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Paper 19
Date: May 23, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
Petitioner,

v.

RESEARCH CORPORATION TECHNOLOGIES, INC.,
Patent Owner.

Case IPR2016-00204
Patent RE38,551 E

Before FRANCISCO C. PRATS, JACQUELINE WRIGHT BONILLA, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

BONILLA, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Argentum Pharmaceuticals LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–13 of U.S. Patent No. RE38,551 E (Ex. 1001, "the '551 patent"). Paper 2 ("Pet."). Research Corporation Technologies, Inc. ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp."). Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted unless it is determined that there is "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Based on the information presented in the Petition and Preliminary Response, we are persuaded that there is a reasonable likelihood Petitioner would prevail with respect to the claims challenged in the Petition. We institute *inter partes* review of claims 1–13 of the '551 patent.

A. Related Proceedings

Patent Owner identifies multiple lawsuits it has filed against different defendants in relation to the '551 patent in several U.S. district courts. Paper 6, 2–3. Most of those cases have been consolidated with *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del.). *Id.*; Pet. 1.

The parties also discuss IPR2014-01126, where a panel previously denied an *inter partes* review based on a petition filed by a different petitioner, challenging the same claims of the same patent at issue here. *Actavis, Inc., v. Research Corporation Technologies, Inc.*, Case No. IPR2014-01126, Paper 22 (PTAB Jan. 9, 2015). Pet. 1; Prelim. Resp. 2.

B. Proposed Grounds of Unpatentability

Petitioner advances eight grounds of unpatentability under 35 U.S.C. § 102(b) or § 103(a) in relation to claims 1–13 of the '551 patent (Pet. 2):

References	Statutory Basis	Challenged Claims
The LeGall thesis[1]	§ 102(b)	1, 3–8
The LeGall thesis and the '729 patent[2]	§ 103(a)	2, 9–13
Choi[3] and Kohn 1991[4]	§ 103(a)	1–9
Choi, Kohn 1991, and the '729 patent	§ 103(a)	10–13
Kohn 1991 and Silverman[5]	§ 103(a)	1–9
Kohn 1991, Silverman, and the '729 patent	§ 103(a)	10–13

[1] Philippe LeGall, *2-Substituted-2-acetamido-N-benzylacetamides. Synthesis, Spectroscopic and Anticonvulsant Properties* (Dec. 1987) ("the LeGall thesis") (Ex. 1008).

[2] Kohn et al., U.S. Patent No. 5,378,729, issued on Jan. 3, 1995 ("the '729 patent") (Ex. 1009).

[3] Choi et al., *Trimethylsilyl Halides: Effective Reagents for the Synthesis of β-Halo Amino Acid Derivatives*, 36(39) TETRAHEDRON. LETT. 7011–14 (1995) ("Choi") (Ex. 1010).

[4] Kohn et al., *Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids*, 34 J. MED. CHEM. 2444–52 (1991) ("Kohn 1991") (Ex. 1012).

[5] Silverman, *The Organic Chemistry of Drug Design and Drug*Action, Academic Press (1992) ("Silverman") (Ex. 1013).

References	Statutory Basis	Challenged Claims
Cortes[6] and Kohn 1991	§ 103(a)	1–9
Cortes, Kohn 1991, and '729 patent	§ 103(a)	10–13

In addition, Petitioner supports its challenges in the Petition with a Declaration by Dr. Binghe Wang ("Wang Decl.") (Ex. 1002). Pet. 4–5.

C. The '551 Patent

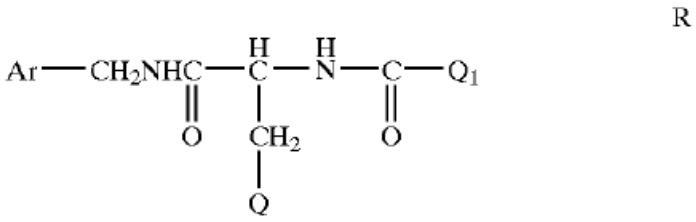
The '551 patent relates to enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other central nervous system ("CNS") disorders. Ex. 1001, 1:21–23. According to the '551 patent, at the time of the invention many anticonvulsant drugs were well known, but they exhibited liver toxicity over chronic administration. *Id.* at 1:45–47, 2:62–3:6. The '551 patent discloses "a group of compounds that is generally potent, exhibit minimal neurological toxicity, has a high protective index and is relatively non-toxic to the body organs, including the liver upon multiple dosing." *Id.* at 3:56–60. One of those compounds is lacosamide, (R)-N-benzyl 2-acetamide 3-methoxy-propionamide. *Id.* at claim 8.

