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Paper No. 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

ALKERMES PHARMA IRELAND LIMITED,
Patent Owner.

Case IPR2018-00943
Patent 7,919,499 B2

Before CHRISTOPHER M. KAISER, JACQUELINE T. HARLOW, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Amneal Pharmaceuticals LLC ("Petitioner") requests an *inter partes* review of claims 1–13 of U.S. Patent No. 7,919,499 B2 ("the '499 patent," Ex. 1001). Paper 1 ("Pet."). Alkermes Pharma Ireland Limited ("Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). Moreover, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial) ("USPTO Guidance").

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '499 patent is unpatentable. Accordingly, we institute an *inter partes* review of all challenged claims (1–13) of the '499 patent, based on all grounds raised in the Petition.

II. BACKGROUND

A. Related Matters

The parties state that there are no pending judicial proceedings involving the '499 patent. Pet. 61; Paper 6, 1. Patent Owner states that U.S. Patent Application No. 15/486,869 claims priority to the '499 patent and is currently pending before the Office. Paper 6, 1.

B. The '499 Patent

The '499 patent, titled "Naltrexone Long Acting Formulations and Methods of Use," issued on April 5, 2011. Ex. 1001, at [45]. The '499 patent relates to "a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long-acting formulation comprising naltrexone." *Id.*, at [57].

According to the '499 patent, "[a]lcohol dependence is a chronic disorder that results from a variety of genetic, psychological and environmental factors." *Id.* at 1:13–14. The '499 patent states that, "[i]n the past, most rehabilitative treatments have been psychosocial." *Id.* at 1:18–19. But, "[w]ith advances in neurobiology, there is increasing interest in drug therapy for alcohol dependence," such as naltrexone therapy. *Id*. at 1:19–27.

The '499 patent states that "[t]he inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone." *Id.* at 1:31–33. Specifically, "[t]his invention arose from the unexpected discovery that substantially improved serum levels of naltrexone can be achieved by administering long acting formulations of naltrexone, such as the Alkermes, Inc. formulation, Vivitrex® injectable suspension, made employing its Medisorb® delivery system." *Id.* at 2:29–34.

In one embodiment, the "invention includes a method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising naltrexone." *Id.* at 2:22–25. The formulation dosage preferably ranges from about 310 to about 480 mg of naltrexone. *Id.* at 1:45–46. The '499 patent states that the long acting formulation "may be achieved through the use of polymers (preferably poly-lactide or poly-lactide-co-glycolide polymers) to entrap or encapsulate the naltrexone." *Id.* at 3:11–16. The '499 patent identifies a preferred polylactide-co-glycolide ("PLGA") polymer as MEDISORB® 7525 DL polymer. *Id.* at 5:43–46; 6:44–51.

The '499 patent states that the disclosed method unexpectedly achieves a serum AUC of naltrexone that is "preferably at least about three times" that achieved by 50 mg/day oral administration of naltrexone. *Id.* at 2:22–28. The '499 patent provides a "semi-quantitative comparison" of the efficacy of long-acting naltrexone with oral naltrexone. *See id.* at 18:4–19:34 (Example 3). The '499 patent states that "oral naltrexone significantly decreased the relapse rate by 36% relative to placebo," whereas "Vivitrex suspension 380 mg significantly decreased the relapse rate by 45% relative to placebo." *Id.* at 18:57–67.

C. Illustrative Claim

Petitioner challenges the patentability of claims 1–13, but not claims 14 and 15, of the '499 patent. Of the challenged claims, claim 1 is independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is about three times

> greater than that achieved by 50 mg/day oral administration and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

Ex. 1001, 21:2–9.

D. The Prior Art

Petitioner advances the following references as prior art on which it relies for the asserted grounds challenging the claims of the '499 patent:

1. Sandra D. Comer et al., *Depot naltrexone: long-lasting antagonism of the effects of heroin in humans*, 159(4) PSYCHOPHARMACOLOGY 351–30 (2002) ("Comer," Ex. 1010);

2. Elie S. Nuwayser, U.S. Patent No. 7,157,102 B1 (issued Jan. 2, 2007) ("Nuwayser," Ex. 1014);

3. G. Rubio et al., *Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment*, 36(5) ALCOHOL & ALCOHOLISM 419–25 (2001) ("Rubio," Ex. 1028);

4. Steven G. Wright et al., U.S. Patent No. 6,264,987 B1 (issued July 24, 2001) ("Wright," Ex. 1018);

5. Henry R. Kranzler et al., *Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study*, 22(5) ALCOHOLISM CLINICAL & EXPERIMENTAL RES. 1074–79 (1998) ("Kranzler," Ex. 1011);

6. Alkermes, Inc., *Form 10-K: Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934* (July 2002) ("Alkermes 10-K," Ex. 1016); and

7. U.S. Trademark Application No. 76/271,990 for Vivitrex (Aug. 2002) ("Vivitrex Specimen," Ex. 1017).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–13 of the '499 patent on the following grounds:

Claims	Basis	Reference(s)
1, 3–5, and 10–12	35 U.S.C. § 102	Comer
1, 3–5, 11, and 12	35 U.S.C. § 102	Nuwayser
1–13	35 U.S.C. § 103	Comer, Nuwayser, Rubio, and Wright
1–13	35 U.S.C. § 103	Nuwayser, Comer, Rubio, and Wright
1–13	35 U.S.C. § 103	Nuwayser, Kranzler, Rubio, and Wright
1–13	35 U.S.C. § 103	Alkermes 10-K, Vivitrex Specimen, Wright, and Rubio

Pet. 4. Petitioner also relies on the Declaration of Kinam Park, Ph.D. *See id.* (citing Exs. 1030; 1031). Patent Owner disputes that Petitioner's asserted grounds render the challenged claims unpatentable. *See generally* Prelim. Resp.

III. ANALYSIS

We organize our analysis into four sections. First, we address the level of ordinary skill in the art. Second, we address claim construction. Third, we provide an overview of the asserted references. Fourth, taking account of the information presented, we consider whether the grounds asserted in the Petition meet the threshold showing for instituting an *inter partes* review under 35 U.S.C. § 314(a).

A. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends, and Dr. Park testifies, that a person of ordinary skill in the art would have a

doctorate level degree in pharmaceutics or related formulation sciences (such as a Pharm.D. or Ph.D.) and at least two years of experience in controlled release formulation. Pet. 15–16; Ex. 1030 ¶¶ 28–31. Petitioner and Dr. Park also contend that "[a] lesser degree of formal education balanced by additional practical experience could also qualify as a [person of ordinary skill in the art]." *Id.* In response, Patent Owner states that it "does not necessarily disagree with [Petitioner's] proposed definition of a [person of skill in the art] and reserves the right to offer another definition should the Board institute trial." Prelim. Resp. 15 n.8 (citations omitted).

