2019 WL 101791 (Patent Tr. & App. Bd.)
Only the Westlaw citation is currently available.

INSYS DEVELOPMENT COMPANY, INC., Petitioner,
v.
GW PHARMA LIMITED and Otsuka Pharmaceutical Co., Ltd., Patent Owner.

Patent Trial and Appeal Board.
Case IPR2017-00503
Patent 9,066,920 B2
Entered: January 3, 2019

Attorneys and Law Firms

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FOR PATENT OWNER: Dorothy P. Whelan, Michael Kane, Martina Hufnal, FISH & RICHARDSON P.C., whelan@fr.com, kane@fr.com, hufnal@fr.com

Before ERICA A. FRANKLIN, SUSAN L. C. MITCHELL, and ZHENYU YANG, Administrative Patent Judges.

FINAL WRITTEN DECISION

***Inter Partes* Review**

35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

MITCHELL, Administrative Patent Judge.

I. INTRODUCTION

***1** This is a final written decision in *inter partes* review of claims 1–13 of U.S. Patent No. 9,066,920 B2 (Ex. 1001, "the '920 patent") entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1 and 2 of the '920 patent are unpatentable under 35 U.S.C. § 103(a). *See* 35 U.S.C. § 316(e).

A. Procedural History

Petitioner Insys Development Company, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") req an *inter partes* review of claims 1–13 (the "challenged claims") of the '920 Patent. *See* 35 U.S.C. §§ 311–319. Petitioner relied upon Declarations of Professors Marson and Benet. *See* Exs. 1002, 1003, respectively; *see* Pet. 2–64. Patent Owner GW Pharma Limited and Otsuka Pharmaceutical Co., Ltd. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp.").

Pursuant to 35 U.S.C. § 314(a), on July 7, 2017, we instituted an *inter partes* review of challenged claims 1–13 as obvious under 35 U.S.C. § 103(a) based on Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697, and also based on Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697. Paper 9, 24 ("Dec.").

Patent Owner filed its Patent Owner Response (Paper 17, "PO Resp.") along with a Declaration of H. Steve White, Ph.D., (Exhibit 2008) to support its positions. Petitioner filed a Reply (Paper 20, "Reply") to the Patent Owner Response.

An oral hearing was held on April 4, 2018. A transcript of the hearing is included in the record. Paper 35 ("Tr.").

On May 2, 2018, in response to *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018), we modified our institution decision "to include review of all grounds presented in the Petition that each address all challenged claims." Paper 26, 2. We also invited the parties to "confer to determine whether they desire[d] any additional briefing, and, if so, [to] request a conference call with the panel to seek authorization for such briefing ...." *Id.* The parties responded by e-mail on May 8, 2018, that

> Petitioner seeks limited additional briefing (no more than 10 pages) and the opportunity to introduce new evidence only with respect to publication date of Jones. Patent Owner does not seek any additional briefing. However, in the event that the Board grants Petitioner's request, both parties request that the order be limited to briefing and no new oral hearing. Patent Owner also requests that the Board prohibit submission of any additional evidence.

Ex. 3001.

We authorized the parties to file additional briefing on the newly added ground of obviousness over Jones, Cunha, Lowenstein, and WO 2009/007697, and also authorized the Petitioner to file a motion to submit supplemental information, pursuant to 37 C.F.R. § 42.123(b), limited to evidence with respect to the publication date of Jones. *See* Paper 27.

On May 29, 2018, Petitioner filed a Motion for Submission of Supplemental Information under 37 C.F.R. § 42.123(b) (Paper 28), which Patent Owner opposed (Paper 30). For the reasons set forth below, we deny Petitioner's motion as moot. *See infra* Section II.F. Petitioner also filed its supplemental brief concerning the added ground of obviousness over Jones, Cunha, Lowenstein, and WO 2009/007697. Paper 29. Patent Owner filed a response to Petitioner's briefing (Paper 31), and Petitioner filed a reply (Paper 32).

B. Related Proceedings

***2** Both parties indicate that the '920 Patent is not involved in any co-pending litigation, and neither party identifies any other related proceeding. Pet. 4; Paper 4, 2.

C. The '920 Patent (Ex. 1001)

The '920 Patent involves the use of cannabinoids in the treatment of epilepsy, and more particularly, generalized or partial seizures. Ex. 1001, Abst. One embodiment identifies the phytocannabinoid as cannabidiol or CBD. *Id.*

One objective stated in the '920 Patent is "to determine dose ranges which are likely to prove effective" in treating seizure associated with epilepsy. *Id.* at 3:33–34. The '920 Patent identifies the following dose ranges for CBD: "The CBD is preferably present in an amount which will provide a daily dose of at least 400 mg, more preferably at least 600 mg and as much as 800 mg or more, but preferably less than 1200 mg." *Id.* at 3:54–57.

D. Illustrative Claims

Of the challenged claims, claim 1 is the sole independent claim of the '920 Patent. The remaining challenged claims 2–13 depend directly or indirectly from claim 1. Claim 1 is illustrative of the challenged claims and recites:

1. A method for treating partial seizure comprising administering cannabidiol (CBD), to a patient wherein the CBD is present in an amount which provides a daily dose of at least 400 mg.

Ex. 1001, 15:5–8.

E. The Instituted Grounds of Unpatentability

We instituted the instant trial based on the following grounds of unpatentability. Dec. 24; Paper 26, 2.

References	Basis	Claims Challenged
Cunha, [1] Bhattacharyya, [2] Ames, [3] Lowenstein, [4] and WO 2009/007697 [5]	§ 103(a)	1–13
Cunha, Pertwee, [6] Malfait, [7] Lindamood, [8] Mechoulam, [9] Zuardi, [10] and WO 2009/007697	§ 103(a)	1–13
Jones, [11] Cunha, Lowenstein, and WO 2009/007697	§ 103(a)	1–13

1 Jomar M. Cunha et al., *Chronic Administration of Cannabidiol to Healthy Volunteers and Epileptic Patients*, 21 PHARMACOLOGY 175–185 (1980) (Ex. 1004, "Cunha").

2 Sagnik Bhattacharyya et al., *Modulation of Mediotemporal and Ventrostriatal Function in Humans by #9-Tetrahydrocannabinol*," 66 ARCH GEN. PSYCHIATRY 442–451 (April 2009) (Ex. 1012, "Bhattacharyya").

3 Ames et al., *Anticonvulsant Effect of Cannabidiol*, 69 SOUTH AFRICAN MED. J. 14 (Jan. 4, 1986) (Ex. 1011, "Ames").

4 Daniel H. Lowenstein, *Seizures and Epilepsy*, in HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 2498–2512 (A.S. Fauci et al., eds., McGraw-Hill 2008) (Ex. 1019, "Lowenstein").

5 Geoffrey Guy et al., WO 2009/007697 A1, published Jan. 15, 2009 (Ex. 1020, "WO 2009/007697").

6 Roger G. Pertwee, *The Pharmacology and Therapeutic Potential of Cannabidiol,* in CANNABINOIDS 32–83 (Vincenzo Di Marzo, ed., Springer Science & Bus. Media 2004). (Ex. 1022, "Pertwee").