D. Claims

Among the challenged claims, claim 1 is the sole independent claim. It reads:

[6] Cortes et al., *Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity*, 28 J. MED. CHEM. 601–06 (1985) ("Cortes") (Ex. 1015).

1. A compound in the R configuration having the formula:



wherein
Ar is phenyl which is unsubstituted or substituted with at least one halo group;
Q is lower alkoxy, and
Q_1 is methyl.

Claims 2–9 are compound claims that depend directly or indirectly from claim 1. Claim 8 is directed specifically to lacosamide. Claim 10 is directed to a therapeutic composition:

> 10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1–9 and a pharmaceutical carrier therefor.

Claims 11–13 are method claims. Claim 11 reads:

> 11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1–9.

II. ANALYSIS

A. Claim Construction

For *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the patent specification. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015), *cert. granted, sub nom. Cuozzo Speed Techs. LLC v. Lee*, 136 S.Ct. 890 (2016) (No. 15-446). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary

skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Both parties provide proposed constructions of certain terms in the challenged claims. Pet. 7–11; Prelim. Resp. 10–16. Specifically, the parties dispute the meaning of a "compound in the R configuration" in claim 1, and "therapeutic composition" in claim 10. Pet. 7–11; Prelim. Resp. 10–16. For the purpose of institution, we construe those terms, but determine that construction of other terms is not necessary to our analysis on whether to institute. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only claim terms in controversy need to be construed, and only to the extent necessary to resolve the controversy).

1. A "compound in the R configuration" (claim 1)

According to Petitioner, the term "a compound in the R configuration" in claim 1 excludes "pure S-isomer, which would have no R-isomer," but otherwise encompasses anything that includes an R-isomer, such as a racemic mixture (having both R- and S-isomers) or an isomerically enriched compound. Pet. 10. Petitioner contends that dependent claim 2, which recites "substantially enantiopure," and dependent claim 9, which recites "contains at least 90% (w/w) R stereoisomer," confirm this construction. *Id.* at 10–11 (citing Ex. 1002 ¶¶ 9–13).

Patent Owner, on the other hand, contends that the specification of the '551 patent indicates "a compound in the R configuration" refers to "a compound containing greater than 50% R enantiomer," and therefore

excludes a racemic mixture (a 50/50 mix) or an isomerically enriched compound having greater than 50% S-isomer. Prelim. Resp. 10–13.

Neither party points us to where the '551 patent specification defines the term expressly. As Patent Owner notes, however, the specification states in a relevant part that "the R stereoisomer at the asymmetric carbon at the asterisk is significantly more efficacious than the corresponding S enantiomer or a racemic mixture thereof." Ex. 1001, 5:1–4; *see also id.* at 23:28–33 (stating that "the R enantiomers of the present invention have quite potent anticonvulsant activity," and "the R stereoisomer is unexpectedly more potent than the corresponding S stereiosomer and the racemic mixture"); Prelim. Resp. 10. We agree with Patent Owner that this description in the specification indicates that "a compound in the R configuration" in claim 1 does not refer to a racemic mixture, but rather a compound containing more than 50% of the R stereoisomer, including, for example, a compound that is "substantially enantiopure" (claim 2) or "contains at least 90% (w/w) R stereoisomer" (claim 9).

2. A "therapeutic composition" (claim 10)

In a related district court litigation involving Patent Owner and the patent at issue here, a district court judge construed "therapeutic composition" in the preamble of claim 10 as a claim limitation, and to mean "suitable for use as a treatment regimen over an extended period of time (chronic administration)" Ex. 1007, 5, 8; Prelim. Resp. 16 n.6.

Patent Owner argues that the specification supports that same interpretation here. Prelim. Resp. 13–16 (citing Ex. 1001, 2:62–3:61, 8:62–9:26, 10:29–52, 21:13–24, 24:30–29:29, 37:5–51). Petitioner counters that the district court construction is not the "broadest reasonable interpretation

('BRI')." Pet. 7–10. Petitioner argues that the "preamble, 'a therapeutic composition,' does not 'give life, meaning, and vitality' to the claim, but merely describes an intended purpose," and the body of claim 10 "sets forth all limitations of the claimed invention." *Id.* at 8 (quoting *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997)). Thus, according to Petitioner, "BRI cannot be limited to only a composition that is administered 'over an extended period of time' and for 'chronic administration.'" *Id.* at 9.