We adopt Petitioner's definition for purposes of this decision. We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art). Further, based on the information presented at this stage of the proceeding, we consider Petitioner's declarant—Dr. Park—qualified to opine from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1031 (Dr. Park's curriculum vitae).

B. Claim Interpretation

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Petitioner proposes interpretations for claim terms: "a long acting formulation," "the serum AUC of naltrexone . . . than that achieved by 50 mg/day oral administration," "about three," "five or more days," "initial oral dose," and "about 35% by weight." Pet. 16–21. In response, Patent Owner asserts that Petitioner's claim interpretations are unnecessary or incorrect. Prelim. Resp. 62–63.

To determine whether to institute an *inter partes* review, we need not explicitly interpret every claim term for which Petitioner proposes a construction. *See* 35 U.S.C. § 314(a); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy."). We determine that, to resolve whether Petitioner has demonstrated a reasonable likelihood of prevailing, we need only address Petitioner's proposed interpretations of "the serum AUC of naltrexone . . . than that achieved by 50 mg/day oral administration" and "about three."

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

Claim 1 recites that "the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration." Ex. 1001, 21:6–7. Petitioner asserts that the '499 patent does not define "AUC," but, relying on the declaration testimony of Dr. Park, asserts that an ordinarily skilled artisan would understand serum "AUC" to refer to "area under the curve." Pet. 17 (citing Ex. 1030 ¶¶ 36, 37, 56–59). Petitioner also asserts that an ordinarily skilled artisan would understand that serum AUC "is merely the area under the curve created by plotting plasma drug concentration versus time." *Id.* (citing Ex. 1030 ¶¶ 38, 60).

We agree with Petitioner's interpretation of serum "AUC." As the record reflects, AUC is a well-known pharmacokinetic parameter referring to area under the curve. We also agree with Petitioner that serum AUC is represented by a plasma concentration-time curve. *See*, *e.g.*, Ex. 1012, 3 (referring to "AUC" as "area under plasma concentration-time curve"); Ex. 1044, 261–62 (accord); *see also* Ex. 1044, 261 (stating that AUC is used to evaluate the extent of drug absorption).

By 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. Petitioner asserts that the '499 patent "does not define or specify the AUC of the claimed formulation or oral dosing." Pet. 17. Because of this lack of information, Petitioner asserts, "a POSA must look to the art" but "would find . . . that there is no single accepted data set, particularly for the AUC resulting from administering 50 mg/day orally." Pet. 17–18. Petitioner asserts therefore that "the BRI . . . allows the use of *any data* for the AUC of the claimed naltrexone dose compared to *any data* for the AUC of a 50 mg/day oral dose." *Id.* at 18–19 (citing Ex. 1030 ¶ 43) (emphases added).

We agree with Petitioner that the '499 patent does not provide a value (or underlying data) for the serum AUC of the disclosed long-acting formulation of naltrexone, or a value (or underlying data) for the serum AUC of the 50 mg/day oral formulation. *See* Pet. 17–18. We observe, instead, that the written description describes the serum AUC of the

disclosed long-acting formulation of naltrexone in comparative terms: as "preferably at least about three times . . . greater over the course of the month than that achieved by 50 mg/day oral administration" of naltrexone. Ex. 1001, 1:37–40.[1]

Even so, we disagree with Petitioner on this record that the broadest reasonable interpretation allows for the use of *any* available data set for the claimed serum AUCs. Pet. 18–19. Petitioner does not address the '499 patent's prosecution history in its claim construction analysis. But in interpreting claims, "[a] patent's specification, together with its prosecution history, constitutes intrinsic evidence to which the Board *gives priority* when it construes claims." *WesternGeco LLC v. ION Geophysical Corp.*, 889 F.3d 1308, 1323 (Fed. Cir. 2018) (emphasis added). Thus, we must "consult the patent's prosecution history in proceedings" such as this one, "in which the patent has been brought back to the agency for a second review." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017) (*en banc*).

During prosecution of the '499 patent, applicants 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

[1] The written description of the '499 patent also refers to the claimed serum AUC of the long-acting naltrexone formulation as "unexpected," Ex. 1001, 2:29, and further states that "the pharmacokinetic profile of long-acting injectable naltrexone differs substantially from that of the oral formulation," *id.* at 17:49–51.

serum AUC differential). Ex. 1003, 1–18. 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,[2] which is 3.37 times the serum AUC value of 1.278 for the 50 mg oral naltrexone dose. *Id.* at 2. Similarly, for Cohort B, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.921, which is 3.35 times the 1.468 serum AUC value for the 50 mg oral naltrexone dose. *Id.* In her 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. 1009, 4.

Because these serum AUC data points were presented during prosecution and were relied on by the Examiner in allowing the application issuing as the '499 patent, an ordinarily skilled artisan would understand that the serum AUC achieved by 50 mg/day oral administration encompasses these data points. Indeed, Dr. Park admits that "[b]ecause the patent provides no data, a POSA would look at the Ehrich Declaration." Ex. 1030 ¶ 72. For purposes of this decision, therefore, we interpret the reference to a "50 mg/day" AUC in "than that achieved by 50 mg/day oral administration"

[2] The Declaration explains that the $AUC_{0\text{-}t}$ ($AUC_{0\text{-}28days}$) for a single dose of 380 mg long-acting naltrexone formulation on a per day basis can be calculated for Cohort A by dividing 120.6 ng•day/ml (the $AUC_{0\text{-}t}$ for Cohort A) by 28 days (120.6÷28=4.307), and by dividing 137.8 ng•day/ml (the $AUC_{0\text{-}t}$ for Cohort B) by 28 days (137.8÷28=4.921). Ex. 1003, 2.

as encompassing at least serum AUCs of 1.278 ng•day/ml and 1.468 ng•day/ml.

We acknowledge Petitioner's arguments and evidence suggesting that the comparative AUC values for the claimed long-acting naltrexone formulation and the 50 mg/day oral naltrexone render the claims difficult to understand. For example, Petitioner asserts that "the art reports varying data sets for oral dosing, none of which is consistent." Pet. 18 (citing Ex. 1030 ¶¶ 41, 81–86). Dr. Park cites to Baek[3] for showing a serum AUC of 1.80 ng•day/ml and 1.810 ng•day/ml for the 50 mg/day oral naltrexone formulations having the trade names Levia and Traxone, respectively. Ex. 1030 ¶ 82 (citing Ex. 1039, 72 (Table 1)). And Dr. Park points out that the serum AUC of the 380 mg long-acting naltrexone formulation would not be about three times the serum AUC of either Levia or Traxone. *See id.* ¶ 83 (calculating the serum AUC of the claimed 380 mg long-acting naltrexone formulation as 2.4 times the serum AUC of the Traxone 50 mg/day oral formulation).