7 A. M. Malfait et al., *The Nonpsychoactive Cannabis Constituent Cannabidiol is an Oral Anti-Arthritic Therapeutic in Murine Collagen-induced Arthritis*, 97 PROC. NAT'L ACAD. SCI. 9561–9566 (2000) (Ex. 1023, "Malfait").

8 Charles Lindamood III and Brenda K. Colasanti, *Effect of of #^{9}-Tetrahydrocannabinol and Cannabidiol on Sodium-Dependent High Affinity Choline Uptake in the Rat Hippocampus*, 213 J. PHARM. EXPERIMENTAL THERAPEUTICS 216–221 (1980) (Ex. 1024, "Lindamood").

9 Raphael Mechoulam et al., *Cannabidiol: An Overview of Some Pharmacological Aspects*, 42 J. CLIN. PHARM. 11S-19S (2002) (Ex. 1021, "Mechoulam").

10 Antonio Waldo Zuardi, *Cannabidiol: From an Inactive Cannabinoid to a Drug with Wide Spectrum of Action*, 30 REV. BRAS. PSIQUIATR. 271–280 (2008) (Ex. 1025, "Zuardi").

11 Nicholas A. Jones et al., *Cannabidiol Displays Antiepileptiform and Antiseizure Properties in Vitro and in Vivo*, 332 J. PHARM. EXPERIMENTAL THERAPEUTICS 569–577 (2010) (Ex. 1018, "Jones").

II. ANALYSIS

A. Claim Interpretation

***3** In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b) [12]; *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). "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). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In the absence of such a definition, limitations are not to be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993). Only terms in controversy must be construed and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

12 The Final Rule changing the claim construction standard to the federal court claim construction standard that is used to construe a claim in a civil action under 35 U.S.C. § 282(b) does not apply here, as the Petition was filed before the effective date of the Final Rule, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,344 (Oct. 11, 2018).

1. *"Partial Seizure"*

Petitioner asserts that the broadest reasonable interpretation of "partial seizure" is "a seizure which originated in a specific brain region, which can be simple or complex, and which may remain localized or become secondarily generalized, i.e. become a secondary generalized seizure." Pet. 18. Petitioner asserts that this construction is in accordance with the 1981 International League Against Epilepsy ("ILAE") classification. *Id.*

Dr. Marson, Petitioner's declarant, explains that as of July 2009, the 1981 ILAE classification was widely referred to in medical textbooks, and widely used in clinical practice and scientific literature. Ex. 1002 ¶¶ 16–17; Pet. 8. Petitioner notes that the '920 Patent relied on the ILAE in categorizing general and partial seizures. Pet. 9 (citing Ex. 1001, 2:32–53).

Petitioner offers that the key distinction between partial and generalized seizures is "that even though partial seizures may evolve into secondary generalized seizures, *such seizures are still classified as partial seizures*." Pet. 11. Petitioner asserts that although the '920 Patent relies on the 1981 ILAE, it does not follow the ILAE's classification when distinguishing between partial and generalized seizures because it does not recognize that a partial seizure remains classified as partial even when it evolves into a generalized seizure, and attributes this incorrect understanding to the ILAE. Pet. 19–22.

The '920 Patent states with emphasis on the allegedly incorrect statements:

> Neuronal activity is a prerequisite for proper brain function. However, disturbing the excitatory-inhibitory equilibrium of neuronal activity may induce epileptic seizures. These epileptic seizures can be grouped into two basic categories: partial and generalized seizures. Partial seizures originate in specific brain regions and remain localized—most commonly the temporal lobes (containing the hippocampus), whereas *generalized seizures* appear in the entire forebrain *as a secondary generalization of a partial seizure. This concept of partial and generalized seizure classification did not become common practice until the International League Against Epilepsy published a classification scheme of epileptic seizures in 1969*.
>
> ***4** The International League Against Epilepsy further classified partial seizures, separating them into simple and complex, depending on the presence or the impairment of a consciousness state.

Ex. 1001, 2:31–50 (citations omitted) (emphasis added).

In its Preliminary Response, Patent Owner countered that it is unnecessary to construe the term "partial seizures" to determine whether an *inter partes* review should be instituted. Prelim. Resp. 14–15. Patent Owner asserts that even under Petitioner's construction of "partial seizure" to include secondary generalized seizures, "Petitioner fails to meet its burden to show that a person of ordinary skill would have been motivated to increase the dosage of CBD administered by Cunha and would have reasonably expected that higher dosage to treat partial seizures." *Id.* at 14.

In our Decision on Institution, we determined that we did not need to construe expressly the term "partial seizure" to resolve whether an *inter partes* review should be instituted because Patent Owner did not attack the application of Petitioner's asserted prior art based on Petitioner's asserted allegedly flawed distinction that the '920 Patent makes between partial and general seizures. Dec. 7–8. In its Response, Patent Owner again reiterates its position that we need not construe the term "partial seizure."

Patent Owner states:

> Petitioner proposes construing "partial seizures" to include secondary generalized seizures. Petition, p. 18. However, even under its preferred construction of the term "partial seizures," Petitioner fails to meet its burden to show that a person of ordinary skill would have been motivated to increase the dosage of CBD administered by Cunha (EX. 1004) and would have reasonably expected that the higher dosage would successfully treat partial seizures. Accordingly, it is not necessary to construe the term "partial seizures" to find that claims 1–13 are not unpatentable.

PO Resp. 19.

Consistent with its position in the Preliminary Response, Patent Owner does not rely on a distinction between generalized and partial seizures in its Response to assert that the art does not render the claims unpatentable because the art addresses only generalized seizures. *See, e.g.,* PO Resp. 7 (stating "[a]t most, Cunha suggested the possibility that CBD could treat seizures and recommended further study. At this point, much remained uncertain and unknown regarding CBD's efficacy against partial seizures. Ex. 2008 (White), ¶ 46."), 10 (attacking application of Ames, like Cunha, as an "invitation to experiment"); Tr. 38:2–4 (stating Patent Owner does not contest that "partial seizures includes secondary generalized seizures, which are focal seizures that then evolve into generalized seizures"), 38:5–7 (Patent Owner agreeing that Cunha treated patients with partial seizures). Therefore, because Patent Owner does not dispute that the asserted art applies to the treatment of partial seizures, and based on our review of the record as a whole, we do not find it necessary to construe expressly the term "partial seizure" to resolve the patentability of the challenged claims. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.' ") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Principles of Law

***5** A patent claim is unpatentable under 35 U.S.C. § 103(a) 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 the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *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). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see Translogic*, 504 F.3d at 1259. In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.' " *In re Kubin*, 561 F.3d 1351, 1359−60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