As noted by Patent Owner, although not binding us, claim construction by a district court in a relevant case is instructive and persuasive here. Prelim. Resp. 16 n.6 (citing Ex. 1007). In this instance, we determine the district court's claim construction under *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) also presents the broadest reasonable interpretation in light of the specification. The district court opinion discusses in detail why the preamble in claim 10 is limiting, and how the specification supports its construction. Ex. 1007, 5–10. Petitioner does not persuade us that the "BRI" standard of claim interpretation dictates a different result in view of the record before us (Pet. 7–10). Thus, we adopt the district court's claim construction (Ex. 1007, 5), and interpret "therapeutic composition" in claim 10 to be limiting, and to mean "suitable for use as a treatment regimen over an extended period of time (chronic administration)."

B. The LeGall Thesis as "Printed Publication" Prior Art Under 35 U.S.C. §102

35 U.S.C. § 311(b) states that a "petitioner in an *inter partes* review may request to cancel . . . claims of a patent only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications." Before considering Petitioner's two

grounds based on the LeGall thesis, we must address whether that thesis constitutes prior art under 35 U.S.C. § 102—a legal question based on underlying factual determinations.[7] *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987); *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008).

The Federal Circuit has held that "public accessibility" is the touchstone in determining whether a reference is a "printed publication" under § 102. *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986). "A reference is publicly accessible 'upon a satisfactory showing that such document 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 . . . .'" *Kyocera*, 545 F.3d at 1350 (quoting *SRI Int'l, Inc. v. Internet Sec. Sys. Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008)); *In re Lister*, 583 F.3d 1307, 1315 (Fed. Cir. 2009).

A party seeking to introduce a reference "should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art to which the document relates and thus most likely to avail themselves of its contents." *In re Wyer*, 655 F.2d 221, 227 (CCPA 1981) (quoting *Philips Elec. & Pharm. Indus. Corp. v. Thermal & Elecs. Indus., Inc.*, 450 F.2d 1164, 1171 (3d Cir. 1971)). As

[7] We decline to deny the two grounds relying on the LeGall thesis under 35 U.S.C. § 325(d) based on the premise that the current Petition constitutes a "second bite at the apple." Prelim. Resp. 17. Petitioner here differs from the petitioner in IPR2014-01126, and the petition in the earlier case raises different arguments. *Actavis, Inc., v. Research Corporation Technologies, Inc.*, Case No. IPR2014-01126, Paper 22, slip op. at 10–13 (PTAB Jan. 9, 2015)

explained by the Federal Circuit, a "determination of whether a reference is a 'printed publication' under 35 U.S.C. § 102(b) 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).

Petitioner asserts that the LeGall thesis (Ex. 1008) constitutes prior art under 35 U.S.C. § 102(b) because: (1) "Patent Owner has now admitted that LeGall qualifies as prior art"; (2) the University of Houston (where the thesis is located) has denied Petitioner's request for information regarding public access to the thesis; and (3) evidence indicates "that the University of Houston's theses were generally accessible to the public" in the relevant time frame. Pet. 21–23 (citing Ex. 1004 ¶ 87; Ex. 1028, 5, 11, 15–16; Ex. 1029, 42–43 nn.8, 11, 20; Ex. 1029, 1135 nn.21, 28; Ex. 1030, 157–158; Ex. 1031, 649 n.9).

As an initial matter, Petitioner relies on a "Joint Statement of Uncontested Facts" submitted in a district court case involving Patent Owner and defendants other than Petitioner. Pet 22 (Ex. 1004 ¶ 87). There, among other things, the Joint Statement states that "*for purposes of this litigation*, the LeGall thesis was publicly accessible more than one year before the earliest priority date for the '551 patent and constitutes a 'printed publication' within the meaning of 35 U.S.C § 102(b)." 1004 ¶ 87 (emphasis added). We are unpersuaded that this "Joint Statement" provides a sufficient "threshold showing" of public accessibility. *Apple, Inc. v. DSS Tech. Mgmt., Inc.*, Case IPR2015-00369, Paper 14, slip op. at 5 (PTAB Aug. 12, 2015) (requiring a "threshold showing" of public availability in order to institute trial); *Hughes Network Systems, LLC v. California Institute of*

Technology, IPR2015-00059, Paper 34, slip op. at 4 (PTAB Dec. 30, 2015). During the district court litigation, Patent Owner may have agreed to stipulate to certain facts to streamline matters at trial there, for example, or had other reasons to stipulate on the issue in a case involving different parties in a different forum, regardless of whether the thesis was, in fact, publicly accessible or not. Prelim. Resp. 20–21.

