depotrex—a formulation comprising biocompatible polymer, PLGA—was administered to six heroin addicts. Thus, Nuwayser discloses Element [1.5].

173. For all of the foregoing, it is my opinion that Nuwayser renders obvious Claim 1 of the '499 Patent.

2. Claim 2

174. Because the art used in this Ground is identical to that used in Ground 2 except that the order of primary and secondary references is switched, the dependent claims are obvious for at least the reasons I generally described in Ground 2. Claim 2 is obvious because Nuwayser does not require any prior oral dose

and Comer contemplates this as well. Six or more treatments every 4 weeks was also well known. EX1004, at 352; EX1006, at 419, 420.

3. Claim 3

175. Nuwayser's 28-day release satisfies claim 3, requiring at least two weeks of naltrexone release. Indeed, both Nuwayser and Comer teach one-month dosing and render obvious claim 3.

4. Claim 4

176. Nuwayser's 28-day release satisfies claim 4, requiring release for four weeks. Indeed, both Nuwayser and Comer teach one-month dosing and render obvious claim 4.

5. Claim 5

177. Claim 5 is obvious because both Nuwayser and Comer teach administering about 380 mg of naltrexone and render a difference in AUC of 3.3 obvious. As I noted just above, Nuwayser teaches administering about 380 mg and the resulting AUC. This is the same dose as Comer, and the AUC differential (assuming the same oral data is used) should be the same as Comer as well.

6. Claim 6

178. Claim 6 is obvious for the reasons I discussed in connection with Claim 2.

7. Claims 7-9

179. Claims 7-9 are obvious because both Nuwayser and Comer teach monthly dosing and a POSITA would use as many of these same dosage forms as needed throughout the course of treatment.

8. Claim 10

180. Claim 10 is obvious as Comer teaches that naltrexone for treatment of alcoholism was safe and effective.

9. Claim 11

181. Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. Nothing in Nuwayser discloses giving any prior dose of naltrexone.

10. Claim 12

182. Claim 12 requires that the parenteral administration be an injection. Nuwayser teaches subcutaneous injection (“SC”) and therefore discloses claim 12. Comer also discloses administration by injection.

11. Claim 13

183. Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight. EX1005, 19:22-23. It was well known that drug loading could be in the range of 30-75% by weight of the formulation. EX1007, 7:65-8:1. Thus, the claimed naltrexone concentration is encompassed by the range

contemplated by the prior art and is not patentable, *e.g.*, given that a POSITA would have had reason to optimize the concentration of the naltrexone formulation in view of the fact that the prior art teaches the general conditions of the Challenged Claims.

XI. OTHER CONSIDERATIONS

A. Any Purported Secondary Considerations Evidence Does Not Overcome the Strong Evidence of the Obviousness of the Claims

184. All elements of the Challenged Claims are known in the art, and it is my opinion that any differences between the Challenged Claims of the '499 Patent and Comer would have been obvious to a POSITA based on the disclosures of the applied references and the knowledge in the art. As I explained above, the prior art demonstrates that it was already known to administer the same amount of naltrexone with the same biocompatible polymer (PLGA) resulting in the purported unexpected result of the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration, as that claimed. The purported unexpected results were not only expected, the AUC results were in fact already realized and obtained in the prior art, as explained above. That is, the purported invention of the '499 Patent merely calls for use of a known drug (naltrexone) at a known dose (384 mg) with a known sustained release additive (PLGA), to address the known problem of patient compliance. The serum AUC is merely a predictable result of the combination of known elements, and that too is also expressly disclosed in the prior art. The Challenged Claims are not patentable.

XII. CONCLUSION

185. For the reasons described herein, it is my opinion that all elements of Claims 1-13 of the '499 Patent are disclosed or suggested by the prior art. In my opinion, Claims 1-13 would have been anticipated or obvious over the prior art.

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

187. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date 1/23/2025



Thomas Charles Dowling, Pharm.D., Ph.D.