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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BRECKENRIDGE PHARMACEUTICAL, INC.  
Petitioner

v.

RESEARCH CORPORATION TECHNOLOGIES, INC.  
Patent Owner

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Case No. To Be Assigned  
Patent No. RE38,551

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**PETITION FOR *INTER PARTES* REVIEW  
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.***

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## EXHIBIT LIST

Ex. #	Exhibit Name
1001	U.S. Patent No. RE38,551 (“the ’551 patent”)
1002	Declaration of Dr. Binghe Wang
1003	Declaration of Dr. Clayton Heathcock from IPR2014-01126
1004	Joint Statement of Uncontested Facts
1005	U.S. Patent No. 5,773,475 (“the ’475 Patent”)
1006	Excerpt from U.S. Patent Application No. 08/818,688
1007	District Court Claim Construction Opinion
1008	Philippe LeGall, 2-Substituted-2-acetamido-N-benzylacetamides. Synthesis, Spectroscopic and Anticonvulsant Properties (Dec. 1987) (“LeGall”)
1009	U.S. Patent No. 5,378,729 (“the ’729 Patent”)
1010	Choi et al., <i>Trimethylsilyl Halides: Effective Reagents for the Synthesis of <math>\beta</math>-Halo Amino Acid Derivatives</i> , Tet. Lett., Vol. 36(39), pg. 7011 (1995) (“Choi 1995”)
1011	Purdie et al., <i>The Alkylation of Sugars</i> , J.A.C.S. Vol. 83, pg. 1021 (1903) (“Purdie”)
1012	Kohn et al., <i>Preparation and Anticonvulsant Activity of a Series of Functionalized <math>\alpha</math>-Heteroatom-Substituted Amino Acids</i> , J. Med. Chem. Vol. 34, pg. 2444 (1991) (“Kohn 1991”)
1013	Silverman, R. B., <i>The Organic Chemistry of Drug Design and Drug Action</i> , Academic Press (1992) (“Silverman”)
1014	Development of New Stereoisomeric Drugs, U.S. F.D.A., May 1, 1992
1015	Cortes et al., <i>Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity</i> , J. Med. Chem., Vol. 28, pg. 601 (1985) (“Cortes 1985”)
1016	LeGall et al., <i>Synthesis of Functionalized Non-Natural Amino Acid Derivatives via Amidoalkylation Transformations</i> , Int. J. Peptide Protein Res. Vol. 32, pg. 279 (1988) (“LeGall 1988”)

1017	Kohn <i>et al.</i> , <i>Synthesis and Anticonvulsant Activities of <math>\alpha</math>-Heterocyclic <math>\alpha</math>-Acetamido-N-benzylacetamide Derivatives</i> , J. Med. Chem. Vol. 36, pg. 3350 (1993)
1018	Kohn <i>et al.</i> , <i>Preparation and Anticonvulsant Activity of a Series of Functionalized <math>\alpha</math>-Aromatic and <math>\alpha</math>-Heteroaromatic Amino Acids</i> , J. Med. Chem. Vol. 33, pg. 919 (1990)
1019	U.S. Patent No. 5,654,301 (“the ’301 Patent”)
1020	Patent Term Extension Request in U.S. Patent No. 5,654,301
1021	FDA Guideline for Industry, November 1994
1022	Schmidt, R., <i>Dose-Finding Studies in Clinical Drug Development</i> , Eur. J. Clin. Pharmacol, Vol. 34, pg. 15 (1988)
1023	Isbell, H. S., <i>The Optical Rotation of the Various Asymmetric Carbon Atoms in the Hexose and Pentose Sugars</i> , B. S. Jour. Research, Vol. 5, pg. 1041 (1929)
1024	Wilson and Gisvold’s Textbook of Organic Medicinal Chemistry, Physicochemical Properties in Relation to Biologic Action, (Delgado J. N. & Remers W. A., eds. 1991) (Wilson)
1025	Thorner, C. W., <i>Isosterism and Molecular Modification in Drug Design</i> , Chem. Soc. Rev., Vol. 8(4) (1979)
1026	Reissue Declaration in Reissue of U.S. Patent No. 5,773,475
1027	Subpoena directed to The University of Houston
1028	Texas Public Information Act Requests and Responses
1029	Zhou <i>et al.</i> , <i>Decisions under Uncertainty: the Fuzzy Compromise Decision Support Problem</i> , Eng. Opt. Vol. 20, pg. 21 (1992)
1030	Mistree <i>et al.</i> , <i>A Decision-Based Perspective for the Design of Methods for Systems Design</i> , (1989)
1031	Mistree <i>et al.</i> , <i>A Decision-based Approach to Concurrent Design, Concurrent Engineering: Contemporary Issues and Modern Design Tools</i> , (Parsaei, H. R. & Sullivan W. G. Eds. 1993)
1032	Ingram W. T., <i>Concerning Periodic Points in Mappings of Continua</i> , J. Am. Math. Soc., Vol. 104(2) (1988)
1033	Mattson, <i>Current Challenges in the Treatment of Epilepsy</i> , Neurology, Vol. 44(suppl. 5), pg. 84 (1994)

1034	Löscher <i>et al.</i> , <i>New Avenues for Anti-Epileptic Drug Discovery and Development</i> , Nature Reviews: Drug Discovery, Vol. 12, pg. 12 (2013)
1035	Cohen authorized amendment in U.S. Patent Application No. 08/818,688

Petitioner Breckenridge Pharmaceutical, Inc. (“Petitioner” or “Breckenridge”) requests that the Board institute *inter partes* review (“IPR”) of claims (1-13) of U.S. Patent No. RE 38,551 to Kohn (“the ’551 patent”) (Ex. 1001), and that these claims be canceled as unpatentable over the prior art. *Inter partes* review of claims 1-13 of the ’551 patent, was instituted in IPR2016-00204 on May 23, 2016, based on a petition filed by Argentum Pharmaceuticals LLC (“Argentum”). For the sake of completeness and efficiency, the present Petition is substantially identical to the petition in IPR2016-00204. Petitioner is requesting however, that the Board institute only on the Grounds instituted in IPR2016-00204, *i.e.*, Grounds 3A and 3B as to claims 1-13. A Motion for Joinder with IPR2016-00204 is filed concurrently with this Petition.

## **I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8**

### **A. Real Parties-In-Interest under 37 C.F.R. § 42.8(b)(1)**

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Breckenridge, Pensa Pharma S.A., and Corporacion Quimico Farmaceutica Esteve, S.A., MSN Laboratories Pvt. Ltd., MSN Pharmachem Pvt. Ltd., and Vennot Pharmaceuticals, LLC are the real parties-in-interest.

### **B. Related Matters under 37 C.F.R. § 42.8(b)(2)**

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner is aware of the following matters: *Argentum Pharmaceuticals LLC v. Research Corporation Technologies*,

*Inc.*, IPR2016-00204; *Mylan Pharmaceuticals Inc. v. Research Corporation*

*Technologies, Inc.*, IPR2016-01101; *Actavis, Inc. et al. v. Research Corporation*

*Technologies, Inc.*, IPR2014-01126; *Ex Parte* Reexamination Control No.

90/013,709; and the proceedings listed in the table below.

<b>Case Caption</b>	<b>Disposition</b>
<i>UCB, Inc. et al. v. Teva Pharmaceuticals USA Inc. et al.</i> , 1:13-cv-01148-LPS (D. Del.)	closed
<i>UCB, Inc. et al. v. Accord Healthcare Inc. et al.</i> , 1:13-cv-01206-LPS (D. Del.)	pending
<i>UCB, Inc. et al. v. Alembic Pharmaceuticals Ltd.</i> , 1:13-cv-01207-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Amneal Pharmaceuticals, LLC et al.</i> , 1:13-cv-01208-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Apotex Corp. et al.</i> , 1:13-cv-01209-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Aurobindo Pharma Ltd. et al.</i> , 1:13-cv-01210-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Breckenridge Pharmaceutical Inc. et al.</i> , 1:13-cv-01211-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Glenmark Generics Inc. USA et al.</i> , 1:13-cv-01212-LPS (D. Del.)	closed
<i>UCB, Inc. et al. v. Hetero USA Inc. et al.</i> , 1:13-cv-01213-LPS (D. Del.)	closed
<i>UCB, Inc. et al. v. Mylan Pharmaceuticals Inc. et al.</i> , 1:13-cv-01214-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Ranbaxy Laboratories Ltd. et al.</i> , 1:13-cv-01215-LPS (D. Del.)	closed
<i>UCB, Inc. et al. v. Sandoz Inc.</i> , 1:13-cv-01216-LPS (D. Del.)	closed
<i>UCB, Inc. et al. v. ScieGen Pharmaceuticals Inc. et al.</i> , 1:13-cv-01217-LPS (D. Del.)	closed
<i>UCB, Inc. et al. v. Sun Pharma Global FZE et al.</i> , 1:13-cv-01218-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Watson Laboratories Inc. - Florida et al.</i> , 1:13-cv-01219-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)

<i>UCB, Inc. et al. v. Zydus Pharmaceuticals (USA) Inc. et al.</i> , 1:13-cv-01220-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Apotex Corp. et al.</i> , 1:14-cv-00834-LPS (D. Del.)	pending, consolidated with 1:13-cv-01206-LPS (D. Del.)
<i>UCB, Inc. et al. v. Sun Pharma Global FZE et al.</i> , 1:13-cv-05514 (N.D. Ill.)	closed
<i>UCB, Inc. et al. v. Zydus Pharmaceuticals (USA), Inc. et al.</i> , 3:13-cv-04021 (D.N.J.)	closed
<i>UCB, Inc. et al. v. Aurobindo Pharma Ltd. et al.</i> , 1:16-cv-00451-UNA (D. Del.)	pending
<i>UCB, Inc. et al. v. Hetero USA Inc. et al.</i> , 1:16-cv-00452-UNA (D. Del.)	pending

In IPR2014-01126, Patent Owner avoided trial against the '551 patent by challenging the prior art status of LeGall.<sup>1</sup> Prelim. Resp. 27-30. In *UCB, Inc. et al. v. Accord Healthcare, Inc. et al.*, C.A. No. 1:13-cv-1206-LPS (D. Del.), Patent Owner admitted that LeGall “constitutes a ‘printed publication’ within the meaning of 35 U.S.C. § 102(b).” Ex. 1004 at ¶ 87.

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<sup>1</sup> Breckenridge recognizes the Board’s decision to institute Grounds 3A and 3B in IPR2016-00204 does not rely on LeGall. Discussions of LeGall are included herein to provide consistency with Argentum’s petition in IPR2016-00204 and also a subsequent petition filed by Mylan Pharmaceuticals Inc. in IPR2016-01101, which is substantially identical to Argentum’s petition.

**C. Lead and Backup Counsel under 37 C.F.R. § 42.8(b)(3)**

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A Power of Attorney is being filed concurrently herewith in accordance with 37 C.F.R. § 42.10(b).

**D. Service Information under 37 C.F.R. § 42.8(b)(4)**

Papers concerning this matter should be served by EXPRESS MAIL, hand-delivery, or electronic mail at the following address:

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## **II. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104**

### **A. Grounds For Standing Under 37 C.F.R. § 42.104(a)**

Pursuant to 37 C.F.R. § 42.104(a), Petitioner hereby certifies that the '551 patent is available for *inter partes* review, and that the Petitioner is not barred or estopped from requesting *inter partes* review of the challenged claims of the '551 patent on the grounds identified in this Petition. Neither Petitioner nor any privy of Petitioner has received a final written decision under 35 U.S.C. § 318(a) with respect to any claim of the '551 patent on any ground that was raised or could have been raised by Petitioner or its privies in any *inter partes* review, post grant review, or covered business method patent review.