We likewise are not persuaded that the University of Houston's refusal to provide information in response to Petitioner's request is a sufficient threshold showing. The record before us does not explain adequately the University's rationale for declining Petitioner's request for information, and we do not agree that the University's action "gives rise to a rebuttable presumption that the information both exists and establishes a reasonable likelihood that LeGall is prior art," as proposed by Petitioner. Pet. 22–23. The request relates to two different theses (Ex. 1028, 2), and a statement that "releasing the dates when each thesis was checked out of the University library would cause the University competitive harm" (*id*. at 5) is insufficient to create a presumption as to when or if the LeGall thesis was ever publicly accessible.

Patent Owner also persuades us that articles cited by Petitioner that reference "theses of other students in other departments at the University of Houston" likewise fail to provide threshold evidence that the LeGall thesis was publicly accessible in the relevant time frame. Prelim. Resp. 21–22. As noted by Patent Owner (*id.* at 22), "in each of Petitioner's examples, just like Dr. Kohn's articles citing the LeGall Thesis, the article was authored by the student who wrote the thesis or by the student's thesis advisor," thereby indicating the authors had personal knowledge regarding the cited thesis

work, even if others did not have public access to any of those theses per se.

Absent in the evidence cited by Petitioner is information related to whether the LeGall thesis itself was publicly accessible in the relevant time frame, how one might have obtained a copy of the thesis, or whether the thesis was reasonably accessible through generally available means. Without more here, contentions and evidence cited by Petitioner do not rise to the level of "threshold evidence" that justifies going forward with a trial on any ground that relies on the LeGall thesis as "printed publication" prior art.

C. Asserted Anticipation by the LeGall Thesis and Obviousness over the LeGall Thesis and the '729 patent

Petitioner contends that the LeGall thesis anticipates challenged claims 1 and 3–8, and that challenged claims 2 and 9–13 are rendered obvious over the LeGall thesis and the '729 patent (Ex. 1009). Pet. 21–34. Both grounds rely on teachings in the LeGall thesis. *Id.* As discussed above, we are not persuaded that Petitioner has made a threshold showing that the LeGall thesis was sufficiently publicly accessible to qualify as a "printed publication" under § 102(b). Thus, Petitioner has not demonstrated that there is a reasonable likelihood that it would prevail in showing that challenged claims of the '551 patent are unpatentable based on the two asserted grounds that rely on the LeGall thesis.

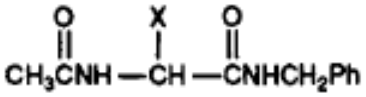
D. Asserted Obviousness of Claims 1–9 over Kohn 1991 and Silverman

Petitioner contends that claims 1–9 of the '551 patent would have been obvious over Kohn 1991 (Ex. 1012) and Silverman (Ex. 1013). Pet. 44–48. Patent Owner disagrees. Prelim. Resp. 46–50. Petitioner contends, and Patent Owner does not dispute, that Kohn 1991 and Silverman both

qualify as prior art under § 102(b) because they were published in 1991 and 1992, respectively, which is more than one year before the earliest possible priority date of the '551 patent. Pet. 44; Prelim. Resp. 46–50, 58; Ex. 1001.

1. Kohn 1991 (Ex. 1012)

Kohn 1991 discloses the preparation and anti-convulsive activity of "functionalized α-heteroatom-substituted amino acids." Ex. 1012, 2444. Kohn states that "comparison of the two individual enantiomers of **2a, b, d** revealed that in each case the anticonvulsant activity resided primarily in the R stereoisomer." *Id.* at 2444, 1st col. Table 1 in Kohn 1991 presents physical and pharmacological data, including ED_{50},[8] for those compounds, as well as derivatives 3a–3z, prepared as racemates. *Id.* at 2444, 2nd col., 2445, Table 1. Table 1 lists the "X" group for different derivatives having the following formula:



Id. The formula depicted above is similar to the formula recited in claim 1 of the '551 patent.