Although Petitioner's arguments may raise issues of claim clarity—or even indefiniteness—that are beyond the scope of this *inter partes* review, because we discern, based on the present record, that the serum AUC of a 50 mg/day oral formulation encompasses at least the values reported in the Ehrich Declaration, we determine, for purposes of this decision, that the phrase is broad enough to create a reasonable likelihood that it reads on the prior art that is asserted here. *See infra* §§ III.D., III.E. Thus, it is

[3] In-hwan Baek et al., Evaluation of the Bioequivalence of Two Brands of Naltrexone 50 mg Tablet in Healthy Volunteers, 16(1) KOR. J. CLIN. PHARM. 69–74 (2006) ("Baek," Ex. 1039).

unnecessary at this point to determine the precise contours of the claim limitation for purposes of this decision. *Vivid Techs.*, 200 F.3d at 803. We leave for trial the issue of whether, on a fully developed record, this term is capable of construction, as well as the final construction it should be given. Accordingly, the parties are encouraged to explore this issue further at trial.

2. *"about three"*

Turning to the claim language "about three," we agree with Petitioner that—although not defined in the '499 patent—"about three necessarily encompasses at least 3.3" and "at least about 2.7." Pet. 19 (citing Ex. 1030 ¶¶ 45–47) (quotations omitted). As Petitioner points out, the Ehrich Declaration provides data of a serum AUC for long-acting naltrexone formulation that is 3.3 times greater than that achieved by oral dosing. *Id.*; Ex. 1003, 2. Dr. Park also testifies, and supports with evidence, that the term "about" as used in the art "indicate[s] a quantity within 10%." Ex. 1030 ¶ 47 (citing Ex. 1043, 8). For these reasons, we agree with Petitioner that the broadest reasonable interpretation of "about three" encompasses values as high as 3.3 and as low as 2.7.

C. Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. *Comer*

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. 1010, 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.*

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.* at 351 (Abstract). Comer states, however, that "[s]ustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness." *Id.* at 352. In particular, "[a] new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long-lasting 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.* at 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.*

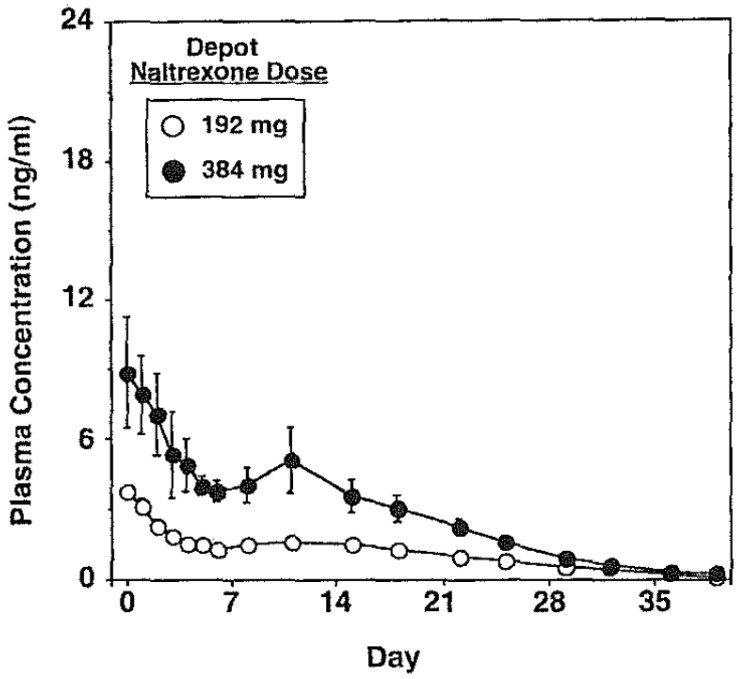


Figure 1 shows mean plasma levels of depot naltrexone over time following either a 192 mg depot dose (○) or a 384 mg depot dose (●). Ex. 1010, 354.

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.* at 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.*

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.* at 359. And thus, "a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications." *Id.*

2. *Nuwayser*

Nuwayser teaches a multi-layered microcapsule containing one or more active ingredients and a process for preparing the microcapsule. Ex. 1014, 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.* at 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.*

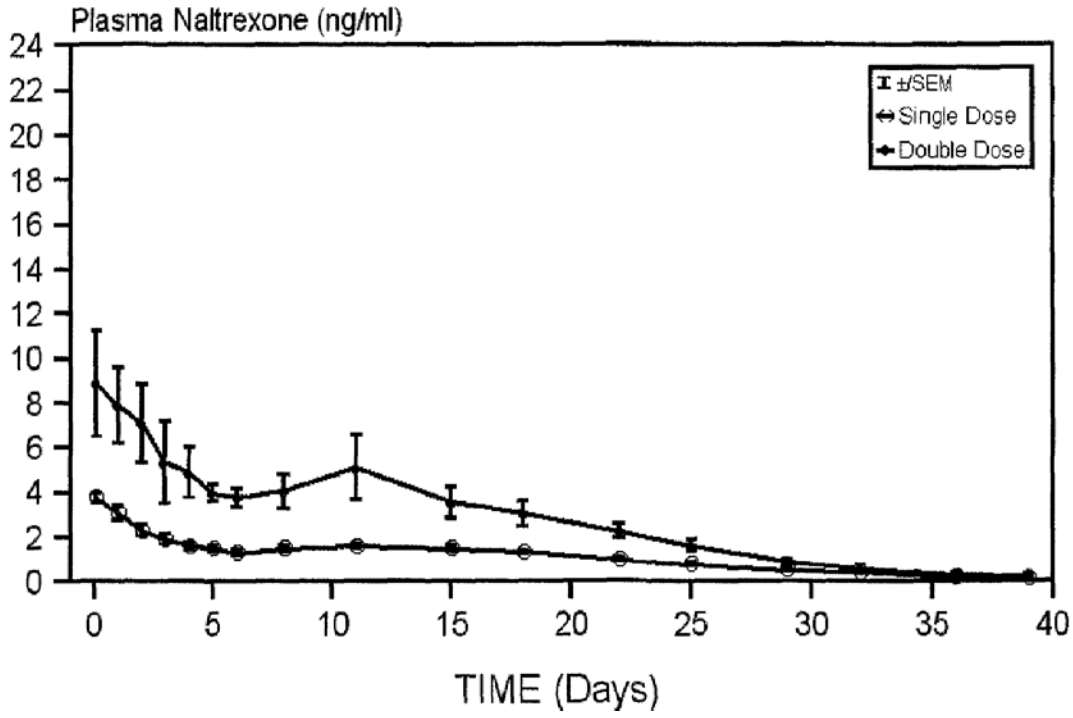


Figure 7 shows mean plasma levels of naltrexone over time following either a single dose (○) or a double dose (●) of naltrexone. Ex. 1014.