### **B. Identification of Challenge and Precise Relief Requested, 37 C.F.R. § 42.104(b)**

Petitioner requests cancellation of claims 1-13 of the '551 patent on Grounds 3A and 3B, but has listed the grounds of unpatentability found in the Petition for IPR2016-00204 to provide full disclosure of the record:

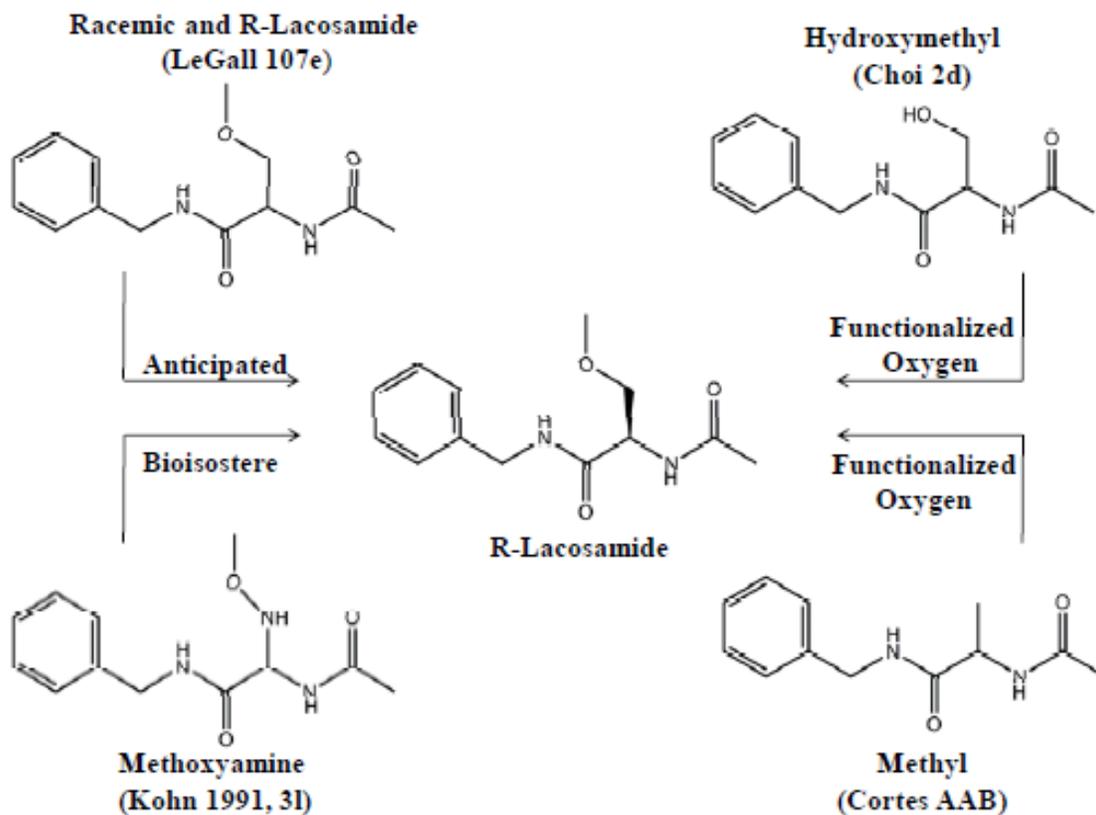
Ground	Claims	Basis	Reference(s)
1A	1, 3-8	§ 102(b)	LeGall
1B	2, 9-13	§ 103	LeGall and '729 patent
2A	1-9	§ 103	Choi and Kohn 1991
2B	10-13	§ 103	Choi, Kohn 1991, and '729 patent
3A	1-9	§ 103	Kohn 1991 and Silverman
3B	10-13	§ 103	Kohn 1991, Silverman, and '729 patent
4A	1-9	§ 103	Cortes and Kohn 1991
4B	10-13	§ 103	Cortes, Kohn 1991, and '729 patent

Grounds 1-4 are substantially identical to the grounds presented in the petition in IPR2016-00204, including Grounds 3A and 3B that were instituted by the Board, challenging the same claims over the same prior art and using the same arguments and expert testimony. Each of Grounds 1-4 identifies a different prior art compound that independently would have served as a “starting reference point or points,” from which a person of ordinary skill in the art (“POSA”) would have easily arrived at lacosamide—the compound claimed in the '551 patent. *See Eisai Co. Ltd. v. Dr. Reddy’s Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008-1009 (Fed. Cir. 2009) (affirming the selection of up to “18 exemplary compounds” as lead compounds and rejecting the notion that chemical obviousness requires “only a single lead compound”).

This case presents a unique set of facts that establish the uncommon instance in which a patent claim to a compound is anticipated and/or rendered obvious. Here, the compound lacosamide was first disclosed in the thesis of the graduate student of the '551 patent's named inventor approximately eight years before the relevant patent application was filed. Even putting aside that novelty destroying reference, at least three other specific combinations of prior art would have directed a person of ordinary skill in the art directly to lacosamide and its use. This is not a case of selecting a single favorable lead compound so that one preordains the obviousness analysis. Rather, this petition presents four separate examples of applying clear teachings in the prior art (as summarized in the figure below) to establish that the claims to lacosamide are unpatentable.

Moreover, the prior art contained repeated statements directing one to use the R-isomer. The various references stressed that the R-isomer was the biologically active isomer. Finally, the therapeutic composition and method claims in the '551 patent add no specific limitations other than standard, generic limitations, such as a "pharmaceutical carrier" and "administering to said animal." With the prior art data confirming the anticonvulsant activity of the compounds, those generic limitations cannot render the claimed subject matter patentable.

**Prior Art Compounds Disclosed in Grounds I - IV**



Petitioner supports its challenges with a Declaration of Dr. Binghe Wang (“Wang Decl.”) (Ex. 1002) prepared for IPR2016-00204<sup>2</sup>, as well as a Declaration

<sup>2</sup> The Wang Decl. is an exact copy of Dr. Wang’s declaration from IPR2106-00204, which was relied upon by the Board in that proceeding. Dr. Wang’s IPR2016-00204 Declaration is cited in this Petition to avoid unnecessary cost and to advance efficiency in this instance. As mentioned above, this Petition is presented along with a motion to join IPR2016-00204, and by using the same



Ar is phenyl which is unsubstituted or substituted with at

least one halo group;

Q is lower alkoxy, and

Q1 is methyl.

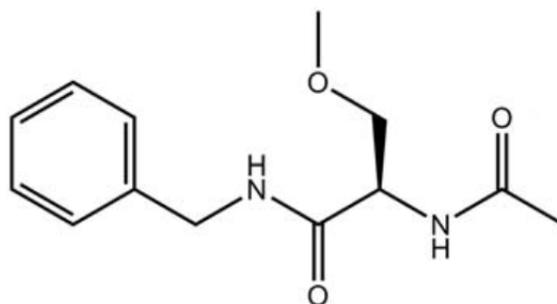
Claims 2-9 are compound claims depending directly or indirectly from claim 1.

Claim 8 is lacosamide, specified by its chemical name: “The compound according

to claim 1 which is (R)-N-Benzyl 2-Acetamido-3-methoxypropionamide.” The

structure of lacosamide is shown below (wherein Ar is benzyl, Q is methoxy, and

Q1 is methyl):



Claim 10 recites “[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.

Claim 12 depends from claim 11 and specifies that the “the animal is a mammal.” Claim 13 depends from claim 12 and specifies that “the mammal is a human.”

#### **IV. PREVIOUS PETITIONS**

As mentioned above, in IPR2016-00204, filed by Argentum Pharmaceuticals LLC, an unrelated party, the Board instituted review of claims 1-9 (Ground 3A), based on Kohn 1991 and Silverman, and of claims 10-13 (Ground 3B), based on Kohn 1991, Silverman, and the '729 patent. On May 25, 2016, Mylan Pharmaceuticals Inc. filed a petition which is substantially identical to the petition in IPR2016-00204 along with a Motion for Joinder requesting joinder as to Grounds 3A-3B only. *See* IPR2016-01101, Paper Nos. 2 and 3.

The Board previously declined to institute a review in IPR2014-01126. There, Patent Owner argued that LeGall was not shown to be prior art, and the Board agreed. (Prelim. Resp. 27-30.) The Board also found that the petition failed to establish a reasonable likelihood on three asserted grounds of unpatentability: (1) anticipation by the '301 patent, (2) anticipation by LeGall, and (3) obviousness over LeGall and the '729 patent. *See* IPR2014-01126, Paper 22 (“Dec.”). For the first ground (anticipation by the '301 patent), the petitioners alleged that claims 39-44 of the '301 patent, together with preferences recited in the '301 patent, anticipate lacosamide. The Board disagreed, finding no anticipation based on the preferred

genus of compounds. Dec. 6-9. For the second ground (anticipation by LeGall), the Board found that LeGall was not shown to be a “printed publication” under § 102(b). *Id.* at 12-13. Finally, the third ground was denied for the same reason as the second. *Id.* at 14.

Breckenridge was one of many petitioners in IPR2014-01126. The petitioners in IPR2014-01126 were Actavis, Inc., Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Amneal Pharmaceuticals of New York, LLC, Aurobindo Pharma Ltd., Aurobindo Pharma USA, Inc., Breckenridge, Vennot Pharmaceuticals, LLC, Sandoz Inc., Sun Pharma Global FZE, and Sun Pharmaceuticals Industries, Ltd. Breckenridge notes Grounds 3A and 3B for which it requests joinder in its accompanying Motion for Joinder are different from the three asserted grounds of unpatentability in IPR2014-01126, which the Board denied. Breckenridge also notes that in IPR2016-00204, the Board found that the asserted grounds in IPR2014-001126 were different than the asserted grounds in IPR2016-00204. Paper 19, p. 9, footnote 7 in IPR2016-00204.

## **V. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)**

### **A. “Therapeutic Composition” in Claim 10**

In *UCB, Inc. et al. v. Accord Healthcare Inc. et al.*, 1:13-cv-01206-LPS (D. Del.), the court construed one term in the ’551 patent: “therapeutic composition,” which appears only in the preamble of claim 10. To the extent Patent

Owner attempts to rely on the district court's construction, that construction was unnecessary and, in any event, is not the broadest reasonable interpretation ("BRI").

First, claim 10 is a product claim that recites two limitations: an "anticonvulsant effective amount" of the compound, and a "pharmaceutical carrier."<sup>3</sup> The body of the claim sets forth all limitations of the claimed invention. The preamble, "a therapeutic composition," does not "give life, meaning, and vitality" to the claim, but merely describes an intended purpose, and is therefore non-limiting. *See Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997) ("[W]here a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation.").

Second, the term "therapeutic composition" does not specify any additional physical structure or physical components other than the two recited in the body of the claim. The '551 patent does not provide a definition of the term "therapeutic composition", nor does the patent use that term in any special manner, other than introducing the claimed compound in a pharmaceutical carrier. By definition, a

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<sup>3</sup> Claim 10 reads in full: "A therapeutic composition comprising [1] an anticonvulsant effective amount of a compound according to any one of claims 1-9 and [2] a pharmaceutical carrier therefor."

compound within the genus, together with a pharmaceutical carrier, is a therapeutic composition within the meaning of claim 10.

Third, the BRI of “therapeutic composition” is not confined to the additional limitations imposed by the district court. Specifically, applying *Phillips*, the district court construed the term to mean “[a] composition suitable for use as a treatment regimen over an extended period of time (chronic administration).” Ex. 1007 at 5. The BRI cannot be limited to only a composition that is administered “over an extended period of time” and for “chronic administration.” Nothing in the claim limits the composition to “chronic administration.” *See* Ex. 1001 cols. 9-10 (reciting a litany of acceptable dosage forms and excipients).

Additionally, the claims do not numerically limit the term “anticonvulsant effective amount.” Applying the BRI, this term should be construed to mean any amount that could provide an anticonvulsant effective amount of the compound when administered. The specification again does not define a specific range, but does provide various ranges as guidance. For instance, the ’551 patent states that “[a] unit dosage form can, for example, contain the principal active compound in amounts ranging from about 5 to about 1000 mg.” Ex. 1001 at 10:52-57. The ’551 patent also states that the compositions can contain “from about 1 to about 750 mg/ml of carrier,” *id.* at 10:59, or “preferred . . . between about 5 and 100 mg of active compound,” *id.* at 9:23-26, or “at least 1% of active compound,” *id.* at 9:17-

18. At a minimum, a composition containing about 5 to about 1000 mg of the claimed compound, and a pharmaceutical carrier, is a “therapeutic composition” within the meaning of claim 10.

**B. “A Compound in the R Configuration” in Claim 1**

Petitioner does not believe that the phrase “a compound in the R configuration” in claim 1 needs to be construed. Patent Owner, however, put that phrase into issue in IPR2014-01126. Patent Owner’s preliminary response did not propose a construction of the term but instead quibbled that the petitioners’ construction “improperly fails to treat the R stereoisomer, the S stereoisomer and the racemic mixture as the different compounds that they are.” Prelim. Resp. at 13.

Here, the BRI of “a compound in the R configuration” covers R-isomer compounds, whether the R-isomer is substantially pure or mixed with the S-isomer, such as a racemic mixture or isomerically enriched mixture. But the claim does not cover pure S-isomer, which would have no R-isomer. The declaration of Prof. Wang explains why a POSA would have this understanding. Ex. 1002, Section IA, ¶¶ 9-13.