Kohn 1991 teaches that "[i]mportantly, in the most potent analogues (**2d, 3l, and 3n**), a *functionalized* oxygen atom existed two atoms removed from the α-carbon atom." *Id.* at 2447, 1st col. As depicted in Table 1,

[8] ED_{50} refers to an "effective dose, for 50% of people receiving the drug." Effective dose (pharmacology), Wikipedia, The Free Encyclopedia, https://en.wikipedia.org/wiki/Effective_dose_ (pharmacology) (last visited May 18, 2016); *see also* Bourne, *Drug Receptors & Pharmacodynamics, in* BASIC & CLINICAL PHARMACOLOGY 29 (Katzung, Apple & Lange 7th ed. 1998) (stating that "the median effective dose (ED50)" is "the dose at which 50% of the individuals exhibit the specified quantal effect"). A lower ED_{50} indicates a compound is more effective than one with a higher ED_{50}.

derivative 2d (where X is "2-furanyl") has an ED_{50} of 10.3 mg/kg, derivative 3l (where X is $NH(OCH_3)$) has an ED_{50} of 6.2 mg/kg, and derivative 3n (where X is $N(CH_3)OCH_3$) has an ED_{50} of 6.7 mg/kg. *Id.* at 2445, Table 1. Table 1 indicates that other derivatives have a higher ED_{50}. *Id.* For example, derivative 3a (where X is NH_2) has an ED_{50} of 65.1 mg/kg, and derivative 2a (where X is CH_3) has an ED_{50} of 76.5 mg/kg. *Id.*

2. Silverman (Ex. 1013)

Silverman presents a chapter entitled "Drug Discovery, Design, and Development" in a book entitled "The Organic Chemistry of Drug Design and Drug Action." Ex. 1013, 1–3.[9] In a section discussing "Bioisosterism," Silverman teaches that:

> *Bioisosteres* are substituents or groups that have chemical or physical similarities and which produce broadly similar biological properties. Bioisosterism is a lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead, and it may have a significant role in the alteration of metabolism of a lead. There are classical isosteres and nonclassical isosteres.

Ex. 1013, 18 (citations omitted). Table 2.2 on the same page of Silverman presents "Classical Isosteres," including:

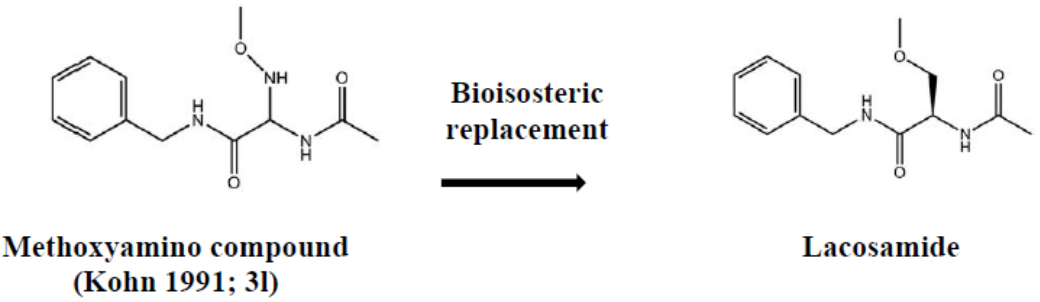
2. Bivalent atoms and groups					
a.	$-CH_2-$	$-NH-$	$-O-$	$-S-$	$-Se-$
b.	$-COCH_2R$	$-CONHR$	$-CO_2R$	$-COSR$	

Id.

3. Analysis

Petitioner presents the following diagram in relation to derivative 3l disclosed in Kohn 1991:

[9] We cite page numbers added to Exhibit 1013, rather than page numbers in the reference itself.



Methoxyamino compound (Kohn 1991; 3l) **Lacosamide**

Pet. 44; *see also id.* at 4, 14–15. This diagram depicts the chemical structure of a "methoxyamino compound" (3l) disclosed in Kohn 1991, as compared to lacosamide, a relevant compound encompassed by challenged claim 1 and specifically recited in dependent claim 8.

Petitioner contends that an ordinary artisan would have had reason to choose derivative 3l (i.e., the "methoxyamino compound") from Kohn 1991 as a lead compound because the reference teaches that derivative 3l, which has an ED_{50} of 6.2 mg/kg, is the most potent compound tested. Pet. 44 (citing Ex. 1012, Table 1; Ex. 1002 ¶ 105), 37. According to Petitioner, "[t]his compound would have been of immediate interest to a [person of ordinary skill in the art, 'POSA'] based on its activity and would have been selected for optimization." *Id.* (citing Ex. 1002 ¶ 105).