3. *Rubio*

Rubio states that both naltrexone and acamprosate "reduce relapse in alcohol dependence," but they "have not yet been compared in a published trial." Ex. 1028, 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.

4. *Wright*

Wright teaches a method for preparing microparticles having a selected polymer molecular weight. Ex. 1018, 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.

5. *Kranzler*

Kranzler describes a "preliminary study" of the use of sustained-release naltrexone for alcoholism treatment. Ex. 1011, 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.*

6. *Alkermes 10-K*

Alkermes 10-K states that "we are developing Vivitrex™, a Medisorb formulation of naltrexone, for the treatment of alcoholism and opiate dependence." Ex. 1016, 3. Alkermes 10-K states that naltrexone is "an

FDA-approved drug used for the treatment of alcohol and opioid dependence, which is currently available in daily oral dosage form." *Id.* at 5. Alkermes 10-K states that "Vivitrex is based on our Medisorb injectable extended-release technology and is designed to provide once-a-month dosing to enhance patient adherence by removing the need for daily dosing." *Id.*

7. *Vivitrex Specimen*

The "Vivitrex Specimen" consists of an "Allegation of Use of a Mark under 15 U.S.C. §§ 1051(c) or (d)," filed in U.S. Trademark Application No. 76/271,990 for "Vivitrex," accompanied by one specimen of the mark as used in commerce, a transmittal letter, and a fee. Ex. 1017, 1–5. The Allegation states that the mark was "first used at least as early as August 7, 2002; and was first used in commerce at least as early as August 7, 2002." *Id.* at 4. The specimen of the mark appears to be a label for Vivitrex, which identifies the contents as "Medisorb® Naltrexone (190 mg or 380 mg) (for injectable suspension)." *Id.* at 5.

D. Asserted Anticipation Grounds

Petitioner contends that Comer, as evidenced by Nuwayser, anticipates claims 1, 3–5, and 10–12 of the '499 patent. Pet. 22–26. Petitioner also contends that Nuwayser anticipates claims 1, 3–5, 11, and 12. *Id.* at 26–27. A claim is anticipated, and therefore unpatentable under 35 U.S.C. § 102, if all of its limitations are disclosed either explicitly or inherently in a single prior art reference. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). That single prior art reference must disclose all the limitations of the claim "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008). We address each asserted anticipation ground individually below.

1. *Anticipation by Comer as Evidenced by Nuwayser*

Petitioner argues 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) [naltrexone] and PLGA (evidenced by Nuwayser)." Pet. 23–24 (citing Ex. 1030 ¶ 89). Petitioner argues that Comer teaches the claimed serum AUC differential of about 3, by comparing Comer's serum AUC values with the Ehrich Declaration's serum AUC values for 50 mg/day oral naltrexone in Cohort A. Pet. 24 (citing Ex. 1030 ¶¶ 67–74, 81, 89). Petitioner also argues that Comer inherently teaches the claimed AUC differential because (1) Comer's dose is 384 mg, which is about the claimed dose of 380 mg, and (2) Patent Owner admitted before the Office during prosecution of a related patent application that serum AUC is dose dependent. *Id.* at 24–25 (citing Ex. 1030 ¶¶ 81, 89). Having considered the

arguments and evidence before us, we find that the record establishes a reasonable likelihood that Petitioner would prevail on its asserted ground of anticipation by Comer, as evidenced by Nuwayser.

Specifically, we are satisfied on this record that Comer teaches, either explicitly or inherently, each and every limitation of claim 1. As to the preamble ("method for treating an individual in need of naltrexone"), Comer discloses administering naltrexone to opioid-dependent patients, and discloses that naltrexone is a treatment for heroin dependence. Ex. 1010, 351 (Abstract). As to the method step ("parenterally administering a long-acting formulation comprising about 310 mg to about 480 mg of naltrexone"), Comer discloses giving two naltrexone injections of 192 mg naltrexone base (for a total of 384 mg) into the buttocks of patients. *Id.* at 354. And, as to the composition of the long-acting formulation ("where the biocompatible polymer is a polylactide-co-glycolide polymer"), Comer discloses "[a] new depot formulation of naltrexone (Depotrex®)" "that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side effects." *Id.*

As to this latter limitation, we agree with Petitioner on this record that an ordinarily skilled artisan would understand Comer's "Depotrex®" formulation refers to "naltrexone and a biocompatible polymer . . . wherein the biocompatible polymer is a polylactide-co-glycolide polymer," as recited in claim 1. *See* Pet. 22–23. Specifically, Nuwayser describes the preparation of naltrexone microcapsules by coating naltrexone microspheres with poly-L-(-)-lactide-co-glycolide polymer. Ex. 1014, 19:3–25. Nuwayser then states that "[t]his formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (see Fig. 7)." *Id.* at

19:23–25. Turning to Figure 7, Nuwayser refers to "single and double [subcutaneous] injections of Depotrex™." *Id.*, Fig. 7. Taken together, these passages identify Depotrex as a formulation comprising naltrexone and a poly-lactide-co-glycolide polymer, and thus an ordinarily skilled artisan would understand that Comer's Depotrex also refers to a formulation comprising naltrexone and a poly-lactide-co-glycolide polymer.

Turning to the remaining limitation of claim 1 ("wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration"), we are satisfied—on this record and for institution—that Comer teaches the serum AUC differential either explicitly or inherently. On the present record, we credit and rely on Dr. Park's calculation of Comer's serum AUC as 103.7 ng•day/ml, based on his analysis of Figure 1 using Photoshop software. *See* Ex. 1030 ¶¶ 67–74. Dr. Park explains that this serum AUC is 2.9 (or "about three") times the serum AUC achieved by 50 mg/day oral naltrexone in Cohort A of the Ehrich Declaration. Ex. 1030 ¶ 72.[4] Alternatively, Dr. Park explains that, because AUC is dose dependent and Comer administers about the same dose of long-acting naltrexone, Comer inherently teaches the same or substantially the same serum AUC values. *Id.* ¶ 70 (citing Ex. 1027, 7). Dr. Park reasonably supports this analysis by showing that Comer's AUC value of 103.7 ng•day/ml is "statistically the same" as the Ehrich Declaration's 120.6 ng•day/ml AUC value, given that the Ehrich Declaration discloses a mean standard deviation of 19.6. *Id.* (citing Ex. 1003, 6).

[4] Specifically, the serum AUC of Comer's 384 mg naltrexone dose is 3.703 (103.7 ng•day/ml÷28 days), which is 2.90 times the 1.278 serum AUC value for Cohort A's 50 mg oral naltrexone dose. Ex. 1030 ¶ 72.