Claim 2 confirms this construction, which further limits claim 1 to “substantially enantiopure.” Applying claim differentiation, claim 2 further restricts the amount of S-isomer that is included in the scope of the claim, specifying that the compound be “substantially enantiopure.” The ’551 patent

explains that “substantially enantiomerically pure” can include at most about 10% (w/w) of the S-isomer. Ex. 1001 at 5:11-19.

Claim 9 also confirms the above construction, which specifies the “compound according to claim 8”—*i.e.*, (R)-N-benzyl-2-acetamido-3-methoxypropionamide—“contains at least 90% (w/w) R stereoisomer.” Because claim 9 depends from claim 1, and because claim 9 includes compositions having up to 10% (w/w) of the S-isomer, so must claim 1. Moreover, claim 1 does not limit the amount of R- or S-isomer present in the composition—only that it cannot be solely S. Nor does the specification provide any lower numerical limit for claim 1, other than that it cannot be solely S. To the extent Patent Owner argues that claim 1 requires any level of enantiomeric purity beyond the presence of a single R-isomer molecule, then claims 2 and 9 are nonsensical and the Board should hold all claims indefinite under 35 U.S.C. § 112, second paragraph. *See BlackBerry Corp. v. MobileMedia Ideas LLC*, IPR2013-00036 (Paper 65) (terminating IPR after finding claims indefinite).

## **VI. LEVEL OF SKILL AND KNOWLEDGE IN THE ART**

As of March 15, 1996 (the earliest possible effective date), a hypothetical POSA would “be aware of all the pertinent prior art” at the time of the alleged invention. *Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 962 (Fed. Cir. 1986). Factors relevant in determining the level of skill include: the “type of

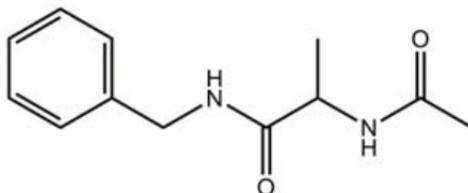
problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *Id.*

The relevant field is medicinal chemistry, and a POSA would have a Ph.D. in organic or medicinal chemistry and at least a few years of experience in medicinal chemistry, including in the development of potential drug candidates. Ex. 1002, Section IV, ¶ 13. The POSA would also include a person having a Bachelor’s or Master’s degree (organic chemistry or medicinal chemistry) if such a person had more years of experience in medicinal chemistry and the development of potential drug candidates. *Id.* With experience in drug development, the POSA would have an appreciation of the diseases and ailments a particular drug candidate is intended to treat, but would not necessarily be a medical doctor or clinician. The POSA would know how to evaluate the physical and biological properties of chemical compounds and would be able to conduct, or otherwise have access to resources that could conduct, *in vitro* and *in vivo* evaluations of biological and toxicity properties of chemical compounds. *Id.*

The following prior art references, summarized below, would have further informed a POSA’s skill and understanding of the art.

### A. Cortes (Ex. 1015)

In 1985, Sergio Cortes co-authored an article with Dr. Harold Kohn which reported the synthesis and anticonvulsant activity four amino acid derivatives (as well as nitrogen-containing compounds). Ex. 1015 at 601 abstr. Cortes reported that N-acetyl-D,L-alanine benzylamide (compound 6d, “AAB”) was “[a]mong the most active compounds.” *Id.* This compound is the “methyl compound,” depicted below:



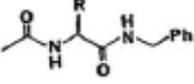
**Methyl Compound (AAB)**

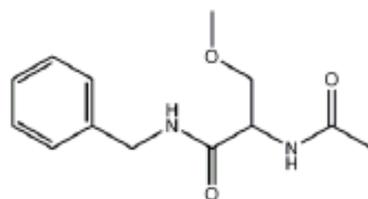
With its favorable data, the methyl compound (AAB) was “slated for additional screening,” which yielded “[p]romising results.” *Id.* at 604. The methyl compound (AAB) of Cortes became the starting point for several projects developing additional anticonvulsant agents. Ex. 1002, ¶¶ 120-128.

### B. LeGall (1987) (Ex. 1008)

Petitioner recognizes the Board did not institute *inter partes* review in IPR2016-00204 on a ground based on LeGall. However, in order to remain consistent with Argentum’s and Mylan’s petitions in IPR2016-00204 and IPR2016-01101, respectively, Petitioner includes arguments pertaining to LeGall. As set forth by Argentum and Mylan, LeGall (Ex. 1008) (also referred

to as the “LeGall Thesis”) is a 1987 master’s thesis by Philippe LeGall, a student of inventor Dr. Harold Kohn. LeGall describes the synthesis and anticonvulsant activity of “analogues of the potent anticonvulsant agent” AAB, i.e., the methyl compound, from Cortes, thus conducting the “additional screening” that Cortes recommended. Ex. 1008 at 42, 132, 173 n.102. LeGall synthesized five compounds 107a-e that were “selected as polar analogues of the potent anticonvulsant” lead methyl compound (AAB, compound 68a). The data for those compounds is provided in the following table:

 <b>107</b>	
No.	R
<b>68a</b>	CH <sub>3</sub>
<b>107a</b>	CN
<b>107b</b>	CONH <sub>2</sub>
<b>107c</b>	COOCH <sub>2</sub> CH <sub>3</sub>
<b>107d</b>	CH <sub>2</sub> OH
<b>107e</b>	CH <sub>2</sub> OCH <sub>3</sub>



**Racemic Lacosamide 107e**

*Id.* at 133, Tbl. 35. Compound 107e depicts racemic lacosamide, whose R substituent is methoxymethyl (-CH<sub>2</sub>OCH<sub>3</sub>), and which includes both the R- and S-isomers. Ex. 1002, ¶¶ 20, 57-59. Furthermore, a POSA would immediately

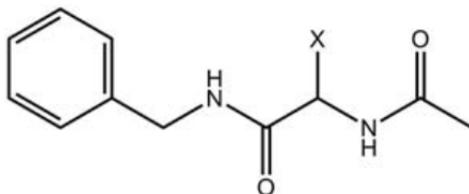
recognize that the structure shown discloses both R-lacosamide and S-lacosamide.

*Id.*

Further, as explained by Argentum and Mylan, LeGall taught an express preference for the R configuration, *i.e.*, the “D-enantiomer,” of the methyl compound (AAB), observing that the R-isomer is “thirteen times more active” than the S stereoisomer and “more potent and less toxic than the corresponding racemates.” Ex. 1008 at 42, 164; Ex. 1002, ¶ 26.

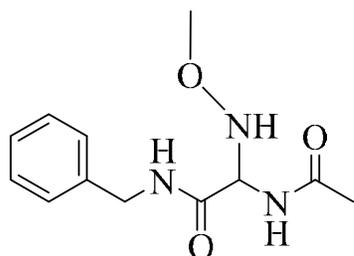
### C. Kohn 1991 (Ex. 1012)

In 1991, Kohn and LeGall (along with others) published a paper in the *Journal of Medicinal Chemistry* which adopted Cortes’s suggestion to make analogues of the highly potent lead, the methyl compound (AAB) (compound 2a in Kohn 1991). Ex. 1012 at 2444. Kohn 1991 tested numerous methyl compound derivatives which retained the core structure and varied only the R group on the  $\alpha$ -carbon (shown as “X” below):

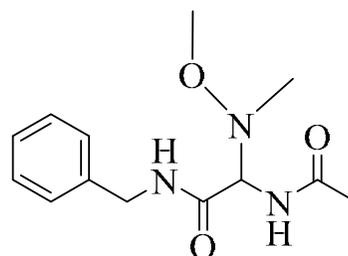


*Id.* at 2445, Tbl. I.

Of the multiple compounds that were prepared and tested, Kohn 1991 reported that the most active was the methoxyamino compound (3l), whose structure is shown below:



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



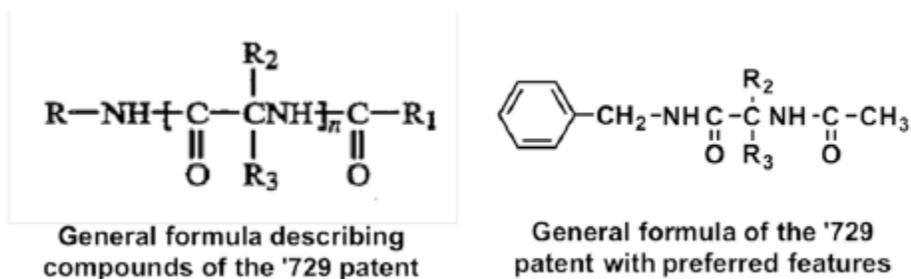
**Methoxymethylamino compound  
(Kohn 1991; 3n)**

*Id.* at 2444, abstr.; *id* at 2445, Tbl. I. The methoxyamino compound (3l) had an ED<sub>50</sub> 6.2 mg/kg. A close analogue, the methoxy(methyl)amino (3n) was also quite potent, with an ED<sub>50</sub> of 6.7 mg/kg. *Id.* at 2445, Tbl. I.

Reviewing the potency of all tested compounds, Kohn 1991 taught “several important observations” about the structure-activity relationships for compounds based on the lead methyl compound AAB. First, Kohn 1991 explained that amino compound “displayed anticonvulsant activit[y] comparable to that observed for the  $\alpha$ -methyl analogue.” Ex. 1002, ¶ 30; Ex. 1012 at 2447. Second, there are “stringent steric requirements that exist for maximal anticonvulsant activity in this class of compounds,” referring specifically to the size of the group on the  $\alpha$ -carbon. *Id.* Third, in the most potent analogues, “a functionalized oxygen atom existed two atoms removed from the  $\alpha$ -carbon atom.” *Id.*

#### D. '729 Patent (1991) (Ex. 1009)

In 1991, a U.S. patent application was filed which named Dr. Kohn as an inventor, and issued as U.S. Patent No. 5,378,729 (“’729 patent”). The ’729 patent discloses a genus of anticonvulsant compounds covering lacosamide. Ex. 1009; Ex. 1002, ¶ 32. The general structure is depicted below; along with the more specific formula applying Kohn’s expressly “preferred” substituents:



Ex. 1009, col. 1:30-2:20 and 5:14-19. The ’729 patent described the preferred substituents as follows: “n is 1,” R is “especially benzyl,” and “[t]he most preferred R1 group is methyl.” *Id.* at 5:14-19.

The above genus of the ’729 patent covers lacosamide. Lacosamide is the R-enantiomer of the claimed compound, where R is “aryl lower alkyl,” *i.e.*, the “especially [preferred] benzyl,” *id.* at 5:17-18, R1 is “lower alkyl,” *i.e.*, the “most preferred . . . methyl,” *id.* at 5:17-19, and one of R2 and R3 is “hydrogen” and the other “lower alkyl,” *i.e.*, methylene, “substituted with at least one . . . electron donating group,” *i.e.*, “methoxy,” *id.* at 1:55-61 and 4:37.

As with other prior art references, the '729 patent reiterates the preference for the R-isomer (*i.e.*, the D-stereoisomer). Ex. 1002, ¶ 34; Ex. 1009 at 10:27 (“The D stereoisomer is preferred.”). The '729 patent also includes data supporting the preference for the R-isomer. Ex. 1009, 58-61, Tbl. 1; Ex. 1002, ¶ 34. The '729 patent cites known techniques for synthesizing and separating stereoisomers. Ex. 1009, 15:31-16:4.

Finally, the '729 patent discloses that “compounds of the present invention exhibit excellent anticonvulsant activity,” *id.* at 16:5-7, that the compounds are administered with a “pharmaceutically acceptable carrier,” *id.* at 17:53-54, and that “[t]he use of such media and agents for pharmaceutical active substances is well known in the art,” *id.* at 17:56-58.

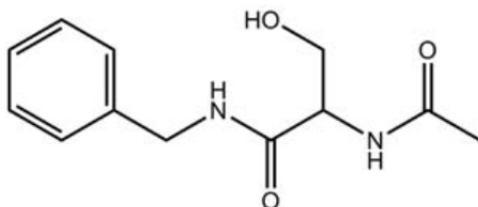
#### **E. Kohn 1993 (Ex. 1017)**

In 1993, Dr. Kohn published additional results in the *Journal of Medicinal Chemistry* providing further information about preferences in the chemical structure of potent anticonvulsants derived from the methyl compound AAB of Cortes. Ex. 1017. The report evaluated an “expanded set of C( $\alpha$ )-heteroaromatic analogs” of the methyl compound AAB as the lead compound. Ex. 1017 at 3350. Based on these studies, a POSA knew that “improved activity resulted by the ***positioning of a heteroatom two atoms removed from the C( $\alpha$ )-site [i.e., the  $\alpha$ -carbon.***” *Id.* at 3354 (emphasis added).