C. Level of Ordinary Skill

Petitioner states that a skilled artisan at the time of the invention is a person who has an "M.D. or a Ph.D. in pharmacology, chemistry, biochemistry, neurology, or in a related field in the biological or chemical sciences. A POSITA would also be familiar with the 1981 International League Against Epilepsy (ILAE) classification of seizures and be up-to-date on the developments in the field of treatment of seizures." Pet. 5–6; *see* Ex. 1002 ¶ 9; Ex. 1003 ¶ 9. Before institution, Patent Owner did not challenge Petitioner's definition or offer its own definition for a person of ordinary skill in the art ("POSITA"). *See generally* Prelim. Resp. For purposes of the institution decision, we applied Petitioner's stated level of ordinary skill in the art, which is supported by the declarations of Drs. Marson and Benet, because of the sophistication of the technology and the educational level of those who work in this area. *See In re GPAC*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

In its Response, Patent Owner questions the qualification of Dr. Benet to opine on the patentability of the challenged claims and offers its own definition of POSITA, supported by Dr. White's testimony. Patent Owner states that a POSITA for evaluating the obviousness of the challenged claims is one who

> would be familiar with both AED's [anti-epilepsy drugs] and with preclinical animal models of epilepsy for early drug discovery. EX. 2008 (White), ¶ 18. Such a person would have a Ph.D. or M.D. or equivalent in pharmacology, neurology, or a related biological discipline and five or more years of experience in epilepsy basics and clinical science or a Bachelors or Master's degree with at least 10 years of relevant experience in epilepsy research. *Id.* A person of ordinary skill in the art would also have some familiarity with the use of antiseizure drugs for the treatment of epilepsy. *Id.*

***6** PO Resp. 22–23; *see* Ex. 2008 ¶ 18.

Patent Owner asserts that although Dr. Benet has studied the toxicity of AEDs, he has not evaluated their efficacy, and, as a pharmacologist, he has no expertise in either treating epilepsy or using animal models to screen AEDs. PO Resp. 23 (citing Ex. 2010, 10:8–10).

We do not agree that a POSITA must possess the stringent qualifications involving years of specific work in epilepsy research set forth by Patent Owner. We continue to hold the view that the sophistication of the technology and the

educational level of those who work in the area involving the treatment of epilepsy support Petitioner's definition of a POSITA for purposes of evaluating the patentability of the claims of the '920 patent, especially in light of the fact that the claims require no particular level of efficacy. *See* Ex. 1001, 1:20–3:38 (discussing prior studies investigating the anti-epilepsy potential of CBD); Tr. 29:11–20, 33:2–34:7 (counsel for Patent Owner stating treating means better than placebo); *see Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (ordinary skill in the art is reflected by the prior art of record); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

Petitioner's definition of a POSITA does require that person to be "up-to-date on the developments in the field of the treatment of seizures," which we find to be an appropriate level of knowledge to analyze the patentability of the challenged claims. *See* Ex. 1034, 12:14–15:4 (Dr. White stating that a POSITA would have knowledge of the basic and clinical signs of epilepsy, and some familiarity with the use of the antiseizure drugs for the treatment of epilepsy); Ex. 2008 ¶ 18.

We conclude that a POSITA is a person with an M.D. or a Ph.D. in pharmacology, chemistry, biochemistry, neurology, or in a related field in the biological or chemical sciences, is familiar with the 1981 International League Against Epilepsy (ILAE) classification of seizures, and is up-to-date on the developments in the field of treatment of seizures. We also find that Drs. Marson, Benet, and White meet the criteria as a POSITA. *See* Ex. 1002 ¶¶ 3–9, Appendix A (curriculum vitae of Dr. Marson); Ex. 1003 ¶¶ 3–10, Appendix (curriculum vitae of Dr. Benet); Ex. 2008 ¶¶ 2–15, Ex. 1 (curriculum vitae of Dr. White); Tr. 21:21–25 (counsel for Patent Owner stating a POSITA "has to be a person with some familiarity with epilepsy and the use of antiepileptic drugs. And Dr. White fits that description and so does Dr. Marson, Petitioner's expert"). *See also* Notice of Update to Office Patent Trial Practice Guide, 83 Fed. Reg. 156, (Aug. 13, 2018) (text of update available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf) (stating an expert does not need to be a person of ordinary skill in the art, but must be qualified in the pertinent art).

D. Obviousness over Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009l007697

Petitioner contends that claims 1–13 are unpatentable under 35 U.S.C. § 103 as obvious over Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697. Pet. 34–50. Petitioner asserts that claims 1–13 would have been obvious because Cunha teaches treatment of epilepsy with CBD and one of ordinary skill in the art would have concluded that the claimed daily dosage of at least 400 mg of CBD is predictable, safe, and expected in view of Cunha, Bhattacharyya, and Ames. *Id.* As support, Petitioner provides an explanation as to how claim limitations are met by the references and a rationale for combining the references as well as supporting Declarations of Dr. Marson (Ex. 1002) and Dr. Benet (Ex. 1003). Pet. 35–64.

***7** Patent Owner counters that "CBD was, at best, a promising candidate for further study. That is all it was. A person of ordinary skill simply had no reasonable expectation that CBD would treat partial seizures at all, let alone at doses of 400 mg or higher, as the '920 patent claims." PO Resp. 3.

We have reviewed the complete record before us, including the parties' explanations and supporting evidence presented during this trial. We determine that given the evidence on this record, Petitioner has shown by a preponderance of the evidence that claims 1 and 2 of the '920 patent are obvious over the following combinations: (1) Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697; and (2) Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697. [13]

13 Petitioner offers Lowenstein (Ex. 1019) for its distinction between partial and generalized seizures, "as there may be substantial differences in the evaluation and treatment of partial versus generalized seizure disorders," Pet. 12, 22, 38, and its teaching of an overlap between drugs used to treat partial and generalized seizures, Pet. 46. Petitioner offers WO 2009/007697 for teaching that CBD and tetrahydrocannabivarin (THCV) may be coadministered for the treatment of epilepsy. Pet. 50. Patent Owner asserts that Bhattacharyya, Lowenstein, and WO 2009/007697 "add nothing to Cunha and Ames." PO Resp. 27, 28–

> 29 (stating that the two purposes for which Petitioner cites Lowenstein relating to the distinction between generalized and partial seizures and their treatment is irrelevant), 29 (stating that WO '697 is only cited to show that CBD could be combined with THCV, a feature only in dependent claims 3–5 and 10–13, but does not address treatment of partial seizures with at least 400 mg of CBD).

1. *Cunha (Ex. 1004)*

Cunha described studies involving the effect of chronic administration of CBD to epileptic patients. Ex. 1004, Abst. Cunha carried out a two phase study. *Id.* at 3. "In phase 1, 3-6 mg/kg of CBD roughly corresponding to 200-400 mg/subject was administered daily to healthy human volunteers for 30 days. In phase 2, patients suffering from secondary generalized epilepsy with temporal irritative activity received 200-300 mg of the drug for periods of up to 4.5 months." *Id.* at 3.