Petitioner further contends that "[h]aving recognized the desire to modify the methoxyamino moiety, a POSA would utilize the well-known concept of bioisosterism and bioisosteric replacements." *Id.* at 45 (citing Ex. 1002 ¶ 107). Citing Silverman, Petitioner also argues that in the relevant time frame, an ordinary artisan would have known that "a methylene group ($-CH_2-$) is a bioisosteric replacement for a secondary amino group (-NH-)." *Id.* (citing Ex. 1013, 18; Ex. 1002 ¶ 107). Petitioner also refers to ED_{50} data in Kohn 1991 to support the contention that an ordinary artisan would have

known "the equivalence between the amino and the methylene group off the α-carbon." *Id.* at 45–46.

In addition, Petitioner argues "the predicted activity based on the prior art data and the use of bioisosteres provides a strong reason for a POSA to modify the methoxyamino compound (3l) to make racemic lacosamide." *Id.* at 46. Petitioner also contends that an ordinary artisan would have had a reasonable expectation of success in making racemic lacosamide, and in making or isolating the R-isomer using known techniques in the art. *Id.* at 46–47 (citing Ex. 1002 ¶ 109; Ex. 1012, 2444; Ex. 1009, 15:31–16:4).

Patent Owner responds that Petitioner fails to demonstrate sufficiently that an ordinary artisan would have selected derivative 3l from Kohn 1991 as a lead compound. Prelim. Resp. 46. Patent Owner contends that Petitioner and experts admit that "the methoxyamino moiety may present synthetic and stability issues," and "might be susceptible to acid catalyzed dehydration." *Id.* (citing Pet. 45; Ex. 1002 ¶ 106; Ex. 2012, 137:10–138:5).

We are persuaded that Petitioner sufficiently articulates reasoning, with adequate rational underpinnings, as to why an ordinary artisan would have chosen derivative 3l from Kohn 1991 as a lead compound for the purposes of making compositions exhibiting anticonvulsant activity. *See In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (stating that determination of unpatentability on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

As Petitioner points out (Pet. 44), Kohn 1991 identifies derivative 3l as the most potent derivative, among many tested, in terms of a "median effective dose ED values required to prevent seizures" in a maximal

electroshock seizures ("MES") test in mice. Ex. 1012, 2444, 1st col., 2445, Table 1, 2447, 1st col. Based on the record before us, the potential synthetic or stability issues cited by Patent Owner do not persuade us that an ordinary artisan would have failed to consider derivative 3l as a lead compound for study. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012) ("In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties," including "positive attributes such as activity and potency" and "adverse effects such as toxicity.").

In addition, we are persuaded that Petitioner adequately shows at this stage that an ordinary artisan reading Silverman would have had reason to substitute the amino group (-NH-) in the X moiety of $NH(OCH_3)$ in derivative 3l from Kohn 1991 with a methylene group ($-CH_2-$), thereby producing a compound having the formula recited in challenged claims 1 and 8. As stated in Silverman, bioisosterism "is a lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead, and it may have a significant role in the alteration of metabolism of a lead." Ex. 1013, 18. In this context, Silverman teaches that $-CH_2-$ is a "classical isostere" of -NH-. *Id.* at 18, Table 2.2. Petitioner reasonably contends that those teachings in Silverman suggest substituting one bioisostere for the other in a lead compound modification (e.g., in the X moiety in derivative 3l from Kohn 1991), in an effort to attenuate toxicity, modify activity, or positively affect the metabolism of a compound.

We acknowledge Patent Owner's contentions that one would have known that such a substitution "affects the size, shape, solubility, pKa, and hydrogen bonding of the molecule," citing district court testimony by Dr.

Heathcock and Silverman. Prelim. Resp. 47 (citing Ex. 2012, 190:18–191:13; Ex. 1013, 18–22). Silverman itself states, however:

> It is actually quite surprising that bioisosterism should be such successful approach to lead modification. Perusal of Table 2.2, and especially of Table 2.3 [listing nonclassical bioisosteres], makes it clear that in making bioisosteric replacement, one or more of the following parameters will change: size shape electronic distribution, lipid solubility, water solubility pKa, chemical reactivity, and hydrogen bonding.

Ex. 1013, 20. Silverman then lists other effects that modifications can have in relation to structure, receptor interactions, pharmacokinetics, and metabolism, and states "[i]t is *because* of these subtle changes that bioisosterism is effective." *Id.* (emphasis added).