Further, the art taught a POSA that oxygen was the best heteroatom to have at that position, *i.e.*, two atoms removed from the  $\alpha$ -carbon. Ex. 1002, ¶ 38. Kohn 1993 explains prior results demonstrating that “the anticonvulsant activity . . . decreased in proceeding from oxygen to nitrogen to sulfur containing C( $\alpha$ )-heteroaromatic derivatives.” *Id.* Moreover, Kohn 1993 confirmed that an alkylated heteroatom provided increased activity. *Id.* (“[I]ncreased anticonvulsant activity generally accompanied the placement of a substituted (*alkylated*) *heteroatom two atoms removed from the amino acid  $\alpha$ -carbon.*” (emphasis added)). Overall, the teachings in Kohn 1993 would have confirmed that the methoxymethyl group was a preferred substituent on the  $\alpha$ -carbon.

#### F. Choi (1995) (Ex. 1010)

In 1995, Kohn and Choi published a report in *Tetrahedron Letters* (“Choi” Ex. 1010) describing the synthesis of additional derivatives  $\beta$ -halogen amino acid derivatives in one step from the corresponding serine compound and trimethylsilyl halide. Ex. 1010 at 7011, abst. Choi identifies several compounds as being particularly useful as an intermediate in the formation of new anticonvulsants, including the hydroxymethyl compound 2d (-CH<sub>2</sub>OH bound to the  $\alpha$ -carbon):



**Hydroxymethyl Compound (Choi 2d)**

In particular, Choi stated that, “[f]or an ongoing project to prepare bioactive amino acid derivatives, we needed the  $\beta$ -halogen compounds 2a-2c” (*id.* at 7011) and that, for this purpose, “(2d) was converted to 2a-2c in acetonitrile” (*id.* at 7012).”

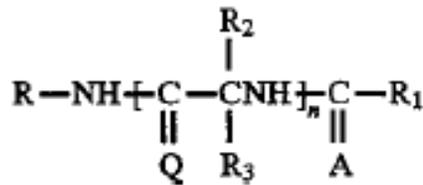
Notably, the hydroxymethyl compound (2d) of Choi is the same as compound 49 in Kohn 1993, Ex. 1017 at 335, and compound 107d in LeGall, Ex. 1008 at 133, Tbl. 35, to which Choi expressly refers the reader, Ex. 1010 at 7013 n.16 (citing LeGall).

#### **G. ’301 Patent (1995) (Ex. 1019)**

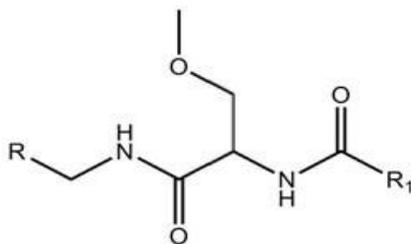
In August 1995, U.S. Patent No. 5,654,301 (“’301 patent”) issued to Patent Owner, Research Corporation Technologies, Inc., based on an application filed in 1993 that named Dr. Harold Kohn as a co-inventor. Ex. 1019.<sup>4</sup> Like the ’729 patent, the ’301 patent discloses compounds that “hav[e] central nervous system (CNS) activity [and] which are useful in the treatment of epilepsy and other CNS disorders” having the following general formula claimed in claim 39:

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<sup>4</sup> In IPR2014-01126, Patent Owner did not dispute the ’301 patent’s status as § 102(e) prior art. Petitioner reserves the right to examine any antedating evidence if introduced, and also to request *ex parte* reexam based on double patenting and move to consolidate the reexam with this IPR under 37 C.F.R. § 42.122(a).



*Id.* at 1:29-40; cl. 39. Dependent claim 40, which depends from claim 39, specifies that “one of R2 and R3 is hydrogen and the other is lower alkyl substituted with an electron donating group.” *Id.* at cl.40. Dependent claim 42 further specifies that “one of R2 and R3 is methyl substituted with an electron donating group.” *Id.* at cl.42. Dependent claim 43 specifies that the “electron donating group” of claim 42 “is lower alkoxy,” *id.* at cl.43, and claim 44 further specifies that the “lower alkoxy” of claim 43 “is methoxy,” *id.* at cl.44. Thus, claim 44 of the '301 patent discloses that one of R2 and R3 is hydrogen, and the other is methoxymethyl. Claim 45 specifies that n is 1. This combination of substituents leads a POSA to the following structure:



Regarding R and R1, the '301 patent states that the preferred value of R is “especially benzyl,” and “[t]he most preferred R1 group is methyl.” Ex. 1019,

5:12-14. The patent further states that “it is especially preferred that n is 1,” *id.* at 10:19, and that the “D stereoisomer is preferred,” *id.* at 11:20.

After the '301 patent issued, Patent Owner filed a request with the PTO for an extension of patent term of the '301 patent. (Ex. 1020). In that request, Patent Owner represented to the PTO that the claims of the '301 patent “read on the approved product and claim the active ingredient of the final approved product lacosamide.” Ex. 1020 at 5.

## **VII. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS FOR UNPATENTABILITY**

### **A. Ground 1A: Claims 1 and 3-8 Are Anticipated by LeGall**

Petitioner recognizes the Board’s decision in IPR2016-00204 with regard to LeGall. However, in order to remain consistent with Argentum’s petition in IPR2016-00204 and Mylan’s petition in IPR2016-01101, Petitioner includes arguments pertaining to LeGall. As set forth by Argentum and Mylan, LeGall discloses both “racemic lacosamide” and R-lacosamide which falls within the scope of claims 1 and 3-8. Those claims are anticipated.

#### **1. New evidence establishes that LeGall is prior art**

As explained by Argentum and Mylan, Patent Owner previously avoided an IPR by disputing whether LeGall was a “printed publication” under § 102(b). Prelim. Resp. 27-30; Dec. 8-9. Contrary to its earlier position, Patent Owner has now admitted that LeGall qualifies as prior art. Ex. 1004 at ¶ 87. Given the Patent

Owner's about-face, the only reasonable inference is that the Patent Owner no longer has a basis upon which to dispute the prior art status of LeGall. Patent Owner has stipulated, "for purposes of this litigation [*i.e.*, the district court litigation], LeGall 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)." Ex. 1004 at ¶ 87. This new evidence establishes that LeGall is prior art, particularly given the lower burden of proof in this IPR proceeding.

Second, Argentum and Mylan explained that the University of Houston, which was the original assignee of the '551 patent, Ex. 1027 at 0014, offered a fascinating and damning response to a Texas Public Information Act request filed by Argentum's representative seeking information regarding the public's access to the LeGall thesis, including a copy of the deposition transcript taken of a University representative Dr. John Lehner pursuant to the defendants' subpoena in the litigation. Ex. 1028 at 0011. The University denied the information request, stating that its "revenue stream will be lost or severely diminished . . . as a result of the requested information being produced," and that "it is critical that this information be withheld in order to protect the University from competitive interests." *Id.* at 0005, 0015. Rather than deny the information's existence, the University admitted that the "information is crucial to the litigation" and that

“releasing the deposition transcript” and “releasing the dates when each thesis was checked out” would “cause the University competitive harm.” *Id.* at 0005-6, 0015-16. These admissions by a financially interested, original assignee should give rise to a rebuttable presumption that the information both exists and establishes a reasonable likelihood that LeGall is prior art.<sup>5</sup>

Third, Argentum and Mylan stated additional evidence confirms that the University of Houston’s theses were generally accessible to the public. From the late-1980s to early-1990s (before the ’551 patent’s critical date), several publications cited University of Houston theses. Ex. 1029 at 42-43 nn.8, 11, 20; Ex. 1029 at 1135 nn.21, 28; Ex. 1030 at 157-158; Ex. 1031 at 649 n.9. The public citations to other University of Houston theses during the relevant time period creates, by itself, a strong inference that LeGall was publicly accessible. Taken together, all the evidence firmly establishes a reasonable likelihood that LeGall qualifies as prior art under 35 U.S.C. § 102(b).

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<sup>5</sup> As a financially interested, original assignee who admits it possesses “crucial” and “critical” information to patentability of the ’551 patent within its control, the University is a real party in interest of Patent Owner in this IPR proceeding.

## **2. LeGall discloses “racemic lacosamide” and R-lacosamide and therefore anticipates claims 1 and 3-8**

As explained by Dr. Wang and argued by Argentum and Mylan, LeGall discloses both R-lacosamide and “racemic lacosamide” and therefore anticipates claims 1 and 3-8. There can be no dispute that racemic lacosamide and R-lacosamide, *i.e.*, compound 107e, possesses each of the Ar, Q, and Q1 substituents of those claims (including wherein Ar is benzyl, Q is methoxymethyl, and Q1 is methyl). Ex. 1002, ¶ 56.

Furthermore, Argentum and Mylan argued “racemic lacosamide” of LeGall meets the limitation “a compound in the R configuration” under the BRI, which covers R-isomer compounds, whether the R-isomer is substantially pure or mixed with the S-isomer. Ex. 1002, ¶ 55-58. Compound 107e meets this limitation because 50% of the molecules in the racemate that LeGall made are in the R configuration.

Finally, as explained by Argentum and Mylan, the structure of compound 107e depicted in LeGall describes a genus of exactly two isomers: R-lacosamide and S-lacosamide. *Id.* ¶ 58. When LeGall made racemic lacosamide, he necessarily made both the R and S-isomers. When the spectral properties of compound 107e were tested, it was dissolved in solvent (DMSO), thereby dissociating any crystal into its two component R- and S-isomers. Ex. 1008 at 149-150. Whether as a crystal or when dissolved in solution, a POSA would “at

once envisage each member of this limited class” of R-lacosamide and S-lacosamide (107e). *E.g., In re Petering*, 301 F.2d 676, 681 (CCPA 1962). This disclosure falls within the scope of claims 1 and 3-8 and therefore those claims are anticipated.

**B. Ground 1B: Claims 2 and 9-13 Are Obvious Over LeGall And The '729 Patent**

**1. Claims 2 and 9 to “substantially” or “90%” pure R- enantiomer are obvious over LeGall and '729 patent**

Claim 1 is unpatentable because its dependent claims are obvious. Claim 2 requires the R-enantiomer to be “substantially enantiopure.” Claim 9 requires “at least 90% (w/w) R stereoisomer.” For the same reasons set forth in Argentum’s petition and Mylan’s petition, these claims are, at a minimum, obvious over LeGall and the '729 patent, which together disclose: (1) both a reason to select R-lacosamide and “racemic lacosamide”; and (2) a reason to isolate and use R-lacosamide in substantially enantiopure form.

Under controlling law, there is “no need to find an express teaching to prove sufficient motivation to modify the prior art to arrive at the claimed invention, where various techniques to purify the isomers were reported in the art and, importantly, it was known that the [claimed] isomer alone provided the therapeutic effect.” *Spectrum Pharms., Inc. v. Sandoz Inc.*, 802 F. 3d 1326, 1335 (Fed. Cir. 2015); *see Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293,

1301 (Fed. Cir. 2007) (“[I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.”).

Here, as explained by Argentum and Mylan, LeGall provides a POSA with both (a) a reason to select the racemic lacosamide and R-lacosamide (107e) for further study, as well as (b) a reason to isolate and prepare pure R-lacosamide from the racemic mixture. Racemic lacosamide is identified as a promising drug candidate. Ex. 1002, ¶ 26; Ex. 1008 at 155 (stating that the “close structural analogy of this compound [i.e., lacosamide] with 86b suggests that this adduct [i.e., lacosamide] may have good anticonvulsant activity”). LeGall’s statement that lacosamide “may have good anticonvulsant activity” is an explicit reason to select it for further development. A POSA would also have recognized the attractiveness of racemic and R-lacosamide based on the ’729 patent’s statement that this class of compounds—which includes both racemic and R-lacosamide—“exhibit excellent anticonvulsant activity.” Ex. 1009 at 16:7.

Furthermore, Argentum and Mylan argued LeGall states a clear preference for the R-isomer, *i.e.*, “the D-enantiomer.” LeGall observes that the R-isomer of

compound 68a (AAB) was thirteen times more active than the S-isomer, with a comparable difference for the two stereoisomers of 68b. Ex. 1002, ¶ 70-72; Ex. 1008 at 42. LeGall further states that R-isomers are “more active and less toxic than the corresponding racemates,” therefore suggesting that R-isomers of 69a and 69b “may display even improved pharmacological properties.” *Id.* at 164-65. Given the close structural similarity of 68a and racemic lacosamide, a POSA would reasonably expect that R-lacosamide possesses improved pharmacological properties, including greater activity and less toxicity, and therefore would have been motivated to make and isolate R-lacosamide, for example, from racemic lacosamide.