In describing the results of the phase 1 study, Cunha observed that no patient reported any symptoms of psychotropic effect of CBD during the study, and concluded as follows:

> [T]he present experiment shows that 3 mg/kg/day of CBD administered for 30 days (1 volunteer received 6 mg/kg/day during the last 3 days of experiment) did not induce any psychic or other side effects and was well tolerated by the 8 subjects. Thus CBD does not appear to have any toxic effect in humans when administered at the above dosage over a long period. This confirms our previous data obtained in animal.
>
> In our opinion these findings justified the trial of the drug in epileptic patients.

Id. at 4. The average weight of the patients was 65 kg, *id.* at 3, resulting in a daily dose of approximately 195 mg daily dose for the majority of the patients, with one patient receiving approximately 390 mg on the last three days of the phase 1 study.

In Cunha's phase 2 study, 15 patients with a history of frequent convulsions lasting for at least one year and diagnosed with secondary generalized epilepsy were selected with eight of those patients ultimately receiving CBD during the study. *Id.* at 4. During the study, each patient received, in a double-blind procedure, 200–300 mg of CBD or placebo. *Id.* at 4, Abst. Throughout the experiment, the patients continued to take the AEDs they were prescribed before the experiment, although these AEDs were no longer controlling the signs of epilepsy in these patients. *Id.* at Abst. As in phase 1, none of the patients exhibited any behavioral alterations suggestive of any psychotropic effect. *Id.* Cunha concluded that "[o]f the 8 patients receiving CBD, 4 showed considerable improvement in their clinical condition (median 0)." *Id.* at 8. Of the remaining patients, only 1 showed no improvement at all despite increasing CBD to 300 mg daily for the last two weeks of treatment. *Id.*

***8** Cunha drew the following conclusions from the studies:

> The mechanism by which CBD benefitted our epileptic patients is not known. All 8 patients were also receiving known antiepileptic drugs which were by themselves, however, ineffective. One possibility is that CBD potentiated their action since enhancement by CBD of anticonvulsant activity of phenobarbital and phenytoin in animals has been demonstrated. In man, however, 50–500 µg/kg CBD given in cigarette form is not able to alter plasma concentrations of secobarbital. The possibility that CBD acts *per se* should also be taken into consideration, as shown by several reports describing its direct anticonvulsant effects in animals.
>
> In conclusion, we have found that CBD had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal focus, who did not benefit from known antiepileptic drugs. Further research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans.

Id. at 9.

2. *Bhattacharyya (Ex. 1012)*

Bhattacharyya sought to investigate the effects of #9-tetrahydrocannabinol (#9-THC) and cannabidiol on regional brain function during verbal paired associate learning. Ex. 1012, 1. Bhattacharyya performed three imaging sessions on each patient, each session preceded by ingestion of 10 mg of #9-THC, 600 mg of cannabidiol, or placebo. *Id.* Bhattacharyya states that in contrast to results from tests of patients ingesting #9-THC,

> [f]ollowing administration of cannabidiol, no significant change was noted in psychotic symptoms (PANSS positive syndrome subscale), anxiety (State-Trait Anxiety Inventory state subscale), sedation (Visual Analog Mood Scale mental sedation subscale), or intoxication (Analog Intoxication Scale), nor in PANSS total score, negative syndrome subscale score, or general psychopathology subscale score compared with placebo....

Id. at 4. Therefore, Bhattacharyya concluded that cannabidiol does not affect learning and memory. *Id.* at 7.

3. *Ames (Ex. 1011)*

Ames sought to study the possible anticonvulsant effect of CBD. Ex. 1011, 1. The Ames study involved twelve patients who had mental retardation and frequent seizures that were uncontrolled on conventional anticonvulsant therapy. *Id.* Of the patients receiving CBD instead of placebo, each received three capsules containing 100 mg CBD per day for the first week and 2 capsules containing 100 mg CBD for the next three weeks. *Id.* Ames states that "[t]here was found to be no statistically significant difference in seizure frequency between the two groups." *Id.*

Ames planned to continue the study and "decided to increase the dose of CBD because its lack of efficacy might have been due to the fact that the patients were all brain-damaged and severely epileptic." *Id.* Ames, however, was unable to continue the study due to lack of supply of CBD. *Id.*

4. *Analysis*

Petitioner asserts that Cunha teaches the use of CBD to treat partial seizures. Pet. 35–39. Petitioner concludes that "[a]ccordingly, the only difference between the disclosure of Cunha *et al* and the method recited in claim 1 of the '920 Patent is the recited daily dosage of at least 400 mg." *Id.* at 39.

***9** Petitioner posits that finding the claimed range is nothing more than optimization of the range taught in Cunha. Pet. 39. For instance, Petitioner points out that Cunha teaches that the dosages in the disclosed phase 1 and phase 2 studies were "well tolerated and no toxicity or serious side effects were observed." *Id.* at 40. The upper range disclosed for the phase 1 study of Cunha, 400 mg of CBD, also falls within the range disclosed in Cunha. *Id.* at 41. Petitioner asserts that Bhattacharyya teaches that CBD is extremely well tolerated in humans when dosed at 600 mg, and that Ames suggests increasing the daily amount of CBD from 200–300 mg to treat seizures. *Id.* at 41–42.

Petitioner concludes:

> Therefore, a PHOSITA familiar with the disclosures of Cunha *et al*, Bhattacharyya *et al*, and Ames *et al*, would have understood that CBD administered at 200-300 mg per day was generally effective, although in some patients the improvement was partial. As Professor Marson states, a PHOSITA would have understood that there was a reasonable likelihood that CBD administered at 200-300 mg per day might have efficacy as a treatment for partial seizures, and would have also believed that the amount of CBD administered to a patient could be safely increased to arrive at the optimal dosage. (Exhibit 1002 ¶ 64).

> Accordingly, it would have been obvious for a PHOSITA to optimize the daily dosages of CBD by increasing them to at least 400 mg per day in order to increase the effectiveness of the drug. Thus, to arrive at the daily dosage of at least 400 mg of CBD for the treatment of partial seizures was well within a skill in the art and obvious.

Id. at 42–43.

Patent Owner asserts that Cunha was an early stage study involving a limited set of patients, and as such, it at most "suggested the possibility that CBD could treat seizures and recommended further study." PO Resp. 7, 21, 24. Patent Owner concludes, relying on the testimony of Dr. White, that "[a]t this point, much remained uncertain and unknown regarding CBD's efficacy against partial seizures." *Id.* at 7 (citing Ex. 2008 ¶ 46).

Patent Owner asserts that "[a]t most, the prior art provided an invitation to experiment with CBD to see if it could treat partial seizures. It provided no reasonable expectation that the experiment would be successful, let alone the appropriate dose levels." PO Resp. 22. For instance, Patent Owner asserts that both Drs. White and Marson agree that it was not certain whether CBD's observed efficacy was the result of CBD itself or its ability to enhance the other AEDs that the patients in Cunha's study were taking. PO Resp. 24 (citing Ex. 1004, 9; Ex. 2008 ¶¶ 39–40; Ex. 2009, 42:14–44:2; Ex. 1022, 24–25; Ex. 1025, 2).