On this record, we are not persuaded by any of Patent Owner's arguments and evidence that Petitioner has failed to show a reasonable likelihood of prevailing on this anticipation ground. *See* Prelim. Resp. 15–30. As an initial matter, Patent Owner argues that the anticipation ground is improper because it relies on multiple references. *Id.* at 16–17, 26–30, 32–33. But it appears, at least on this record, that Petitioner relies permissibly on Nuwayser to show that an ordinarily skilled artisan would have understood Comer's "Depotrex®" to be the same "Depotrex™" disclosed in Nuwayser: a formulation comprising naltrexone and polylactide-co-glycolide polymer. *See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 727 (Fed. Cir. 1984) (explaining that, although anticipation must be found in a single reference, a "caveat to that rule permit[s] the use of additional references to interpret the allegedly anticipating reference"). Put differently, we view Nuwayser as evidencing what an ordinarily skilled artisan would have understood Comer's reference to "Depotrex" to have meant; not as supplementing missing limitations in Comer.

Patent Owner asserts that, in any event, Petitioner has failed to show that Comer's "Depotrex®" is, in fact, the same "Depotrex™" in Nuwayser. Prelim. Resp. 26–30. In particular, Patent Owner asserts that "different versions of 'depotrex' existed" as of Comer's publication date, and that Petitioner has presented no evidence about which particular formulation Comer studied. *Id.* at 28–29. Patent Owner also asserts that Comer expressly states that "the same formulation of depot naltrexone used in the present study was also tested by Kranzler," yet Kranzler describes a formulation containing a dose of 206 mg in 2.4 ml solution, whereas Comer

describes Depotrex as containing "a dose of 192 mg in 2.4 ml." *Id.* at 29 (citing Ex. 1010, 354; Ex. 1011, 1075).

Having considered the arguments and evidence before us, we are of the opinion that Patent Owner's arguments highlight disputed issues of fact about whether an ordinarily skilled artisan would have understood Comer's "Depotrex®" formulation to comprise polylactide-co-glycolide as the biocompatible polymer. We conclude that this issue is best resolved following trial with the benefit of a full record, keeping in mind that Petitioner bears the burden of proving that the claims are unpatentable for anticipation. *See* 37 C.F.R. § 42.108(c) (requiring certain "genuine issue[s] of material fact" to "be viewed in the light most favorable to the petitioner . . . for the purpose of deciding whether to institute an *inter partes* review").

Patent Owner's remaining arguments go to whether Comer teaches the claimed serum AUC differential of "about three." See Prelim. Resp. 19–26. In short, Patent Owner argues that "there is no evidence in either the literature or Dr. Park's declaration that Photoshop is an acceptable means for calculating AUC or that Dr. Park's odd use of this software produces accurate results." *Id.* at 22–23. To the extent that Patent Owner's arguments raise admissibility issues under Federal Rule of Evidence (FRE) 702(c), we note that the admissibility of evidence is usually determined at trial upon filing a motion to exclude. *See* 37 C.F.R. §§ 42.64(b)(1) ("Any objection to evidence submitted during a preliminary proceeding must be filed within ten business days of the institution of trial."), 42.64(c) ("[a] motion to exclude must be filed to preserve any objection"). And to the extent that Patent Owner's arguments relate to the weight we should give to Dr. Park's

analysis under 37 C.F.R. § 42.65(a), we determine that this issue is best resolved following trial with the benefit of a full record.

In summary, based on the record before us and the application of the reasonable likelihood standard, we are satisfied that Petitioner has shown sufficiently for instituting trial that it would prevail in showing claim 1 unpatentable for anticipation by Comer, as evidenced by Nuwayser. Patent Owner does not raise additional arguments specific to dependent claims 3–5 and 10–12 at this stage of the proceeding. *See generally* Prelim. Resp. We have reviewed Petitioner's contentions and supporting evidence regarding claims 3–5, and 10–12 as well, and find them sufficient based on the current record for claims 3–5 and 12. *See* Pet. 25 (citing Ex. 1030 ¶¶ 81, 89, 91), 26 (citing Ex. 1010, 354; Ex. 1030 ¶¶ 94).

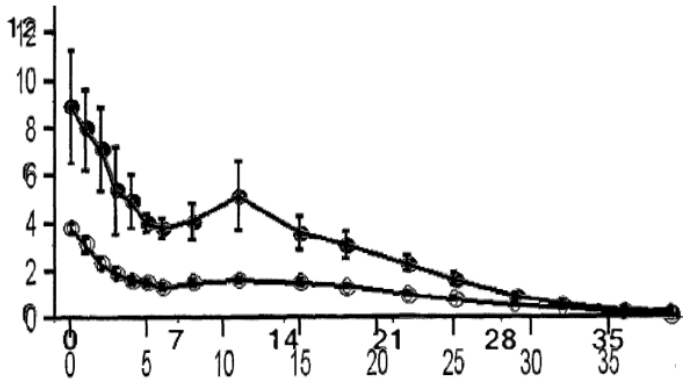
On this record, however, we question whether dependent claims 10 and 11, in particular, are properly challenged for anticipation. For example, claim 10 specifies that the patient is alcohol dependent. Ex. 1001, 22:6–7. Comer does not appear to teach (and at most appears to merely suggest) treating alcohol-dependent patients with a long-acting formulation of naltrexone. *See* Ex. 1010, 352 (stating that naltrexone had already been established to be safe and effective in alcoholics). Nevertheless, in light of *SAS*, the USPTO Guidance, and our determination that Petitioner has met its burden as to its challenge of claim 1, we also determine that it is appropriate to institute *inter partes* review of the remaining challenged claims (3–5 and 10–12) for anticipation by Comer, as evidenced by Nuwayser.

2. *Anticipation by Nuwayser*

We now turn to Petitioner's anticipation challenge based on Nuwayser, which is substantially similar to that based on Comer as

evidenced by Nuwayser. Taking claim 1 as illustrative, Petitioner argues that "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." Pet. 26 (citing Ex. 1014, 14:26–50, 19:4–25; Ex. 1030 ¶¶ 95–97). We agree with Petitioner on this record that Nuwayser teaches expressly treating an individual in need of naltrexone with a naltrexone formulation comprising polylactide-co-glycolide as a biocompatible polymer. Ex. 1014, 19:4–25.