The '729 patent provides further reasons for a POSA to use the R-isomer instead of the S-isomer. The '729 patent discloses and claims a genus of compounds that covers racemic lacosamide and R-lacosamide (which remain covered by the claimed genus even when narrowed to the specific “preferred” substituents disclosed in the '729 patent). Ex. 1002, ¶ 32. The '729 patent teaches that the R-isomer is “preferred.” Ex. 1002, ¶ 34; Ex. 1009 at 10:5-27. The '729 patent discloses biological data demonstrating that the R-isomers of similar compounds were at least ten times more active than their corresponding S-isomers. *Id.* col. 58-61, Tbl. 1. In the three instances where both the R- and S-isomers were

tested (AAB, APB, and the 2-furanyl derivative), the R-isomer was at least ten-fold more potent than the S-isomer. *Id.*

A POSA would have had, at a minimum, a reasonable expectation of success in making and using the claimed invention. Ex. 1002, ¶¶ 71-72, 78. A POSA would have had several known and well-recognized means of preparing and/or separating the R- and S-isomers. For example, the '729 patent explains the racemic mixture can be “separated by recognized techniques known in the art,” including fractional crystallization and chiral chromatography. Ex. 1009, 15:31-16:4. The '551 patent itself acknowledges that “the racemic mixture . . . can be resolved into the R-isomer by standard techniques known in the art such as chiral chromatography.” Ex. 1001, 8:57-61. Furthermore, a POSA could have modified the synthetic procedure in LeGall to make R-lacosamide. Ex. 1002, ¶ 70.

Other prior art references, involving this same family of amino acid derivatives, all confirm that a POSA would have known that the R-isomer was strongly preferred over the S-isomer, thus motivating the POSA to isolate or make the R-isomer. *See, e.g.*, Ex. 1018 at 919 abstr., Tbl. I; Ex. 1017 at 3355. These “background” references, even if not formally recited in a ground of unpatentability, “must be consulted when considering whether a claimed invention would have been obvious.” *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir.

2013) (reversing the Board for applying a “blinkered approach” that “failed to account for critical background information” supporting obviousness).

In summary and consistent with Argentum’s petition and Mylan’s petition, claims 2 and 9 are obvious because a POSA would have had a reason to believe that (a) racemic lacosamide, disclosed in LeGall (107e), would have “good” to “excellent” anticonvulsant activity, Ex. 1008 at 155; Ex. 1009 at 16:7; (b) R-lacosamide would be “more active and less toxic” than the racemate, Ex. 1008 at 164; and (c) it would have been routine to isolate or prepare the R-isomer using “standard techniques known in the art,” Ex. 1001 at 8:52; Ex. 1009 at 15:31-16:4.

**2. Claim 10 to a “therapeutic composition” is obvious over LeGall and the ’729 patent**

Claim 10 recites a “therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1-9 and a pharmaceutical carrier.” Claim 10 is obvious because a POSA knew to use an effective amount of the active agent and also to use a pharmaceutical carrier.

As explained above and by Argentum and Mylan, LeGall discloses racemic and R-lacosamide (107e). Ex. 1002, ¶ 25; Ex. 1008 at 133. Although the anticonvulsant activity of 107e was not reported, LeGall expressly states—and accurately predicts—that racemic lacosamide and R-lacosamide “may have good anticonvulsant activity” in light of the “close structural analogy of this compound with 86b.” Ex. 1008 at 155. LeGall thus provides a clear reason for a POSA to

select racemic lacosamide and R-lacosamide as an active agent in a therapeutic composition. Ex. 1002, ¶ 73.

**“Pharmaceutical carrier”**: The ’729 patent teaches that the genus of compounds disclosed therein—which includes racemic lacosamide and R-lacosamide—can be “compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier.” Ex. 1009 at 18:12-16. The ’729 patent also discloses numerous “pharmaceutically acceptable carriers,” including various “solvents, dispersion media, coatings, . . . absorption delaying agents, and the like,” for formulating compounds including lacosamide into “tablets,” “capsules, elixirs, suspensions, syrups” or “for injectable use.” *Id.* at 17:53-58, 16:33-37, 17:13. The ’729 patent recognizes that “[t]he use of such media and agents for pharmaceutical active substances is well known in the art.” *Id.* at 17:56-58. The pharmaceutically acceptable carriers described in the ’729 patent are mostly the very same pharmaceutical carriers disclosed in the ’551 patent. Ex. 1002, ¶ 76. Therefore, the ’729 patent teaches this limitation.

Furthermore, a medicinal chemist would have been aware of the general types of carriers that satisfy the limitation of the ’551 patent. Ex. 1002, ¶ 76.

**“Anticonvulsant effective amount”**: At the time of the invention, a POSA would have known how to identify an anticonvulsant effective amount of both racemic lacosamide and R-lacosamide. Ex. 1002, ¶ 75. A POSA could have

successfully used established FDA guidelines and known dose-finding studies for determining an effective amount of a drug. *Id.* 74; Ex. 1021 at 9, 14 (disclosing “[a] number of specific study designs . . . to assess dose-response,” including for determining “the relationship of drug dosage[] or drug concentration” to both “clinical beneficial [and] undesirable effects”); Ex. 1022 at 15-19.

Additionally, the ’729 patent, whose claims cover racemic lacosamide and R-lacosamide, expressly teaches specific anticonvulsant effective amounts that exactly coincide with the amounts described and claimed in the ’551 patent. Ex. 1001 at 10:52-59. The ’729 patent states that the compounds “exhibit excellent anticonvulsant activity,” Ex. 1009 at 16:5-8, and can be prepared as, for example, “an oral dosage unit form [that] contains between about 5 and 1000 mg of active compound,” *id.* at 16:44-47. This range is the same range the ’551 patent teaches as being an effective amount. Ex. 1001 at 10:52-59 (“about 5 to about 1000 mg”). Finally, the ’729 patent states that “the administration of an effective amount of the present compounds, in their pharmaceutically acceptable forms or the addition salts thereof, can provide an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia and other related central nervous disorders.” Ex. 1009 at 3:35-40.

A POSA would have had a reasonable expectation of success in making and using the therapeutic composition of claim 10. Ex. 1002, ¶ 78-79. First, the ’729

patent would have presumptively enabled a POSA to make and use the genus of compounds in claim 1 of the '729 patent, which encompasses racemic lacosamide and R lacosamide. *See Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (“[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.”). The '729 patent also presumptively enables a “method of treating central nervous system disorders in animals,” as recited in claim 132 of the '729 patent.

### **3. Claims 11-13 to methods of treatment are obvious over LeGall and '729 patent**

Method claims 11-13 are directed to “treating central nervous system disorders” by administering an “anticonvulsant effective amount” of the compound. Those claims are obvious over LeGall and the '729 patent for the reasons in Argentum’s petition and Mylan’s petition.

As a first point, regarding the intended recipient of the treatment (“animal” in claim 11, “mammal in claim 12, and “human” in claim 13), a POSA would know that, at the time of the invention, anticonvulsants were primarily intended for humans. Ex. 1002, ¶ 81. Indeed, as explained by Argentum and Mylan, LeGall discusses “clinical applications” of anticonvulsants used in the late 1980s as a treatment of epilepsy in humans. Ex. 1008 at 25-30. Notably, the '551 patent does not disclose any meaningful distinction between compositions and methods for use in animals versus mammals versus humans. Thus, a POSA would understand the

prior references, such as LeGall, as discussing the treatment of CNS disorders in humans.

Second, as explained above and by Argentum and Mylan, LeGall discloses racemic lacosamide and R-lacosamide. LeGall describes the compounds disclosed therein as “antiepileptic compounds.” Ex. 1008 at 43. Thus, LeGall teaches compounds that are useful for treating epilepsy, a central nervous system disorder.

Third, according to Argentum’s petition and Mylan’s petition, LeGall recognized that racemic lacosamide and R-lacosamide would have “good anticonvulsant activity.” *Id.* at 155. “[G]ood anticonvulsant activity” is another indication that the compounds could be used for “treating central nervous system disorders,” as required by claims 11-13.

Fourth, as set forth in Argentum’s petition and Mylan’s petition, LeGall screened numerous compounds for anticonvulsant activity in mice. *Id.* at 102-03, 162-63. LeGall’s data demonstrate that compounds of close structural similarity had “good” to “excellent” anticonvulsant activity. Indeed, LeGall expressly predicted that racemic lacosamide and R-lacosamide “may have good anticonvulsant activity” based on its structural analogy to the ethoxy compound. Ex. 1008 at 155; ¶ 73.

Importantly, as explained by Argentum and Mylan, the preclinical data disclosed in LeGall is the same type of preclinical data disclosed in the ’551 patent

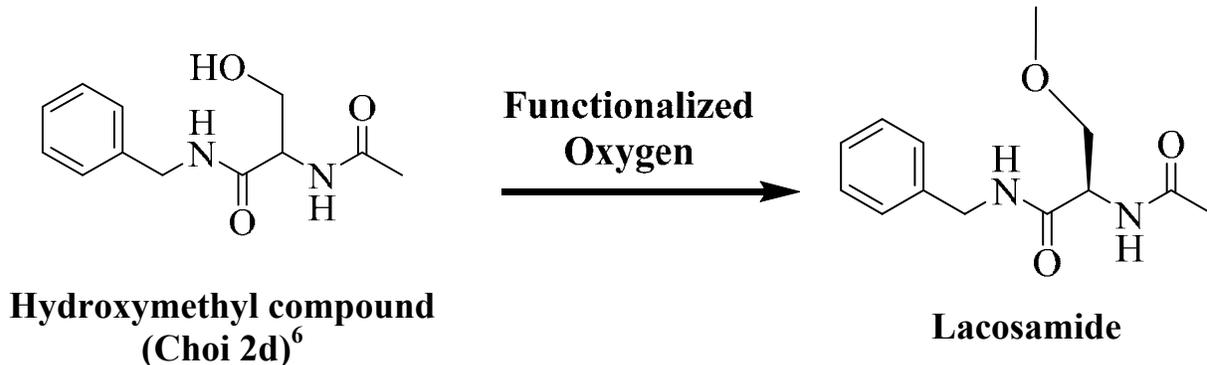
as support for its method of treatment claims. Ex. 1001 at 21:27-22:22; Ex. 1002, ¶ 81. Indeed, the '551 patent itself does not contain data on human subjects but instead relies on screening tests performed on rodents. Ex. 1001 at 21:27-22:22. The rodent tests were deemed enabling for claim 13, directed to humans. Therefore, the prior art enables a POSA to treat humans to the same extent as the '551 patent does. *See In re Epstein*, 32 F.3d 1559, 1658 (Fed. Cir. 1994) (holding that “the Board’s observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board’s finding that one skilled in the art would have known how to implement the features of the references and would have concluded that the reference disclosures would have been enabling”).

Fifth, the '729 patent provides an additional reason for a POSA to expect racemic lacosamide and R-lacosamide, from LeGall, to be useful for treating CNS disorders. 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.” Ex. 1009 at 3:9-17. The '729 patent also specifically claims the compounds in a “method of treating central nervous system disorders in animals.” *Id.* at cl. 132. A POSA would reasonably 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. Ex. 1002, ¶ 80. *See Amgen*, 314 F.3d at 1355.

Sixth, and as noted above, the '729 patent discloses the same ranges (5-1000 mg) that the '551 teaches as an anticonvulsant effective amount. Thus, a POSA would reasonably expect that the amounts disclosed in the prior art are an "anticonvulsant effective amount," as required by claims 11-13.

### C. Ground 2A: Claims 1-9 Are Obvious Over Choi and Kohn 1991



#### 1. Choi and Kohn 1991 are prior art

Choi is prior art under § 102(b) because the '551 patent is entitled only to a priority date of March 1997 (*see* Part IX *infra*), and Choi was published on September 1995. Ex. 1010 at cover page. Even if the '551 patent were entitled to a priority date of March 15, 1996, Choi qualifies as prior art under § 102(a). Kohn

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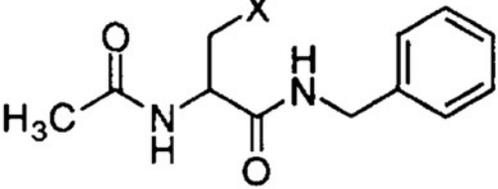
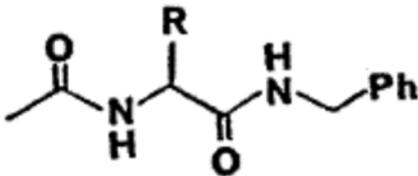
<sup>6</sup> The recited compound ("Hydroxymethyl compound (Choi 2d)") was originally presented as "Methyl compound (Cortes, AAB)." The compound name presented herein is as corrected. *See*, IPR2016-00204, Paper No. 8 at 2-3.