Patent Owner asserts that Ames also is no more than an invitation to experiment and would not provide a reasonable expectation for one of skill in the art that increasing the dosage set forth in Cunha would work at all. PO Resp. 10. Patent Owner states that

> Ames, like Cunha, was a limited study and focused on a unique subset of severely disabled patients. Ames' administration of 200-300 mg of CBD per day to these patients failed. The reason for the failure is unknown. It could have been due to the small sample size, the class of patients, CBD itself, or all of the above.

Id. Patent Owner notes that "[a]ccording to Dr. White, a person of ordinary skill reading Ames' results would conclude that CBD was not effective at treating these patients." *Id.* at 8 (citing Ex. 2008 ¶ 44).

Patent Owner concludes that

> Ames, like Cunha, was no more than an invitation to experiment in a field where very little was known about CBD or its ability to treat seizures of any type at any dose. To say that a person of ordinary skill would have optimized Cunha's dosage by increasing it to at least 400 mg/day based on Ames is pure speculation.

***10** PO Resp. 26.

Petitioner responds that a POSITA reasonably would have expected that the claimed dose of CBD could treat partial seizures because

> 1) the human data in Cunha indicating the 300 mg total daily dose successfully treated partial seizures; 2) 400 mg dose was successfully administered to healthy patients as part of the safety study conducted and reported in Cunha; 3) Cunha encouraged further studying antiepileptic effects of CBD; 4) Ames suggested increasing the total daily dose of CBD from 300 mg in patients suffering from seizures; 5) it was standard pharmacological practice to increase the drug dosage until seizures

> are controlled or as limited by toxicity; 6) CBD of up to at least 600 or 1500 mg total daily dose was shown to be totally safe in humans; and 7) there was no evidence of any teaching away or unexpected results.

Reply 17.

Petitioner further counters Patent Owner's arguments by asserting that the claims for "a method of treating partial seizure" do not require a particular level of efficacy; CBD's mechanism of action is irrelevant to whether administration of CBD in the claimed dosage meets the claim requirements; and whether CBD treats partial seizures by its action alone or in concert with AEDs is irrelevant as the claims do not exclude other AEDs administered in conjunction with CBD. Reply 5–6, 12–17.

On the record before us, we find that Petitioner has shown by a preponderance of the evidence that claims 1 and 2 [14] would have been obvious over Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697. We agree with Petitioner's analysis of the art as described above and why one of skill in the art would have had a reason to increase the dose of CBD to at least 400 mg per day to treat partial seizures and would have had a reasonable success in doing so. *See* Pet. 42–43. We make this determination based on the studies, including Cunha, which show that doses in the claimed range are safe, a POSITA would increase the dosage of CBD to achieve an optimal dose to treat partial seizures as expressly encouraged by Ames, and would have had a reasonable expectation of succeeding based on the explicit informed suggestion by Ames and Cunha and the evidence of a conventional dose curve for CBD treating partial seizures. *See* Ex. 1004, 183 ("Further research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans."); Ex. 1011 (explicit informed opinion that increasing the dose of CBD may be efficacious). We also agree with and credit the testimony of Dr. Marson, a clinician who treats epileptic patients and who has experience assessing interventions and outcomes in epilepsy. Ex. 2009, 8:11–11:10; Ex. 1002 ¶¶ 3–7.

14 Claim 2 requires CBD to be present in an amount which provides a daily dose of from 400 to 800 mg. Ex. 1001, 15:9–10.

Dr. Marson reviewed the teachings of the asserted references and testifies that

> Based on my expert opinion of the state of the art as it existed as of June 29, 2010, I believe that there was a reasonable likelihood that CBD would be an effective treatment for partial seizures at a daily dosage of at least 400 mg.
>
> ***11** As of June 29, 2010, CBD was proposed as a treatment for epileptic seizures, as the '920 patent itself admits. By that time, CBD was also proposed as a treatment for "partial seizures", including secondary generalized seizures. This is evidenced at least by Cunha et al (**Exhibits 1004**), Ames et al (**Exhibit 1011**), and Lowenstein (**Exhibit 1019**). The only feature of the independent claim 1 of the '920 patent that is not explicitly disclosed in these references is administering at least 400 mg per day of CBD for the treatment of partial seizures. However, in my expert opinion, there was evidence to support safety in humans of CBD doses of up to 600 mg per day and it was well within a skill in the art to optimize a treatment dosage, via further empirical research.

Ex. 1002 ¶¶ 47–48. Dr. Marson further notes that Cunha teaches four patients administered CBD were classified as having considerable improvement signaling "that CBD may have a beneficial therapeutic effect that would warrant further investigation. Thus, a POSITA would conclude that further clinical trials of CBD are warranted." *Id.* ¶ 56; Ex. 2009, 43:8–15 (Dr. Marson stating that "a person familiar with the art would observe that a number of patients had quite a substantial improvement in their seizure control such that CBD might be an effective treatment for epilepsy.").

Dr. Marson concludes that

> [A] PHOSITA familiar with the disclosures of Cunha et al, Bhattacharyya et al, Ames et al and Lowenstein would have understood that there was a reasonable likelihood that CBD administered at 200-300 mg per day would have efficacy as a treatment for partial seizures. The PHOSITA would have also believed that the amount of CBD administered to a patient could be safely increased, within the context of a clinical trial, to arrive at the optimal dosage for at least the following reasons: 1) CBD had been shown to be well tolerated in humans without any serious side effects or toxicities at doses up to 600 mg (as shown by Bhattacharyya et al); and 2) others skilled in the art (such as Ames *et al*) explicitly suggested increasing the dosage.

Ex. 1002 ¶ 64.

Patent Owner's attempts to discount the teachings of Cunha and Ames and discredit Dr. Marson's testimony are unpersuasive. Patent Owner asserts that "[a]s of July 2009, the real question was whether CBD would work at all to treat partial seizures," PO Resp. 2, and "[a] person of ordinary skill simply had no reasonable expectation that CBD would treat partial seizures at all, let alone at doses of 400 mg or higher, as the '920 patent claims," *id.* at 3. However, that argument is inconsistent with Cunha's express teaching gleaned from the results of treating epileptic patients who received 200–300 mg of CBD for up to 4.5 months, upon which Dr. Marson relies, that "CBD had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal focus, who did not benefit from known antiepileptic drugs. Further research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans." Ex. 1004, 9; *see* Ex. 1034, 25:4–11 (Dr. White agreeing Cunha reports an improvement with the administration of CBD), 27:7–12 (same).

Dr. White testifies that these statements in Cunha would not have suggested to a POSITA that CBD is "clinically effective" in treating epilepsy. Ex. 2008 ¶ 40. We agree with Petitioner, however, that the claims require no particular level of efficacy. *See* Ex. 1001, 15:5–8 (claims call for a method of *treating* partial seizure); Tr. 29:11–20, 33:2–34:7 (Patent Owner stating treating means achieving a result that is better than observed with a placebo). We also agree with Petitioner that it is clear from Dr. White's testimony that, when analyzing the teachings of Cunha, he is applying an inappropriate heightened standard for treatment of partial seizures with CBD. *See* Ex. 1034, 37:6–38:6 (stating in relation to Cunha as "an invitation to study" that you need "to design the right dose response study" and "have evidence that your drug is working"), 42:6–46:3 (correlating FDA approval with clinical efficacy), 26:17–28:4 (same); 37:6–18 (stating there has to be some "conclusive evidence that the drug is effective").