Patent Owner also relies on testimony by Dr. Heathcock and Kohn 1991 to support its contention that, in some relevant compounds, replacing a nitrogen with a carbon results in a reduction in anticonvulsant activity. *Id.* at 47–48 (citing Ex. 2012, 188:23–189:17; Ex. 1012, 2445). A review of Table 1 in Kohn 1991 in relevant part, however, indicates that substituting a nitrogen ($X = NH_2$) with a carbon ($X = CH_3$) in different but related compounds has what appears to be a relatively small impact on ED_{50} (65.1 mg/kg vs. 76.5 mg/kg, respectively). Ex. 1012, 2445, Table 1 (also indicating that a number of other related derivatives have ED_{50} of ~100 or greater). In addition, Silverman teaches that bioisosterism, using classical isosteres such as $-CH_2-$ and -NH-, can attenuate toxicity of a lead compound, which reasonably provides an additional, but different, reason to do the modification. Ex. 1013, 18, 20. We also are not persuaded by Patent Owner's contention that other Kohn references "explicitly disclose[] that heteroaromatic compounds – not aliphatic compounds like compound 3l or

lacosamide – were 'the most promising compounds.'" Prelim. Resp. 49 (citing Ex. 1017, 3350; Ex. 1018, 919). Although the cited Kohn references may indicate that certain heteroaromatic compounds are promising, we are not persuaded, based on arguments and information before us at this time, that those references undermine teachings in Kohn 1991 that suggest that derivative 3l is also promising as a lead compound. "[T]he lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi Sankyo v. Matrix Labs.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010).

We also are persuaded that Petitioner sufficiently contends, in view of teachings in Kohn 1991, for example, that an ordinary artisan would have been motivated to make or isolate the R-isomer of a modified derivative 3l using known techniques, with a reasonable expectation of success. *Id.* at 46–47 (citing Ex. 1002 ¶ 109; Ex. 1012, 2444; Ex. 1009, 15:31–16:4). For example, Petitioner points to Kohn 1991 as teaching, in relation to a relevant class of compounds, that "in each case the anticonvulsant activity resided primarily in the R stereoisomer." *Id.* at 47 (citing Ex. 1012, 2444).

Having considered the information and arguments presented in the Petition and Preliminary Response, we are persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–9 as obvious over Kohn 1991 and Silverman.

E. Asserted Obviousness of Claims 10–13 over Kohn 1991, Silverman, and the '729 Patent

Petitioner contends that claims 10–13 of the '551 patent would have been obvious over Kohn 1991, Silverman, and the '729 patent (Ex. 1009). Pet. 44–48, 25–34. Patent Owner disagrees. Prelim. Resp. 46–50.

1. The ’729 Patent (Ex. 1009)

The ’729 patent describes “compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders.” Ex. 1009, 1:30–33. In this context, the ’729 patent discloses compounds having a particular general formula, a genus that encompasses the compounds recited in the challenged claims and the compounds disclosed in Table 1 of Kohn 1991. *Id.* at 1:33–2:20; Ex. 1012, 2445, Table 1. The ’729 patent also teaches that the D stereoisomer, i.e., a compound in the R configuration, is preferred. Ex. 1009, 10:22–28. The ’729 patent describes methods for preparing “[o]ptically pure functionalized amino acid derivatives.” *Id.* at 15:29–16:4.

2. Analysis

Patent Owner asserts that Petitioner’s arguments in relation to claims 10–13 depend on the “rationales and prior art disclosures discussed in Ground 1B,” which “concerns patentability over the LeGall Thesis together with the ‘729 patent,” and not the Kohn 1991 and Silverman references at issue in this ground. Prelim. Resp. 50. Thus, according to Patent Owner, the challenge here is “left without support and should be denied.”

We decline to deny a trial in relation to this ground on that basis. In the portion of its Petition expressly referenced in the ground based on Kohn 1991, Silverman, and the ’729 patent, Petitioner contends the ’729 patent “provides further reasons for a POSA to use the R-isomer instead of the S-isomer” because it “teaches that the R-isomer is ‘preferred.’” Pet. 27 (citing Ex. 1009, 10:5–27, claim 82), 48. Petitioner also argues “that the ’729 patent explains that the compounds disclosed therein, which cover racemic lacosamide and R-lacosamide, are ‘useful in the treatment of

epilepsy and other CNS disorders,'" and the '729 patent claims the compounds in a "method of treating central nervous system disorders in animals." Pet. 34 (citing Ex. 1009, 3:9–17, claim 132).