1991 published in 1991 and is therefore prior art under § 102(b), regardless of the '551 patent's priority date.

## **2. POSA had a reason to select Compound 2d of Choi as a lead compound**

A “lead compound” for purposes of obviousness can be “a starting reference point or points” from which a POSA would make additional modifications and arrive at the claimed compound. *Eisai*, 533 F.3d at 1359. A motivation must be identified “that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound).” *Id.* at 1357. “In keeping with the flexible nature of the obviousness inquiry, the requisite motivation can come from any number of sources and need not necessarily be explicit in the art.” *Id.* (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007)). Under some circumstances, a POSA in the field of medicinal chemistry would start further modifications with a potent lead compound. When additional information is available, however, circumstances may dictate that one start with a compound that does not exhibit the highest potency. The prior art in this case presents such a circumstance.

Here, Choi discloses several compounds that are especially useful in the synthesis of new compounds within this class of anticonvulsants. Ex. 1002, ¶ 85. Included among the compounds is the hydroxymethyl compound (-CH<sub>2</sub>OH), identified as compound 2d in Choi and as 107d in LeGall.

Choi	LeGall
 <p data-bbox="354 520 560 724"> <b>2a</b> X = Cl  <b>b</b> X = Br  <b>c</b> X = I  <b>d</b> X = OH  <b>e</b> X = F </p>	 <p data-bbox="1068 499 1128 541"><b>107</b></p> <p data-bbox="873 640 950 682"><u>107d</u></p> <p data-bbox="1247 640 1356 682">CH<sub>2</sub>OH</p>

The prior art provides two reasons to select the hydroxymethyl compound (2d) as the lead. *First*, the biological data provides a reason to select the compound as a lead compound. *Second*, Choi highlights the attractiveness of the hydroxymethyl compound as a synthetic lead, which is also structurally similar to methoxymethyl in terms of the desired “two atoms removed” oxygen atom.

**Biological Data:** Data disclosed in Kohn 1991 demonstrate a marked increase in anticonvulsant activity when the hydroxyl group is converted to a methoxy, thereby creating a functionalized oxygen two atoms from the  $\alpha$ -carbon. Specifically, Kohn 1991 provides the following data:

$\begin{array}{c} \text{O} \quad \text{X} \quad \text{O} \\ \parallel \quad   \quad \parallel \\ \text{CH}_3\text{CNH} - \text{CH} - \text{CNHCH}_2\text{Ph} \end{array}$		
Compound	X group	ED50
3k	-NHOH	~100
3l	-NHOC <sub>3</sub> H <sub>7</sub>	6.2

Ex. 1012 at 2445, Tbl. I. Here, when R is hydroxyamino (-NHOH), the ED50 potency is about 100. *Id.* But when the OH of the hydroxyamino group is functionalized to a methoxy, an approximately 16-fold increase in activity is realized. Ex. 1002, ¶ 92. This is what Kohn 1991 predicts. A POSA would understand the data to support Kohn 1991's statement that "the most potent" compounds are achieved when "a functionalized oxygen atom existed two atoms removed from the  $\alpha$ -carbon atom." Ex. 1002, ¶ 93; Ex. 1012 at 2447.

Applying this teaching, a POSA would then expect a significant increase in the activity of the hydroxymethyl compound (2d) of Choi. This expectation is further supported by the known structural similarity between the hydroxyamino group (-NHOH) and the hydroxymethyl group (-CH<sub>2</sub>OH). Ex. 1002, ¶ 88. In fact, the teachings of Choi and Kohn 1991 lead exactly to what one would expect:

$\begin{array}{c} \text{O} \quad \text{X} \quad \text{O} \\ \parallel \quad   \quad \parallel \\ \text{CH}_3\text{CNH} - \text{CH} - \text{CNHCH}_2\text{Ph} \end{array}$		
Compound	X group	ED50
2d (107d)	-CH <sub>2</sub> OH	100-300
Predicted racemic lacosamide	-CH <sub>2</sub> OCH <sub>3</sub>	Predicted: 6 to about 19
Racemic lacosamide	-CH <sub>2</sub> OCH <sub>3</sub>	8.3

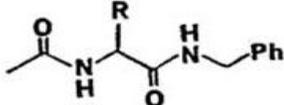
The actual increase in activity going from the hydroxymethyl compound (2d, 107d) to racemic lacosamide is approximately 12- to 36-fold. Ex. 1002, ¶ 93. This is very similar to the approximately 16-fold increase shown for the above modification. Ex. 1002, ¶ 93; Ex. 1008 at 154, Tbl. 44; Ex. 1001 at Tbl. 1.

**Synthetic Attractiveness:** Choi provided a further reason to start with the hydroxymethyl compound (2d). Choi highlighted the particularly useful synthetic characteristics of certain disclosed compounds, particularly the hydroxymethyl compound (2d). Choi states that “[f]or an ongoing project to prepare bioactive amino acid derivatives, we needed the β-halogen compounds 2a-2c,” *id.* at 7011, and that, for this purpose, “(2d) was converted to 2a-2c in acetonitrile,” *id.* at 7012. The reactivity of the -OH group in this family of amino acid derivatives is confirmed throughout Choi, which successfully converted serine derivatives (2d,5a) (each of which contain an exposed -OH group) to 3-chloro derivatives

(2a,5b). *Id.* Moreover, Choi directs the reader to LeGall in connection with compound 2d of Choi (compound 107d of LeGall), *id.* at 7013 n.16, which would have taught a POSA how to make the compound. Ex. 1008 at 135-36 (explaining how the hydroxymethyl compound was prepared).

With that teaching, a POSA would have recognized that the hydroxyl group of compound 2d would present numerous synthetic advantages in the preparation of new compounds, within the '729 patent's genus of compounds described as having "excellent anticonvulsant activity." Ex. 1009 at 16:5-8. A POSA, therefore, would have considered the practical utility of the hydroxymethyl compound (2d) as a synthetic intermediate as one source of motivation to select it as a lead compound for further modification. Indeed, for this practical reason alone, a POSA would have had ample reason to select the hydroxymethyl compound (2d), notwithstanding any alleged lack of pharmaceutical activity. *See Ex Parte Zheng Xin Dong*, 2013 WL 5375700, at \*4 (P.T.A.B. Jan. 28, 2013) ("We are not persuaded . . . that the only compounds useful for evaluating obviousness are those for which the prior art has provided specific comparative data."); *Manual of Patent Examining Procedure* § 2143, 9<sup>th</sup> ed., rev. 07.2015 (Oct. 2015) (explaining that "a proper obviousness rejection of a claimed compound that is useful as a drug might be made beginning with an inactive compound").

In addition to the practical utility of the hydroxymethyl compound (2d) as a synthetic intermediate, the compound also bears close structural similarity to racemic lacosamide and R-lacosamide, disclosed in LeGall. The two compounds are listed next to each other as 107d and 107e in Table 35. Ex. 1008 at 133.

 <u>107</u>	
No.	R
<u>68a</u>	CH <sub>3</sub>
<u>107a</u>	CN
<u>107b</u>	CONH <sub>2</sub>
<u>107c</u>	COOCH <sub>2</sub> CH <sub>3</sub>
<u>107d</u>	CH <sub>2</sub> OH
<u>107e</u>	CH <sub>2</sub> OCH <sub>3</sub>

Notably, both the hydroxymethyl compound (107d) and racemic lacosamide (107e) of LeGall possess the optimal oxygen atom “two atoms removed” from the  $\alpha$ -carbon. To a POSA, this “two atoms removed” placement of the methoxymethyl group (-CH<sub>2</sub>OCH<sub>3</sub>) group would have been a highly desirable feature of anticonvulsant compounds. Ex. 1002, ¶ 91; Ex. 1012 at 2447; Ex. 1017 at 3354. The only difference between these compounds is that the oxygen in 107d is a free

hydroxyl whereas, lacosamide 107e, the oxygen is functionalized (methoxy). This close structural similarity—and the desirable “two atoms removed” arrangement—is yet another reason for a POSA to have selected compound 2d of Choi (compound 107d of LeGall) as a lead compound for further modification towards synthesis of lacosamide 107e, which is discussed next.

### **3. POSA had a reason to modify the hydroxymethyl compound to a “*functionalized oxygen*” group**

The prior art establishes a known structure-activity relationship for anticonvulsant activity that would have motivated a POSA to modify the hydroxymethyl compound (2d) of Choi to arrive at racemic lacosamide and R-lacosamide. The prior art expressly emphasized that “the most potent” compounds were achieved when “a *functionalized oxygen* atom existed two atoms removed from the  $\alpha$ -carbon atom.” Ex. 1012 at 2447 (italics in original). Kohn reiterated this teaching in his 1993 article, stating that “increased anticonvulsant activity generally accompanied the placement of a substituted (alkylated) heteroatom two atoms removed from the amino acid  $\alpha$ -carbon.” Ex. 1017 at 3354. Accordingly, a POSA would use these teachings as an explicit basis to improve the activity of the hydroxymethyl compound (2d) of Choi. Ex. 1002, ¶ 90.

The simplest “functionalized,” or “alkylated,” oxygen atom is a methoxy group (-OCH<sub>3</sub>). Ex. 1002, ¶ 91. Due to its simplicity, methoxy would be the first functional group a POSA would choose as the functionalized oxygen suggested by

Kohn 1991. Modifying the free hydroxyl group of compound 2d follows Kohn 1991's teaching of functionalizing the heteroatom with an alkyl group. Ex. 1002, ¶ 92. Moreover, converting the hydroxyl to methoxy is the smallest addition to the compound possible that will functionalize the hydroxyl group, consistent with Kohn 1991's teaching about the steric limitation on the  $\alpha$ -carbon chain. Ex. 1002, ¶ 92. That modification also does not change the distance between the oxygen and the  $\alpha$ -carbon, thus maintaining the desired "two atom" separation taught by Kohn 1991. Furthermore, even without the express teaching of Kohn, modifying a hydroxyl to a methoxy is a common and routine choice in drug design. Ex. 1002, ¶ 95. This single, simple modification is all that a POSA would need to do in order to yield racemic lacosamide, as required by claims 1 and 3-8 of the '551 patent.

Furthermore a POSA would have had a reason to make or isolate R-lacosamide. Kohn 1991 itself expressly teaches that, with respect to this class of compounds, "in each case the anticonvulsant activity resided primarily in the R stereoisomer." Ex. 1012 at 2444. A POSA would read that teaching as a more than sufficient reason to make or isolate the R-isomer, and would have known how to do so using "recognized techniques known in the art." Ex. 1009, 15:31-16:4.

#### **4. POSA would have a Reasonable Expectation of Success in making Raceamic Lacosamide and R-Lacosamide**

Finally, a POSA would have had a very high expectation of making lacosamide and racemic lacosamide from the prior art. Ex. 1002, ¶ 95. Converting

the hydroxymethyl, as disclosed in Choi, to methoxymethyl is a routine chemical procedure. Ex. 1002, ¶ 95. A well-known example of this synthetic reaction is the Williamson ether synthesis. Ex. 1011 at 1021-1037; Ex. 1023 at 1044. In fact, the '551 patent employed this same process to convert the hydroxymethyl group to the methoxymethyl group of lacosamide. Ex. 1001 at col. 5-6, Scheme 1 (conversion of compound 4 to 5).

Further, the '551 patent itself identifies no particular processing conditions that POSA would need to know to perform this synthetic step, Ex. 1001 at col. 5-6, thus creating a presumption that a POSA would have known how to carry it out. *See Epstein*, 32 F.3d at 1568. A further expectation of success arises from the prior art '301 patent, which claims a methoxymethyl group as the R<sub>2</sub> substituent, *i.e.*, the  $\alpha$ -carbon group in claim 44, Ex. 1019 at 94:13-14, that covers lacosamide and R-lacosamide, Ex. 1020 at 5, which likewise creates a presumption of enablement. *See Amgen*, 314 F.3d at 1355.