***12** Dr. White also seems to equate the lack of clinical effectiveness for CBD as taught by Cunha with the notion that it is unknown whether the improvement in the epileptic patients in Cunha who took CBD "is the result of CBD or the result of an interaction between CBD and the other drugs a patient was taking." *Id.* at 26:17–25, 21:14–25:2 (appearing to equate clinical effectiveness with an improvement that is "solely due to CBD"). The challenged claims use the transitional phrase "comprising" and thus do not exclude treating partial seizures with CBD in conjunction with other AEDs. *See Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."). Therefore, Dr. White's interpretation of Cunha as not teaching that the administration of 200–300 mg/day of CBD to epileptic patients was "clinically effective" because the mechanism of action of CBD is not known is misplaced. *See* Ex. 2009, 41:22–42:5 (Dr. Marson stating for known antiepileptic drugs that are work, the mechanism of action may not be known).

Dr. White also repeatedly states that he is not a clinician and has never treated patients, and cannot opine on whether, when treating a patient with an anti-epileptic drug, one would want to increase the dose as required to control a seizure, or as limited by toxicity or an adverse event. Ex. 1034, 8:5–11; 34:8–16:18. Dr. Marson is, however, such a clinician and does so opine. Ex. 2009, 44:4–7 (agreeing that goal of treatment is to use the lowest effective dose); *see also* Ex. 1033, 23

(stating to minimize dose-related adverse effects, therapy with many drugs is initiated at reduced dosage and increased as required for control of seizures or as limited by toxicity).

Patent Owner takes issue with Dr. Marson's reliance on Ames' explicit suggestion that doses above 300 mg of CBD for treating epileptic seizures should be tried because Ames' administration of 200–300 mg of CBD per day to patients failed, and Ames was merely speculating that increasing the dose might work. PO Resp. 7–10. Ames, however, was not making a suggestion to increase the dose of CBD in a vacuum. The Ames study specifically references the successful Cunha study and reasons that they should increase the dose of CBD "because its lack of efficacy might have been due to the fact that the patients were all brain-damaged and severely epileptic." Ex. 1011, 1. Because Ames could not procure more CBD, further study was abandoned, but Ames concludes that "[t]his is a great pity, because new anticonvulsants are needed and CBD appears to have no immediate side-effects except for mild drowsiness." *Id.*

A reasonable expectation of success does not mean an absolute certainty of success; it means a reasonable probability of success. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Any degree of unpredictability does not equate to patentability. *Id.* We agree with and credit Dr. Marson's testimony that a POSITA would have reasonably believed that the amount of CBD administered to a patient could be safely increased from Cunha's 200–300 mg daily dose, within the context of a clinical trial, to the claimed dosage of at least 400 mg/day because CBD had been shown to be well tolerated in humans without any serious side effects or toxicities at doses up to 600 mg as shown by Bhattacharyya and others skilled in the art, such as Ames. *See* Ex. 1002 ¶ 64. As Ames expressly suggests, it is logical to think that increasing a dose may increase the anticonvulsant effect. As Dr. Benet testifies, "Cunha actually suggests using higher doses of CBD. In the Cunha study, one patient was inadequately treated at 200 mg CBD daily, but when the dose was increased to 300 mg, it brought about complete control of partial seizures." Ex. 1003 ¶ 12.

Patent Owner attempts to inject uncertainty into whether a POSITA would have a reasonable expectation of success in controlling partial seizures by increasing a dosage of CBD. Patent Owner asserts that CBD's dose-response curve for treating partial seizures was unknown in July 2009, PO Resp. 10–17 (citing Ex. 2008 ¶¶ 50–53), taking issue with Dr. Benet's conclusion that "CBD was shown to have a conventional dose response curve where drug response increased with dose in a monophasic fashion." (Ex. 1003 ¶ 22).

***13** Dr. Benet relies on two references, Lindamood (Ex. 1024) and Wallace (Ex. 1027), that define dose response curves for CBD administration in rats to show that the CBD drug response to control convulsions increased with dose in a monophasic fashion. Ex. 1003 ¶¶ 18–23. Dr. Benet opines as follows:

> [T]he literature has clearly shown that, prior to the filing date of the '920 patent, CBD was shown to have a conventional dose response curve where drug response increased with dose in a monophasic fashion.
>
> Accordingly, the skilled person, familiar with the literature relating to CBD in seizures, would expect the response to CBD to increase when the dosage is increased from 300 mg daily to more than 400 mg daily. The skilled person would not expect CBD to have a bell-shaped dose response curve when used in doses acceptable to humans.

Id. at ¶¶ 22–23.

Dr. Benet also testifies that he expressly cited Lindamood and Wallace in his declaration as examples of a dose response curve for CBD for treatment of seizures. Ex. 2010, 27:2–21. Dr. Benet further explains that sixteen different studies that he did not expressly cite, as described in Pertwee (Ex. 1022), also show a sigmoidal response curve. *Id.* at 26:10–28:13. These additional studies further support Dr. Benet's testimony.

According to Dr. White, Dr. Benet cherry-picks these studies and ignores that CBD's in vivo dose-effect relationships can be bell shaped. Ex. 2008 ¶¶ 51–52. Dr. White, however, does not provide any study showing a dose response curve for CBD for the treatment of partial seizures that is bell-shaped. Instead, Dr. White points to bell-shaped dose-response

curves for CBD for indications other than the treatment of seizures. For instance, Dr. White relies upon statements in Pertwee concerning anxiolytic and antipsychotic effects of CBD that reports activity "sometimes with a bell-shaped dose response curve." Ex. 1022, 44, *cited in* Ex. 2008 ¶ 52.

Dr. White's reference to statements in Zuardi are no more specific to administration of CBD to treat partial seizures. *See* Ex. 2008 ¶ 52. In referencing CBD's "wide range of pharmacological effects," Zuardi states "[i]t is important to highlight that many effects of CBD draw a bell-shaped dose-response curve, suggesting that the dose is a pivotal factor in CBD research. The wide range of CBD effects can be explained by the multiple mechanisms through which CBD acts ..." Ex. 1025, 7. Finally, Dr. White points to Malfait showing that in a murine collagen-induced arthritis model CBD had a bell-shaped dose response curve, again not a partial seizure model. Ex. 2008 ¶ 52. Patent Owner would have us credit general statements about CBD action against various indications versus crediting studies specifically examining CBD action against seizures. This we decline to do, as neither Dr. White nor Patent Owner has identified support in the record as a whole for doing so.