Nuwayser does not teach expressly the claimed dosage range (310 to 480 mg), nor the claimed serum AUC differential (about three). *See* Ex. 1014, 19:23–25 (stating that six heroin addicts were administered a "therapeutic level of naltrexone" but not specifying the dosage). But, relying on Dr. Park's Declaration, Petitioner argues that Nuwayser teaches these limitations inherently because Figure 7 of Nuwayser and Figure 1 of Comer provide the same pharmacokinetic plots. *Id.* (citing Ex. 1030 ¶¶ 75–77, 96). Dr. Park asserts that "a POSA would recognize that the Nuwayser AUC is exactly the same as the Comer AUC" because Figures 1 and 7 are "drawn from the same data." Ex. 1030 ¶ 76. Dr. Park creates a figure superimposing Figure 7 onto Figure 1, adjusting the X and Y dimensions to match the sizes:



Id. ¶ 77. Dr. Park concludes that, because the curves are the same, Nuwayser must necessarily disclose the same dose (380 mg) and the same AUC differential (about 3) as Comer. *Id.* ¶¶ 76–77.

Having considered the arguments and evidence before us, we share Patent Owner's concern that Petitioner uses "circular logic" to support its anticipation challenge based on Nuwayser. *See* Prelim. Resp. 31 (citing Pet. 26–27). Specifically, Patent Owner points out that Petitioner's argument comes down to: "the plasma plots in Nuwayser and Comer are allegedly the same so the dose must be the same, and because the dose is the same the AUC must be the same." Prelim. Resp. 26. In light of *SAS* and USPTO Guidance, however, we institute *inter partes* review on the ground of anticipation by Nuwayser for challenged claims (1, 3–5, 11, and 12).

E. Asserted Obviousness Grounds over Comer, Nuwayser, Rubio, and Wright

Petitioner contends that claims 1–13 are unpatentable as obvious over the combination of Comer in view of Nuwayser, Rubio, and Wright, Pet. 29–36, and over the combination of Nuwayser in view of Comer, Rubio, and Wright, *id.* at 36–39. A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that

the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

1. *The Claimed Limitations*

Because these two obviousness grounds are substantially identical, we chose to address them together. Taking claim 1 as illustrative, we are satisfied on this record that Petitioner establishes sufficiently for institution that the combination of Comer and Nuwayser teach each and every limitation of the claim. Specifically, Comer discloses treating opioid-dependent patients with naltrexone by giving two naltrexone injections of 192 mg naltrexone base (for a total of 384 mg) into the buttocks of patients using a needle. Ex. 1010, 351–54. As to the composition of the long-acting formulation ("wherein the biocompatible polymer is a polylactide-co-glycolide polymer"), Comer discloses "[a] new depot formulation of naltrexone (Depotrex®) . . . that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side effects." *Id.* at 352. Nuwayser discloses a formulation comprising PLGA (65% LA:35% GA) and 54.4% naltrexone— also called Depotrex™—delivered at "therapeutic levels" to heroin addicts. Ex. 1014, 19:4–25.

We are not persuaded, on this record, by Patent Owner's argument that "neither Comer nor Nuwayser cures the deficiencies of the other."

Prelim. Resp. 34–35. For example, Patent Owner's argument that "[n]either reference discloses 'treating' someone in need of naltrexone" because "[t]reatment would . . . never involve providing an addict with several ascending doses of heroin," *id.* at 34, lacks evidentiary support. Even so, Patent Owner appears to concede that Nuwayser gives a "therapeutic level" of a naltrexone-PGLA formulation to heroin addicts. *Id.* at 34; *see also* Ex. 1014, 19:23–25. Patent Owner's remaining arguments—that Comer fails to disclose the claimed AUC profile and that Nuwayser fails to disclose the claimed dose—are not persuasive for the same reasons explained above in connection with Petitioner's anticipation grounds. *See supra* § III.D.

On this record and at this stage of the proceeding, therefore, we are satisfied that Petitioner establishes sufficiently for institution that the combination of Comer and Nuwayser satisfies the limitations of claim 1. We have reviewed Petitioner's contentions and supporting evidence regarding claims 2–13 as well, and find them sufficient based on the current record. *See* Pet. 33–36 (Comer in view of Nuwayser), 38–39 (Nuwayser in view of Comer). For example, we agree with Petitioner that Rubio teaches treating alcoholics with naltrexone for a period of 12 months, and thus teaches the limitations of claims 2 and 10. Pet. 33, 35, 38, 39; Ex. 1028, 419–20.

2. *Motivation to Combine/Reasonable Expectation of Success*

Even "[i]f all elements of the claims are found in a combination of prior art references," "the factfinder should further consider whether a person of ordinary skill in the art would [have been] motivated to combine those references, and whether in making that combination, a person of ordinary skill would have [had] a reasonable expectation of success." *Merck*

& Cie v. Gnosis S.P.A., 808 F.3d 829, 833 (Fed. Cir. 2015). The "motivation to combine" and "reasonable expectation of success" factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

Relying on the Dr. Park's Declaration, Petitioner contends that an ordinarily skilled artisan would have had a reason to combine the teachings of Comer and Nuwayser with a reasonable expectation of success. Pet. 30–33 (Comer in view of Nuwayser), 37–38 (Nuwayser in view of Comer). As to the combination of Comer in view of Nuwayser, Petitioner contends that, even "[i]f one did not accept that Nuwayser defined Depotrex to a POSA . . . , a POSA would nonetheless be motivated to use the Nuwayser naltrexone formulation in the method taught by Comer with a reasonable expectation of success." *Id.* at 29–30 (citing Ex. 1030 ¶ 102). And, as to the combination of Nuwayser in view of Comer, Petitioner contends that "[t]he only thing that Nuwayser arguably does not disclose is dose," and therefore, an ordinarily skilled artisan "looking for an appropriate dose" would have been motivated "to use that disclosed in Comer, namely 384 mg (about 380 mg)." *Id.* at 36–37 (citing Ex. 1030 ¶ 106). Petitioner also contends that these combinations lead to successful therapeutic doses of naltrexone. *Id.* at 31, 37.

Having considered the arguments and evidence before us, we are satisfied on this record that Petitioner has shown sufficiently for institution that an ordinarily skilled artisan would have been motivated to combine the disclosures of Comer and Nuwayser to provide an improved method for treating an individual in need of naltrexone. Specifically, we agree with Petitioner that an ordinarily skilled artisan looking to replicate Comer's

naltrexone microcapsules, Ex. 1010, 354, would have had a reason to look to Nuwayser, because Nuwayser expressly discloses a method for preparing naltrexone microcapsules that can be administered therapeutically to heroin addicts, Ex. 1014, 19:4–25. Moreover, on this record, we are persuaded that an ordinarily skilled artisan looking for dosing information to achieve Nuwayser's serum AUC results would have had a reason to use the dose disclosed in Comer, given that Comer discloses the successful administration of Depotrex to heroin-dependent patients. Pet. 37 (citing Ex. 1030 ¶ 106); Ex. 1010, 351 (stating that "[t]hese results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin").