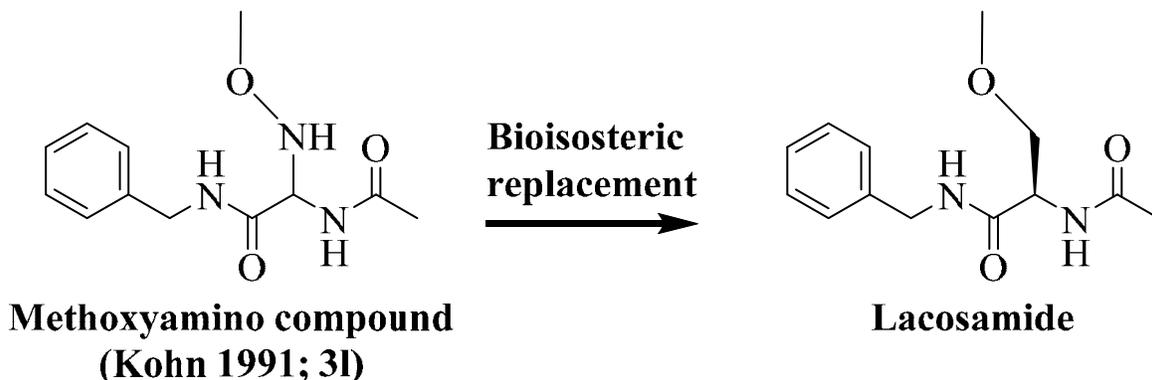
As explained in Ground 1B above, a POSA would have wanted to and would have known how to synthesize the R-isomer or isolate it from the racemate.

**D. Ground 2B: Claims 10-13 Are Obvious Over Choi, Kohn 1991, And '729 Patent**

Choi and Kohn 1991 render obvious each of claims 1-9. Dependent claims 10-13 are obvious over Choi, Kohn 1991, and the '729 patent, based on the same

rationales and prior art disclosures discussed in Ground 1B above. *See also* Claims Chart in Part XI below.

**E. Ground 3A: Claims 1-9 Are Obvious Over Kohn 1991 and Silverman**



**1. Kohn 1991 and Silverman are prior art**

Kohn 1991 (Ex. 1012) and Silverman (Ex. 1013) are both 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.

**2. Activity data and bioisosterism suggest the change from methoxyamino to methoxymethyl (lacosamide)**

A POSA would often, but not always, be motivated to select one of the most potent compounds in the prior art as a lead compound. In this case, Kohn 1991 provided a very potent compound as a starting point—the methoxyamino compound (31) being the most potent. Ex. 1002, ¶ 105. The methoxyamino compound has an ED<sub>50</sub> of 6.2 mg/kg. Ex. 1012, Tbl. I. This compound would have

been of immediate interest to a POSA based on its activity and would have been selected for optimization. Ex. 1002, ¶ 105.

Starting with the methoxyamino compound, a POSA would have had a reason to modify the methoxyamino moiety for at least two reasons. First, the methoxyamino moiety is not a common moiety used in the compounds that result in commercial pharmaceuticals. Ex. 1002, ¶ 106. Second, the methoxyamino moiety may present synthetic and stability issues. Ex. 1002, ¶ 106.

Having recognized the desire to modify the methoxyamino moiety, a POSA would utilize the well-known concept of bioisosterism and bioisosteric replacements. Ex. 1002, ¶ 107. The POSA would have considered a variety of structural modifications to improve the pharmacokinetic properties of the lead compound. At the time, it was well known that a methylene group (-CH<sub>2</sub>-) is a bioisosteric replacement for a secondary amino group (-NH-). Ex. 1002, ¶107; Ex. 1013, Silverman at 19; Ex. 1024, Wilson at 30; Ex. 1025, Thornber at 563, 564 Tbl. 1. Here, substitution of the -NH- group with the -CH<sub>2</sub>- group would result in a methoxymethyl group. Ex. 1002, ¶ 107. A methoxymethyl moiety is a more common and acceptable moiety for pharmaceutically active compounds. Ex. 1002, ¶ 107. The resulting compound is lacosamide. *Id.* ¶ 107.

Prior art data also established the equivalence between the amino and the methylene group off the  $\alpha$ -carbon. Kohn 1991 reported that going from an amino compound to a methyl compound retained the same activity:

<b>R Group</b>	<b>ED<sub>50</sub> (mg/kg)</b>
-NH <sub>2</sub>	65.1
-CH <sub>3</sub>	76.5
-NHOCH <sub>3</sub> (compound 3l)	6.2
-CH <sub>2</sub> OCH <sub>3</sub> (racemic lacosamide)	7.6

When R is -NH<sub>2</sub>, the ED<sub>50</sub> is 65.1 mg/kg. The ED<sub>50</sub> of the methyl compound is essentially the same, 76.5 mg/kg. Ex. 1002, ¶¶ 108, 109. When the R group is changed from -NH<sub>2</sub> group to methoxyamino (compound 3l), one sees an approximately 10-fold increase in activity. Given the bioisosterism, a POSA would expect a similar increase in activity when the R group is changed from methyl to methoxymethyl (lacosamide). In fact, that is exactly what one sees: an approximately 10-fold increase in activity from methyl to methoxymethyl (lacosamide). Likewise, and further confirming the bioisosterism for this class of compounds, substitution of the -NH- in compound 3l with -CH<sub>2</sub>- (to create racemic lacosamide) maintains high potency (ED<sub>50</sub> 6.2 mg/kg vs. 7.6 mg/kg, which are essentially the same). Ex. 1002, ¶ 109. Thus, 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.

A POSA would have succeeded in synthesizing a methoxymethyl at the  $\alpha$ -carbon position: the '551 patent itself provides sparse detail regarding this synthetic step, Ex. 1001, col. 5-6, and methoxymethyl is specifically claimed at the  $\alpha$ -carbon position in the '301 patent, Ex. 1019 at 94:13-14, cl.44, both of which create a presumption of enablement. *See Epstein*, 32 F.3d at 1568; *Amgen*, 314 F.3d at 1355.

Furthermore, as explained in Ground 1B above, a POSA would have wanted to and would have known how to synthesize or isolate the R-isomer from the racemic mixture. Indeed, Kohn 1991 itself expressly teaches that, with respect to this class of compounds, “in each case the anticonvulsant activity resided primarily in the R stereoisomer.” Ex. 1012 at 2444. A POSA would read that teaching as a more than sufficient reason to make or isolate the R-isomer, and would have known how to do so using “recognized techniques known in the art.” Ex. 1009, '729 patent, 15:31-16:4.

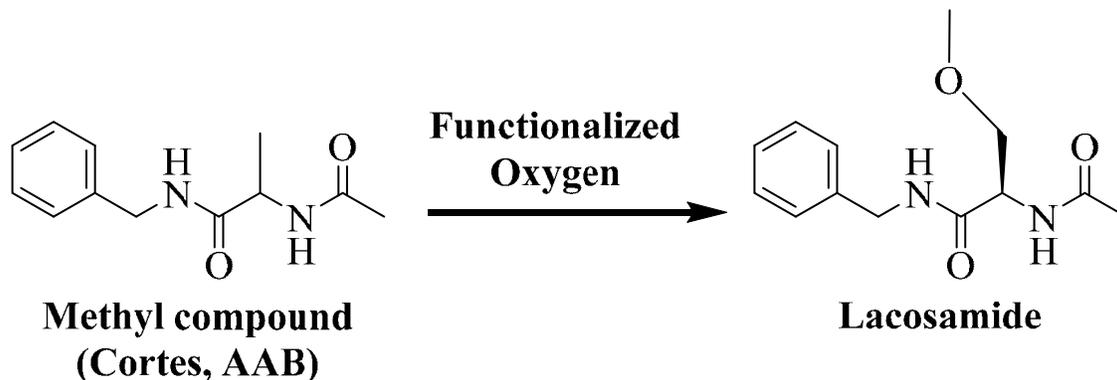
Finally, the mere fact that “better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012); *see In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989). A “lead compound analysis must, in keeping with KSR, not rigidly focus on the selection of a single, best lead compound.” *Daiichi Sankyo Co. v. Matrix Labs.*,

*Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). Notwithstanding any argument the Patent Owner may make, a POSA would have selected the methoxyamino compound (31) as a starting point, even with the existence of other prior art compounds that had similar or marginally lower ED<sub>50</sub> values. Ex. 1002, ¶ 109. A POSA would have known that the methoxyamino compound (31) is indisputably suitable (and presumptively enabled) for use as an anticonvulsant, given its “preferred” structure disclosed and claimed for “treating central nervous system disorders in animals” in the ’729 patent, Ex. 1009 at 1:30-2:20, 5:14-19, cl. 132, and was the most potent analogue disclosed in Kohn 1991. *See Amgen*, 314 F.3d at 1355.

**F. Ground 3B: Claims 10-13 Are Obvious Over Kohn 1991, Silverman, and ’729 Patent**

Kohn 1991 and Silverman render obvious each of claims 1-9. Dependent claims 10-13 are obvious over Kohn 1991, Silverman, and the ’729 patent, based on the same rationales and prior art disclosures discussed in Ground 1B above. *See also* Claims Chart in Part XI below.

**G. Ground 4A: Claims 1-9 Are Obvious Over Cortes and Kohn 1991**



**1. Cortes and Kohn 1991 are prior art**

Kohn 1991 (Ex. 1012) and Cortes (Ex. 1015) are both prior art under § 102(b) because they were published in 1991 and 1985, respectively, which is more than one year before the earliest possible priority date of the '551 patent.

**2. POSA had a reason to select the methyl compound of Cortes or Kohn 1991 as a lead compound**

Consistently repeated throughout the prior art is the teaching that the methyl compound (AAB, from Cortes) is an excellent lead compound for the development of anticonvulsant agents. In fact, the methyl compound was the lead compound used in virtually all of Dr. Kohn's studies, and a POSA would have had a reason to follow this lead in investigating further modifications to that compound. Ex. 1015, Cortes at 604 (stating that "[p]romising results" were observed for the methyl compound, which was "slated for additional screening" for that reason); Ex. 1008, LeGall at 132 ("Compounds 107a-e were selected as polar analogues of the potent

anticonvulsant agent, 2-acetamido-N-benzylpropionamide (68a).”); Ex. 1018, Kohn 1990 at 1018 (“Excellent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing an N-benzylamide moiety, an acetylated amino group, and ... a methyl (2a) ... substituent on the  $\alpha$ -carbon.”); Ex. 1018, Kohn 1991 at 2444 (“(R,S)-2-Acetamido-N-benzyl-2-methylacetamide (2a) represented the parent compound in this study wherein the  $\alpha$ -methyl group was replaced by select functionalized nitrogen, oxygen, and sulfur substituents (Table I).”).

These and other studies detailed the ability to functionalize the methyl compound and prepare other promising anticonvulsant agents having excellent pharmacological activity. Based on these repeated teachings and successes, a POSA would have selected the methyl compound as a lead compound. Ex. 1002, ¶ 119.

### **3. POSA had a Reason to modify the Methyl Substituent to a Methoxymethyl**

Having selected the methyl compound, a POSA would have modified it according to the teachings of Kohn 1991 by adding a functionalized oxygen such that the oxygen was two atoms away from the  $\alpha$ -carbon. Ex. 1002, ¶ 120.

Moreover, Kohn 1991 taught that a small alkyl group was preferred on the functionalized oxygen atom. Ex. 1002, ¶ 120. The simplest and most obvious way

to achieve this would be to add a methoxy group, thus creating the methoxymethyl compound, *i.e.*, lacosamide.

In addition to Kohn's structure-activity relationship guidance, the available biological activity provided a strong reason for a POSA to add a methoxy group to the methyl compound AAB. Ex. 1002, ¶ 121. The corresponding amino compound was about equipotent with the methyl compound AAB. When a methoxy group was added to the amino group, to form the methoxyamino compound, one realized a ten-fold increase in potency:

<b>R Group</b>	<b>ED<sub>50</sub> (mg/kg)</b>
-NH <sub>2</sub>	65.1
-CH <sub>3</sub>	76.5
-NH <sub>2</sub> CH <sub>3</sub> (compound 31)	6.2
-CH <sub>2</sub> OCH <sub>3</sub> (racemic lacosamide)	7.6

Furthermore, a POSA would understand that methylene (-CH<sub>2</sub>-) is a bioisosteric replacement for a secondary amino group (-NH-). Ex. 1002, ¶ 122; Ex. 1013, Silverman at 19; Ex. 1024, Wilson at 30; Ex. 1025, Thornber at 563, 564 Tbl. 1. Thus, a POSA would reasonably expect that the ten-fold increase in potency seen with the amino to methoxyamino conversion would also bear out in the methyl to methoxymethyl, *i.e.*, lacosamide, conversion. Therefore, starting from the methyl compound, a POSA would have had a strong motivation to add a methoxy group in order to produce a similar increase in potency.