We find on this record that Petitioner has shown sufficiently that a POSITA would have a reason to, and a reasonable expectation of success in, increasing the dosage of CBD to at least 400 mg/day to treat partial seizure. Therefore, we conclude that the combination of Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697 teach or suggest each and every element of claims 1 and 2, and that a POSITA would have had reason to combine the teachings of these references with a reasonable expectation of success in achieving the claimed invention.

***14** Concerning dependent claims 3–13, Petitioner states that these claims are obvious over the asserted combination "for at least the same reasons that independent claim 1 is obvious over these references." Pet. 49. Petitioner states that the additional limitations of claims 6 through 9 would be obvious to a POSITA "for all of the same reasons stated above." *Id.* As Patent Owner points out

> Petitioner fails to locate most of those added limitations in the prior art, let alone provide a reasoned explanation for [why] a skilled artisan would have selected those limitations while having a reasonable expectation of success. Petitioner also presents no expert testimony in support of its cursory argument that the dependent claims would have been obvious.

PO Resp. 35–36.

Petitioner offers WO '697 as teaching "that CBD and THCV should be combined for the treatment of various disorders, including epilepsy." Pet. 50 (citing Ex. 1020, Abst, 3:9–18). As Patent Owner states, however, "Petitioner presents no testimony from either of its experts as to [why] claims with these additional limitations would have been obvious" and "Petitioner offers no explanation for why a person of ordinary skill would interpret WO '697 as teaching that the combination of CBD and THCV could be used to treat ***partial seizures*** instead of some other form of epilepsy." PO Resp. 36, 37.

We agree with Patent Owner's assessment of the Petitioner's showing for dependent claims 3–13. *See* Pet. 49–50. In particular, we find that Petitioner has not shown sufficiently where each of the limitations of the dependent claims is taught or why a POSITA would have combined the teachings of the various references to arrive at the claimed invention with a reasonable expectation of success. Accordingly, Petitioner has failed to show that claims 3–13 would have been obvious over Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697, and thus has failed to show by a preponderance of the evidence that these claims are unpatentable over this combination.

E. Obviousness over Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697

Petitioner contends that claims 1–13 are unpatentable under 35 U.S.C. § 103 as obvious over Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697. Pet. 50–60. As in the previous ground, Petitioner here again points out that the only difference between the disclosure of Cunha and the method recited in claim 1 is the recited daily dosage of at least 400 mg. Pet. 54.

Petitioner also relies on Dr. Benet's testimony that CBD has a conventional sigmoidal dose response curve and that a POSITA reading Pertwee, Mechoulam, and Malfait together would realize that, based on these rat and mouse studies and the poor oral bioavailability of CBD in humans, a potential oral anticonvulsant dose of CBD in a 65 kg human subject lies between 144 mg and 2225 mg. Pet. 55–59 (citing Ex. 1003 ¶¶ 14, 17–35). Citing Lindamood and Wallace, [15] which describe Maximal Electroshock Seizure ("MES") studies in rats and mice, respectively, Petitioner asserts that these doses are in the middle of the range of the dose response curve for CBD, where response increases with dose. Pet. 58 (citing Ex. 1003 ¶ 35). Petitioner also points to Zuardi's teaching that up to 1500 mg/day of CBD may be administered without significant side effects. *Id.* at 59. Petitioner concludes that "[t]herefore, it would have been obvious for a PHOSITA to increase the oral dose of CBD from the disclosed 200-300 mg/day to over 400 mg/day for the treatment of partial seizures." *Id.*

15 Melisa J. Wallace et al., *Assessment of the Role of CB_1 Receptors in Cannabinoid Anticonvulsant Effects*, 428 EUROPEAN J. OF PHARM. 51–57 (2001).

***15** In addition to Cunha's alleged shortcomings asserted by Patent Owner discussed above, Patent Owner again asserts that a person of ordinary skill would not reasonably expect that increasing the dose of CBD would also increase its ability to treat partial seizures. Patent Owner again references Dr. White's conclusion that it was not well-established that CBD had a sigmoidal linear dose-response curve for treating any seizures, much less partial seizures. PO Resp. 30. Patent Owner faults Petitioner and Dr. Benet for ignoring "numerous other studies disclosed in Pertwee where CBD had no activity in the same MES model at the same dosage" as those in Table 4 on which Dr. Benet relied. PO Resp. 32.

Patent Owner again touts that CBD has an unknown clinical profile and that it is unclear whether CBD has a direct anticonvulsant effect or if it modulates the anticonvulsant effects of other co-administered AEDs. *Id.* Patent Owner states that "[i]n Dr. White's opinion, 'the inconsistency in the various models [disclosed in Pertwee] would suggest to a person of skill in the art is that it is unclear whether or not CBD is effective for treating seizures and that additional investigation was warranted.' " *Id.* at 33 (quoting Ex. 2008 ¶ 35) (citing Ex. 2008 ¶ 53). Patent Owner concludes that Petitioner's analysis is "nothing more than hindsight." PO Resp. 34.

In looking at all of the evidence presented at trial as a whole, we find that Petitioner has shown by a preponderance of the evidence that claims 1 and 2 of the '920 patent would have been obvious over the combination of Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697. As we have previously stated in analyzing the first ground above, we agree with Dr. Benet that Cunha itself suggests using higher doses of CBD. *See* Ex. 1003 ¶ 12; Ex. 1004, 182 (stating considerable improvement for one patient achieved by increasing the dosage of CBD to 300 mg daily). As we have also stated, we credit Dr. Benet's testimony, based on the teachings of Lindamood and Wallace, that the CBD drug response increased with dose in a monophasic fashion. Therefore, a POSITA would have expected the response to CBD to increase when the dosage is increased, *see* Ex. 1003 ¶¶ 17–23, and there is credible evidence that a CBD dose of up to 1500 mg per day have been administered without significant side effects, *see id.* ¶ 13 (citing Ex. 1025, 4). We also agree with Dr. Benet's premise that low bioavailability of CBD when administered orally would have encourageed use of higher doses for treatment of seizures in human patients. Ex. 1003 ¶¶ 24, 26, 36.

Based on these findings, we conclude that Dr. Benet's statements as to obviousness set forth below are supported by a preponderance of the evidence. Dr. Benet concludes that

> In my opinion, the skilled person would have a reasonable expectation that the oral anticonvulsant doses of CBD of 200-300 mg/day disclosed in Cunha, would be increased without significant side effects up to 1500 mg/day with an improved response.
>
> Accordingly, it would have been obvious for the skilled person to increase the oral dose of CBD from 200-300 mg/day (as in Cunha) to over 400 mg/day in the treatment of partial seizures.

Ex. 1003 ¶¶ 37–38 (citation omitted).