Although we acknowledge Patent Owner's arguments that no reason exists to combine Comer and Nuwayser, we are not persuaded by those arguments on this record. *See* Prelim. Resp. 33–38. For example, Patent Owner argues that an ordinarily skilled artisan seeking to formulate Comer's injectable naltrexone dosage form would have looked, at most, to Kranzler, because "Comer expressly states that the same formulation was used in Kranzler." *Id.* at 36 (citing Ex. 1010, 359); *see also id.* at 40–42. But even if Comer suggests looking to Kranzler, that suggestion would not necessarily dissuade the skilled artisan from seeking out other forms of Depotrex found in the prior art, such as that disclosed in Nuwayser. *See In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) (teaching a way does not necessarily teach away).

We are also not persuaded by Patent Owner's argument that "[h]ow a POSA would find Nuwayser is not explained," Prelim. Resp. 35, because "[t]he person of ordinary skill is a hypothetical person who is presumed to

be aware of all the pertinent prior art." *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). And here, both Comer and Nuwayser are pertinent to each other, because both disclose long-acting naltrexone formulations and both use those formulations to treat opioid addiction. Ex. 1010, 351; Ex. 1014, 19:23–25.

Finally, we are persuaded on this record that Petitioner has shown sufficiently for instituting trial that the ordinarily skilled artisan would have had a reasonable expectation of success in the combination of Comer and Nuwayser. Specifically, we note that both Comer and Nuwayser state that their depot formulations of naltrexone delivered therapeutic levels of naltrexone to patients in need of treatment. Specifically, Comer states that "[t]hese results suggest that this depot formulation of naltrexone provides a safe, effective long-lasting antagonism of the effects of heroin." Ex. 1010, 351. And Nuwayser states that "[t]his formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (see FIG. 7)." Ex. 1014, 19:23–25.

We are not persuaded on this record, however, by Petitioner's argument that "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." Pet. 31 (citing Ex. 1030 ¶¶ 16, 63–65, 81–86, 106–107); *see also id.* at 11–12, 31–33. Even if, as Dr. Park testifies, as little as 1 ng/ml of naltrexone is sufficient to deliver therapeutic levels of naltrexone over a period of 28 days, *see, e.g.*, Ex. 1030 ¶ 60), we are unaware of any principle of law that would allow us to disregard the claimed serum AUC differential as simply "inconsequential," Pet. 2.

3. *Summary*

In sum, we are satisfied that Petitioner establishes a reasonable likelihood that it would prevail in showing that claim 1 is unpatentable under 35 U.S.C. § 103 as obvious over the combination of Comer in view of Nuwayser, Rubio, and Wright, and over the combination of Nuwayser in view of Comer, Rubio, and Wright. In light of *SAS* and USPTO Guidance, we also institute *inter partes* review of dependent claims 2–13 on the same grounds.

F. Asserted Obviousness Ground over Nuwayser, Kranzler, Rubio, and Wright

Petitioner contends that the challenged claims are unpatentable as obvious over Nuwayser in view of Kranzler, Rubio, and Wright. *See* Pet. 39–43. Specifically, Petitioner contends that—even if Nuwayser fails to teach the claimed dose—"[i]t would be obvious to determine the dose that resulted in the disclosed AUC without undue experimentation by generating a standard curve." Pet. at 40 (citing Ex. 1030 ¶ 116). Alternatively, Petitioner contends that Kranzler's disclosed 206 mg dose "would provide at least a starting point for a POSA" to increase the dose until the claimed AUC differential (about three) is achieved. Pet. 40–41. Petitioner also contends that—even if Nuwayser fails to disclose the claimed AUC differential—the "claims are obvious." *Id.*

Having considered the arguments and evidence before us, we find that the record fails to establish a reasonable likelihood that Petitioner would prevail on this asserted ground. For example, Petitioner's statement that "[i]t would require nothing more than routine experimentation to prepare an AUC-dose standard curve to find a dose for any given AUC," Pet. 40, lacks specific and credible evidentiary support. So too Petitioner's assertion that

"the dose should be adjustable as needed and should render the claimed AUC differential obvious." Pet. 41. Such conclusory statements fail to satisfy Petitioner's burden in showing obviousness. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016).

Moreover, Dr. Park's Declaration does not adequately support Petitioner's argument that the ordinarily skilled artisan would create a standard AUC curve to determine a particular dose. Pet. 40–41. For example, Dr. Park states summarily that "a POSA knows how to confirm that they have arrived at the correct dose" and a "POSA can easily conduct an experiment to establish a standard curve . . . correlating the AUC as a function of dose." Ex. 1030 ¶ 116. But Dr. Park does not support these statements with any details about how these calculations would be performed, or provide any specific evidence supporting these statements. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.").

Nevertheless, we institute *inter partes* review of all challenged claims (1–13) for obviousness over Nuwayser in view of Kranzler, Rubio, and Wright in light of *SAS* and the USPTO Guidance.

G. Asserted Obviousness Ground over Alkermes 10-K, Vivitrex Specimen, Rubio, and Wright

Turning to the final asserted ground of unpatentability, Petitioner asserts that claims 1–13 are unpatentable as obvious over Alkermes 10-K, in view of Vivitrex Specimen, Rubio, and Wright. *See* Pet. 44–50. Petitioner asserts that an ordinarily skilled artisan, reading Alkermes 10-K, would have observed the disclosure of "Vivitrex™" in connection with an injectable extended-release formulation of naltrexone, and would have been motivated

to investigate whether Alkermes had filed for trademark registration of "Vivitrex" based on the "™" signal. *Id.* at 45. That investigation, Petitioner asserts, would have led the ordinarily skilled artisan to USPTO records, where she would "find an application and Vivitrex Specimen," which discloses "Medisorb® Naltrexone (190 mg or 380 mg) for injectable suspension." *Id.* at 46 (citing Ex. 1017, 5; Ex. 1030 ¶ 130). Petitioner then asserts that the artisan would have turned to Wright, which "explains the Medisorb technology and how it can be used to produce, *inter alia*, naltrexone microparticles from PLGA." *Id.* at 46 (citing Ex. 1018, 7:48–8:60; Ex. 1030 ¶ 131). Finally, Petitioner asserts that, "[b]ased on Wright, a POSA could make three different types of PLGA naltrexone microparticles," and that "at least one of these three particles . . . would result in the same AUC as identified in the '499 patent." *Id.* at 47 (citing Ex. 1018, 1:33–38; Ex. 1030 ¶¶ 132–134). Having considered the arguments and evidence before us, however, we again find that the record fails to establish a reasonable likelihood that Petitioner would prevail on this asserted ground.