A POSA would have had a reasonable expectation of success in synthesizing lacosamide based on the techniques in Cortes and Kohn 1991. Ex. 1002, ¶ 123. The methyl compound had been used as a lead compound previously and a POSA would have had ample tools at their disposal to generate lacosamide. In addition, the '551 patent itself confirms that basic, well-known synthetic methods can be used to prepare lacosamide and its methoxymethyl group. Ex. 1001, col. 5-6. Moreover, methoxymethyl is specifically claimed at the  $\alpha$ -carbon position in the '301 patent, Ex. 1019 at 94:13-14, cl.44. These facts create a presumption of enablement. *See Epstein*, 32 F.3d at 1568; *Amgen*, 314 F.3d at 1355.

Furthermore, a POSA would have had a reason to make or isolate R-lacosamide. Kohn 1991 itself expressly teaches that, with respect to this class of compounds, “in each case the anticonvulsant activity resided primarily in the R stereoisomer.” Ex. 1012 at 2444. A POSA would read that teaching as a more than sufficient reason to make or isolate the R-isomer, and would have known how to do so using “recognized techniques known in the art.” Ex. 1009, 15:31-16:4.

#### **H. Ground 4B: Claims 10-13 Are Obvious Over Cortes, Kohn 1991, And '729 Patent**

Cortes and Kohn 1991 render obvious each of claims 1-9. Dependent claims 10-13 are obvious over Cortes, Kohn 1991, and the '729 patent, based on the same rationales and prior art disclosures discussed in Ground 1B above. *See also* Claims Chart in Part XI below.

## VIII. THERE ARE NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

If the Patent Owner does present secondary evidence of nonobviousness in its preliminary response, the Board should refuse consideration of that evidence, and institute trial, because “detailed consideration of [a patentee’s] secondary consideration evidence may not be undertaken until [the petitioner] has had an opportunity to test it.” *Amneal Pharms. v. Supernus Pharms.*, IPR2013-00368, at 12-13 (PTAB Dec. 17, 2013) (instituting trial despite patentee’s submission of district court evidence of secondary considerations). Patent Owner did not submit any evidence of secondary considerations with its preliminary response in IPR2014-01126, taking the position instead that “objective indicia typically are better considered in the context of a trial,” and stating that it would present such evidence “as part of its Patent Owner Response.” Prelim. Resp. 56-57.

In any event, any newly-presented secondary considerations would not overcome the strong *prima facie* case of obviousness presented in this petition. **First**, lacosamide’s potency was not unexpected; LeGall recognized that racemic lacosamide, disclosed in LeGall, would have “good anticonvulsant activity.” Ex. 1008 at 155. The prior art expressly taught that the R-isomer of this class of anticonvulsant amino acids was “more active and less toxic” than the racemate. Ex. 1008 at 164; Ex. 1012 at 2444. **Second**, the actual data comparing R-lacosamide to racemic lacosamide (the closest prior art) fail to demonstrate any

unexpected results. Ex. 1002, ¶ 137. Although the R-isomer has a modestly improved potency compared to the racemate, that result is entirely expected based on the prior art knowledge that the anticonvulsant activity “reside[s] primarily in the R stereoisomer.” Ex. 1012 at 2444; Ex. 1002, ¶ 133. **Third**, any alleged commercial success is significantly undermined by the fact that both the ’729 patent and the ’301 patent broadly claimed, and thus would have blocked, the sale of lacosamide. Ex. 1009; Ex. 1019; Ex. 1020 at 5 (Patent Owner stating that “claims 39-45 [of the ’301 patent] . . . claim the active ingredient of the final approved product lacosamide”); see *Galderma Labs. v. Tolmar, Inc.*, 737 F.3d 731, 740-41 (Fed. Cir. 2013). **Fourth**, “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). **Fifth**, any alleged unmet need for an antiepileptic drug (“AED”) prior to 1996 must be evaluated against lacosamide’s rivals at the time—including gabapentin, lamotrigine, felbamate, and vigabatrin. A 1994 review article described these “new AEDs” as having “desirable properties.” Ex. 1033, pp. S7-S8, tbl. 2 (summarizing “desirable properties” of new AEDs). **Sixth**, to the extent a need did exist prior to 1996, lacosamide has not met that need: “current medications” as of 2013, including lacosamide, “fail to control seizures in 20-30% of patients.” Ex. 1034 at 757, abst. **Seventh**, on information and belief, Patent Owner’s licensee has spent

over 25% of net sales of VIMPAT® on marketing the product since it launched in 2009, which is more than most other AEDs in the early years of their launch during this same time frame.

## **IX. THE CLAIMS ARE NOT ENTITLED TO THE PROVISIONAL FILING DATE**

While noncompliance with § 112 is not directly challengeable in IPR, it is a basis to break a priority claim to an earlier application. *See SAP Am., Inc. v. Pi-Net Int'l*, IPR2014-00414 (Paper 11, Aug. 18, 2014). In like manner, noncompliance with the reissue statute, § 251, should be a basis in IPR to break a priority claim that was improperly added via reissue. *See In re Serenkin*, 479 F.3d 1359, 1365 (Fed. Cir. 2007) (reissue unavailable to “undo the consequences of his attorney’s conscious decision to give up an earlier filing date”).

Here, Patent Owner made a “conscious decision to give up an earlier filing date” when its attorney, Mark Cohen, on May 20, 1998, intentionally deleted the provisional priority claim that was originally included in the ’688 application. Ex. 1006 (claiming priority to provisional no. 60/013,522). The ’688 application issued as the ’475 patent on June 30, 1998, without any priority claim. Ex. 1005 at 1 (no priority claim). The reissue application was filed on January 28, 2002, solely to add the priority claim back into the specification. Ex. 1026 at ¶¶ 9, 20-21.

To be sure, reissue can be used to add or perfect a priority claim where such claim was defective or never included in the application by “inadvertence,

accident, or mistake.” *Serenkin*, 479 F.3d at 1364; *see Fontijn v. Okamoto*, 518 F.2d 610, 623 (CCPA 1975) (reissue appropriate where patentee failed to notify PTO of earlier-filed copending applications); *Brenner v. State of Israel*, 400 F.2d 789, 790 (D.C. Cir. 1968) (reissue appropriate where attorney made a clerical error by failing to file a certified copy of foreign application). Such errors of “inadvertence, accident, or mistake” are different from “errors of judgment” that cannot be corrected via reissue. *Serenkin*, 479 F.3d at 1364. Here, Mr. Cohen made an intentional “error of judgment,” as it were. On May 20, 1998, after being contacted by the examiner and told the priority claim was improper, Mr. Cohen specifically authorized the examiner to delete the priority claim. Ex. 1035 (“Attorney authorized” deletion of priority claim). Having surrendered the earlier filing date to the public (and with it any possible “provisional rights” earlier than 18 months after the regular filing date),<sup>7</sup> Patent Owner cannot use reissue to “undo the consequences of his attorney’s conscious decision to give up an earlier filing date.” *Serenkin*, 479 F.3d at 1365. Therefore, the ’551 patent’s effective filing date is March 17, 1997, which makes Choi a § 102(b) reference that cannot be antedated.

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<sup>7</sup> Conversion of a provisional to a nonprovisional application is governed by 37 C.F.R § 1.53(c)(3), the requirements of which can be waived, *id.* § 1.183. Once converted, the application is “accorded the original filing date of the provisional.”

**X. THE BOARD SHOULD NOT DECLINE TO INSTITUTE BASED ON ITS DISCRETIONARY AUTHORITY UNDER 35 U.S.C. § 325(d)**

Only certain aspects of Ground 1 of the Argentum petition were previously presented in IPR2014-01126, which Patent Owner evaded by arguing that LeGall was not a “printed publication.” Prelim. Resp. 27-30. Patent Owner has now admitted that LeGall “constitutes a ‘printed publication.’” Ex. 1004 at ¶ 87. LeGall also was never considered during prosecution or reissue. Ex. 1001; Ex. 1005. Moreover, none of Grounds 3A and 3B were previously presented in IPR2014-01126. Institution is, therefore, justified. *Oracle Corporation v. Crossroads Systems, Inc.*, IPR2015-00854, Paper No. 14.

Additionally, institution of this IPR would not be duplicative of the district court litigation. In *UCB, Inc. et al. v. Accord Healthcare Inc. et al.*, 1:13-cv-01206-LPS (D. Del.), Patent Owner has asserted only claims 9, 10, and 13, Ex. 1004 at ¶¶ 53-81, leaving the remaining claims outside of the litigation and available against the public. Petitioner, by contrast, seeks to cancel all claims of the ’551 patent, and thereby entirely remove the ’551 patent from the Orange Book more expeditiously than would be possible in a protracted and expensive Hatch-Waxman litigation challenging all remaining patent claims. The speedy cancellation of invalid patents, in an effort to further improve patent quality, is precisely the result Congress intended when it passed the America Invents Act. H.R. Rep. No. 112-98, pt. 1, at 85 (2011). Under these circumstances, public policy strongly favors institution.

## XI. CLAIMS CHART FOR DEPENDENT CLAIMS 2 AND 9-13

'551 Patent Dependent Claims		Prior Art Citations
2. The compound according to claim 1 which is substantially enantiopure.	<i>R (or D) configuration preference and isolation techniques:</i> <ul style="list-style-type: none"> <li>• Ex. 1009, '729 patent at cl.82, cl.109, Tbl. 1, 9:56-68, 10:5-27, 15:29-16:4, 16:7.</li> <li>• Ex. 1008, LeGall thesis at 42, 155, 164-65, 166.</li> <li>• Ex. 1017, Kohn 1993 at 3355.</li> <li>• Ex. 1018, Kohn 1990 at 919 abstr.</li> </ul>	
9. The compound according to claim 8 which contains at least 90% (w/w) R stereoisomer.		<ul style="list-style-type: none"> <li>• Same as claim 2.</li> </ul>
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.	<i>Pharmaceutically acceptable carrier:</i> <ul style="list-style-type: none"> <li>• Ex. 1008, LeGall thesis at 43, 155.</li> <li>• Ex. 1009, '729 patent at 16:33-37, 17:13, 17:53-58, 18:12-16.</li> </ul> <i>Anticonvulsant effective amount:</i> <ul style="list-style-type: none"> <li>• Ex. 1021, FDA Guidelines at 9, 13.</li> <li>• Ex. 1022, Schmidt at 15-19.</li> <li>• Ex. 1009, '729 patent at cl.132, 3:35-40, 16:5-8, 16:44-47, 18:12-16.</li> </ul>	
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.	<i>Treatment of CNS disorders in a human:</i> <ul style="list-style-type: none"> <li>• Ex. 1008, LeGall thesis at 25-30, 43, 155, 102-103, 162-163.</li> <li>• Ex. 1009, '729 patent at cl.1, 3:9-17, 16:44-47.</li> </ul> <i>Anticonvulsant effective amount:</i> <ul style="list-style-type: none"> <li>• Same as claim 10.</li> </ul>	
12. The method according to claim 11 wherein the animal is a mammal.		<ul style="list-style-type: none"> <li>• Same as claim 11.</li> </ul>
13. The method according to claim 12 wherein the mammal is a human.		<ul style="list-style-type: none"> <li>• Same as claim 11.</li> </ul>

## XII. PAYMENT OF FEES

Payment of \$23,000.00 for the fees set forth in 37 C.F.R. § 42.15(a)(1-4) accompanies this Petition by way of credit card payment. The undersigned further

authorizes payment for any additional fees that might be due in connection with this Petition to be charged to Deposit Account No. 13-2725.

**CONCLUSION**

For the foregoing reasons, the Petitioner respectfully requests that trial be instituted and that claims 1-13 be cancelled.

Respectfully submitted,

Date: June 21, 2016

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## CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this petition, that the number of words in this paper is 12,737. Pursuant to 37 C.F.R. § 42.24(d), this word count excludes the table of contents, table of authorities, mandatory notices under § 42.8, certificate of service, certificate of word count, appendix of exhibits, and claim listing.

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## CERTIFICATION OF SERVICE

The undersigned hereby certifies that this “PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*” with an accompanying Power of Attorney, Appendix of Exhibits, and Exhibits 1001-1035 were served in their entirety this 21st day of June, 2016 on the Patent Owner by serving via overnight delivery the correspondence address of record for the ’551 patent and also the Patent Owner:

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Courtesy copies of the foregoing were also served via email on counsel of record for the Petitioner and Patent Owner in *Argentum Pharmaceuticals LLC v. Research Corporation Technologies, Inc.*, IPR2016-00204 as follows:

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