We are persuaded that Petitioner reasonably contends that an ordinary artisan would have had reason to make the composition of claim 1, as discussed above in relation to Kohn 1991 and Silverman, as well as a therapeutic composition comprising an anticonvulsant effective amount of that compound (as recited in claim 10), and using such compounds in a method for treating CNS disorders in an animal, such as a mouse or a human (as recited in claims 11–13). Based on the record before us, Petitioner provides adequate reasoning, with sufficient rational underpinning, for its contention that an ordinary artisan would have had reason to expect "that compounds falling within claim 132 of the '729 patent—such as racemic lacosamide and R-lacosamide—would be useful for treating CNS disorders, and would have a reasonable expectation of success in using them for this purpose." Pet. 34 (citing Ex 1002 ¶ 80; Ex. 1009, 3:9–17, claim 132).

Having considered the information and arguments presented in the Petition and Preliminary Response, we are persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 10–13 as obvious over Kohn 1991, Silverman, and the '729 patent.

F. Objective Indicia of Non-Obviousness

Petitioner briefly addresses objective indicia of non-obviousness, and Patent Owner responds. Pet. 52–43; Prelim. Resp. 54–58. In particular, Patent Owner states "although such objective indicia typically are better considered in the context of a trial, Patent Owner here addresses Petitioner's assertions to the extent they mischaracterize the state of the art and

applicable legal principles . . . ." Prelim. Resp. 54. Patent Owner also states "[s]hould the Board institute review on an obviousness ground, Patent Owner plans to present objective indicia evidence." *Id.* Based on a lack of sufficient evidence on the issue at this time, we leave it for resolution at trial.

G. Other Grounds

In addition to the above-mentioned grounds, Petitioner further contends that the challenged claims would have been obvious over Choi and Kohn 1991, or Choi, Kohn 1991, and the '729 patent, or Cortes and Kohn 1991, or Cortes, Kohn 1991, and the '729 patent. Pet. 3, 34–43, 48–52.

Petitioner does not persuade us that an ordinary artisan would have had sufficient reason to choose Choi's "2d" compound as a lead compound for further modification. Pet. 35–41. For example, Choi teaches that for "an ongoing project to prepare bioactive amino acid derivatives, we needed the β-halogen compounds 2a–2c." Ex. 1010, 7011. Choi's compounds 2a–2c present halogens Cl, Br, and I, respectively, in a relevant X moiety, rather than an –OH group, as present in compound 2d. Ex. 1010, 7011–12. Choi also teaches using compound 2d to prepare compounds 2a–2c. *Id.* We are not persuaded that Choi suggests that compound 2d itself is "bioactive," or that Choi explains what it means by "bioactive" in any event.

Petitioner also does not persuade us that an ordinary artisan would have had sufficient reason to modify compound "6d" (called "AAB" by Petitioner) in Cortes, which contains a methyl (–CH3) group in the relevant X moiety, in the manner that Petitioner contends. Pet. 4, 50–52. Petitioner argues that one would have had reason to modify the –CH3 group in that compound "by adding a functionalized oxygen such that the oxygen was two atoms away from the α-carbon," as taught in Kohn 1991. Pet. 50. Petitioner

then asserts, without citation to sufficient evidence in support, that the "simplest and most obvious way to achieve this would be to add a methoxy group, thus creating the methoxymethyl compound, *i.e.*, lacosamide." *Id.* We find, however, that teachings in Kohn 1991, at best, suggest the substitution of $–CH_3$ with $–NHOCH_3$, to create compound 3l in Kohn 1991, or perhaps other substitutions to create compounds 2d or 3n, also disclosed in Kohn 1991, as one of the three "the most potent analogues." Pet. 51; Ex. 1012, 2445, Table 2, 2447, 1st col. In this ground, Petitioner does not sufficiently explain why one would have been motivated to modify any of compounds 3l, 2d, and 3n to create lacosamide.

Having considered the information and arguments presented in the Petition and Preliminary Response, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 1–13 of the '551 patent as obvious over Choi, or Cortes, and Kohn 1991, either combined by themselves or also in view of the '729 patent.

III. CONCLUSION

For the foregoing reasons, based on the present record, we determine that Petitioner has demonstrated that there is a reasonable likelihood that it would prevail in showing that claims 1–13 of the '551 patent are unpatentable. At this stage of the proceeding, the Board has not made a final determination with respect to the patentability of those challenged claims or any underlying factual or legal issues.

IV. ORDER

Accordingly, it is

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is instituted as to the grounds of unpatentability that claims 1–9 of

the ’551 patent would have been obvious over Kohn 1991 and Silverman, and claims 10–13 of the ’551 patent would have been obvious over Kohn 1991, Silverman, and the ’729 patent;

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

FURTHER ORDERED that the trial is limited to the grounds of unpatentability listed above, and no other ground of unpatentability is authorized for *inter partes* review.

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