1. *Printed Publication*

As an initial matter, we agree with Patent Owner that Petitioner's asserted ground fails because Petitioner did not meet its burden to show that at least Alkermes 10-K qualifies as a printed publication. Prelim. Resp. 48–51. Under 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may only challenge the claims of a patent based on "prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). Petitioner has the initial burden of production to establish that there is prior art that renders the challenged claims unpatentable. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379 (Fed. Cir. 2015) (citing *Tech. Licensing*

Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008)). For institution purposes, Petitioner has the burden to establish a reasonable likelihood that it will prevail on the merits, which includes, *inter alia*, making a sufficient showing in the Petition that the relied-upon references qualify as "printed publications" within the meaning of 35 U.S.C. §§ 102 and 311(b). *Cf.* 35 U.S.C. § 314(a).

Whether a reference qualifies as a "printed publication" involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). The Federal Circuit has explained that public accessibility is the "touchstone in determining whether a reference constitutes a 'printed publication.'" *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). A reference is considered "publicly accessible" upon a satisfactory showing that the reference has been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it." *In re Wyer*, 655 F.2d 221, 226 (CCPA 1981).

To establish that Alkermes 10-K is prior art to the '499 patent, Petitioner asserts that Alkermes 10-K was electronically filed on the Securities and Exchange Commission's EDGAR System on July 1, 2002. Pet. 44 n.7 (citing Ex. 1058). Petitioner asserts that the SEC required companies to file their 10-K documents electronically at that time, *id.* (citing Ex. 1059), and thus, Alkermes 10-K "would have been immediately uploaded and available" for public viewing on or about July 1, 2002, *id.* (citing Ex. 1060).

Patent Owner contends that Petitioner has not established that Alkermes 10-K qualifies as a printed publication. Prelim. Resp. 48–51. Specifically, Patent Owner contends that Petitioner "fails to establish that the Alkermes 10-K was *catalogued* or *indexed* in a way that might establish public accessibility." *Id.* at 49. Patent Owner also contends that, even if the Alkermes 10-K was catalogued or indexed, Petitioner presents no evidence that an ordinarily skilled artisan "would have looked for the Alkermes 10-K or even known that it existed, let alone known how to access it." *Id.* at 50. Finally, Patent Owner contends that Petitioner "fails to authenticate the printouts" upon which it relies to show the filing date of Alkermes 10-K and past SEC protocol about EDGAR with testimony from a declarant. *Id.* We agree with Patent Owner's arguments.

Even ignoring the potential admissibility concerns with Exhibits 1058, 1059, and 1060, we also agree with Patent Owner that Petitioner's evidence does not demonstrate that an ordinarily skilled artisan—interested in preparing long-acting naltrexone formulations for the purpose of treating patients in need of naltrexone and exercising reasonable diligence—would have known to locate Alkermes 10-K. *See Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, slip. op. 21 (PTAB Oct. 6, 2017) (Paper 12) (determining that 10-K document did not qualify as a printed publication in part because "Petitioner has not explained that interested persons would have looked for the IDEC 10-K/A to gain information relating to [the at-issue] subject matter, would have known that the IDEC 10-K/A existed, or upon looking, would have been able to access the IDEC 10-K/A on [the relevant date], exercising reasonable diligence.").

2. *Reason to Combine*

Even if we considered Alkermes 10-K, we would find that Petitioner has not shown sufficiently for institution that an ordinarily skilled artisan would have been motivated to combine the teachings of that document with Vivitrex Specimen, Rubio, and/or Wright. First, Petitioner's arguments attempting a connection between Alkerman 10-K and Vivitrex Specimen based on a "™" symbol seems to us both haphazard and tenuous. Second, we view Dr. Park's testimony on this issue conclusory and unsupported by evidence. *See, e.g.*, Ex. 1030 ¶ 129 (stating that, after reviewing Alkermes 10-K, "a next step a POSA would take is to determine what type of trademark was pending, what useful information was provided about the covered product, and if it was approved"). Dr. Park states that he "understand[s] from counsel that USPTO records are public and that the trademark specimen for Vivitrex is part of the prior art." *Id.* ¶ 130. To us, this statement appears to undermine Dr. Park's assertion that an ordinarily skilled artisan would have taken, as a "next step," a search of the USPTO's trademark files. *Id.* ¶ 29.

3. *Summary*

Notwithstanding the above, we institute *inter partes* review of all challenged claims (1–13) for obviousness over Alkermes 10-K, Vivitrex Specimen, Rubio, and Wright in light of *SAS* and the USPTO Guidance.

H. Secondary Considerations

Patent Owner presents evidence and argument relating the secondary considerations of (1) unexpected results, (2) long-felt but unsolved need, (3) industry skepticism, and (4) commercial success. *See* Prelim. Resp. 55–61. Evidence of secondary considerations "must always when present be

considered en route to a determination of obviousness." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quotation omitted). But "secondary considerations are not an element of a claim of anticipation." *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008). In this case, we have instituted trial based on anticipation, and thus we also institute on all obviousness grounds raised in the petition in accordance with *SAS* and USPTO Guidance. We determine that it is appropriate under these circumstances to defer review of Patent Owner's evidence and arguments about secondary considerations, given that we may not deny institution of any obviousness grounds. Any final decision on obviousness *vel non* will be based on the full record developed during the trial.

I. Discretion Under 35 U.S.C. § 325(d)

Finally, Patent Owner asserts that we should exercise our discretion to deny institution under 35 U.S.C. § 325(d) "because the same or substantially the same prior art or arguments previously were presented to the Office." Pet. 61–62 (quoting 35 U.S.C. § 325(d)).

In evaluating whether to exercise our discretion under Section 325(d), we weigh the following non-exclusive factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner

has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, slip op. at 17–18 (Paper 8, Dec. 15, 2017) (informative).

Patent Owner does not analyze these factors, but instead asserts summarily that Comer, Kranzler, and Wright were "of record during prosecution," and that "the claims were allowed over the references." Prelim. Resp. 62. We are not persuaded that the factors weigh in favor of exercising our discretion under 35 U.S.C. § 325(d). Although Comer is listed on the face of the '499 patent, we have no evidence about the extent to which the Examiner evaluated Comer during examination. Moreover, although Kranzler and Wright are cited in the background portion of the '499 patent's written description, Patent Owner does not point us to where in the prosecution history the Examiner actually considered these references. For these reasons, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one claim of the '499 patent is unpatentable. Thus, in accordance with USPTO Guidance and *SAS*, we institute an *inter partes* review of all of the challenged claims on all grounds set forth in the Petition. Our determinations at this stage of the proceeding are based on the evidentiary record currently before us. This decision to institute trial is not a final

decision as to patentability of any claim for which *inter partes* review has been instituted. Any final decision will be based on the full record developed during trial.

V. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–13 of U.S. Patent No. 7,919,499 B2 is instituted with respect to all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the ’499 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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