Pertwee's statements concerning the lack of anticonvulsant effect in some animal models, *see* Ex. 1022, 46, do not negate its conclusion that "CBD exhibits anticonvulsant activity in a number of established behavioural models of epilepsy (Table 4)," *id.*; *see In re Heck*, 699 F.2d 1331, 1332–33 (Fed. Cir. 1983) (suggesting a reference is relevant for all it contains). Also, it appears on the record before us that the MES model is an inappropriate predictor of treatment for partial seizures. Although Castel-Branco questions the use of the MES model because it can, among other things, fail to identify drugs that are clinically effective in treating partial seizures, Castel-Branco concludes that acute models, such as the MES model, are an ideal screening tool for the testing of potential antiepileptic drugs or AEDs. Ex. 1028, 5.

***16** Castel-Branco states:

> In our opinion, taking into consideration that at present there are no validated models of refractory epilepsy, that chronic epilepsy models are technically difficult and not suited to routine screening, and that the mentioned acute models do not require extraordinary experimental logistics, are not time-consuming, are well validated with several AEDs, show good reproducibility between laboratories and are responsible for the initial identification of all the currently approved AEDs, besides having diverse and often distinctive clinical activities, we consider that acute animal screening models are still essential tools in initial AED discovery. Furthermore, these models provide some insight into the central nervous system bioavailability of a particular investigational AED, they are nonselective with respect to mechanism of action, display clear and definable seizure endpoints and require minimal technical expertise. The lack of dependence on molecular mechanism also makes them ideally suited for screening large numbers of chemically diverse entities. In fact, they represent an ideal screening tool for the routine testing of potential AEDs.

Id. (citations omitted).

Therefore, we find that Petitioner has shown by a preponderance of the evidence that claims 1 and 2 would have been obvious based on the combination of Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697.

Concerning claims 3–13, Patent Owner points out that same problems with Petitioner's showing for these claims that it had with the same claims in the first challenge, namely, failure to point to teachings for each additional limitation in the dependent claims and failure to explain why one of skill in the art would combine the teachings with a reasonable expectation of success. Patent Owner states that Petitioner fails to show where the additional limitations of these claims are taught in the art of record and provides no expert testimony to establish that these dependent claims would have been obvious. PO Resp. 35–39. We agree with Patent Owner's assessment of the Petitioner's showing for dependent claims 3–13 for the same reasons discussed for the previous ground. *See* Pet. 64. Accordingly, Petitioner has failed to show that claims 3–13 would have been obvious over Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697, and thus has failed to show by a preponderance of the evidence that these claims are unpatentable over this combination.

F. Obviousness over Jones, Cunha, Lowenstein, and WO 2009/0007697

As set forth below in our discussion of Petitioner's Motion for Submission of Supplemental Information, we determine that Jones is prior art. *See infra* Section IV. Therefore, we address the substance of Petitioner's arguments concerning whether the challenged claims are obvious over Jones, Cunha, Lowenstein, and WO 2009/0007697.

In addressing the substance of this challenge, Patent Owner asserts that Petitioner presents only cursory attorney argument, which neither of Petitioner's declarants addresses. Prelim. Resp. 33. [16] Patent Owner also notes that

> ***17** Petitioner does not even identify the claimed dosage limitation (*i.e.*, a daily dose of CBD of at least 400 mg) in the prior art, but instead baldly asserts that 'a PHOSITA would have found it obvious to use CBD for the treatment of partial seizures at the daily dosage of at least 400 mg with a reasonable expectation of success.' Petition, p. 63. Thus, Petitioner resorts to arguing, in a conclusory manner, that a person of ordinary skill starting with Jones ***would have*** arrived at this claim limitation—which is nowhere in the prior art—but never presents any testimony from someone who qualifies as a person of ordinary skill to corroborate that supposed journey.

Prelim. Resp. 33.

16 Because this ground was added after oral hearing and additional briefing was limited to the prior art status of Jones, *see* Ex. 3001, we address the substantive arguments concerning this challenge as set forth in the Petition and the Patent Owner Preliminary Response.

We agree with Patent Owner's assessment of Petitioner's assertions concerning the obviousness of the challenged claims over the combination of Jones, Cunha, Lowenstein, and WO 2009/0007697, set forth above. Petitioner does not present testimony of a qualified declarant concerning how one of skill in the art would analyze the teachings of the references and fails to present any reason why one of skill in the art would combine such teachings. *See* Pet. 60–64. Therefore, we find that Petitioner has failed to show by a preponderance of the evidence that any challenged claim would have been obvious over the combination of Jones, Cunha, Lowenstein, and WO 2009/0007697.

III. CONCLUSION

After reviewing the information presented in the Petition and the Patent Owner Response, as well as the evidence of record, we determine that Petitioner has shown by a preponderance of the evidence that claims 1 and 2 of the '920 patent are unpatentable under 35 U.S.C. § 103(a) over the combination of the Cunha, Bhattacharyya, Ames, Lowenstein, and WO 2009/007697, and over the combination of Cunha, Pertwee, Malfait, Lindamood, Mechoulam, Zuardi, and WO 2009/007697. We also find that Petitioner has not shown by a preponderance of the evidence that claims 3–13 are unpatentable under any asserted combination of art.

IV. PETITIONER'S MOTION FOR SUBMISSION OF SUPPLEMENTAL INFORMATION UNDER 37 C.F.R. § 42.123(b)

In our Decision on Institution, we initially determined that the evidence presented in the Petition regarding the publication date of Jones was insufficient to satisfy its burden of showing that Jones qualifies as prior art. Dec. 23. In supplemental briefing regarding the publication date of Jones, Petitioner states:

> Evidence of record supports BOTH the publication dates of November 11, 2009 and February 2010, **either of which** would make Jones *et al* PRIOR ART. That is, Jones *et al* was e-published on November 11, 2009. The middle of the right-hand column of page 2 of the '920 patent, subject of this Inter [Partes] Review ("IPR"), lists Jones *et al* and identifies its publication dates as February 2010 and November 11, 2009. *See*, **Exhibit 1001**, page 2.

> This November 11, 2009 date is the same date that Petitioner asserted in the Petition for the IPR as the publication date of Jones *et al*. *See*, Petition, page 61, the second full paragraph. Thus, this date was corroborated by evidence already in the record. Thus, even without resorting to supplemental evidence, there can be no question that the reference identified in the '920 patent is the same reference as Jones et al submitted by Petitioner.

Paper 29, 1–2.

We agree with Petitioner that the face of the '920 patent shows that Jones was published February 2010 and e-published November 11, 2009. We find this evidence sufficient to show that Jones qualifies as prior art because the parties agree that the priority date for the '920 is June 29, 2010. *See* Pet. 27; Prelim. Resp. 31; Pet. 24–27 (discussing why claims of the '920 patent are not entitled to an earlier priority date).

***18** Because we find that the evidence of record supports this finding, we need not decide Petitioner's Motion for Submission of Supplemental Information (Paper 28), as it seeks only to establish the publication date of Jones, and therefore, deny it as moot.

V. ORDER

Accordingly, it is

ORDERED that claims 1 and 2 of U.S. Patent No. 9,066,920 B2 have been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that claims 3–13 of U.S. Patent No. 9,066,920 B2 have not been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that Petitioner's Motion for Submission of Supplemental Information under 37 C.F.R. § 42.123(b) is *denied as moot*; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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