**UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In the Reexamination of:<br>Harold Kohn<br><br>Patent No. RE38,551<br><br>Issue Date: Jul. 6, 2004<br><br>Title: ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES | Control No: Unassigned<br><br>Examiner: Unassigned<br><br>Art Unit: Unassigned |

**REQUEST FOR EX PARTE REEXAMINATION**
**OF U.S. PATENT NO. RE38,551**
**UNDER 35 U.S.C. §§ 301-307 AND 37 C.F.R. § 1.510 et. seq.**

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Commissioner:

This is a request for *ex parte* reexamination pursuant to 37 C.F.R. § 1.510 of claims 1-13 of U.S. Patent No. RE 38,551 ("the '551 patent"). This reexamination should be consolidated under 37 C.F.R. § 42.122(a) with co-pending *inter partes* review of the same '551 patent, styled *Argentum Pharms. Inc v. Research Corporation Techs.*, IPR2016-00204 (petition filed Nov. 23, 2015; institution decision due May 25, 2016).

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## EXHIBIT LIST

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| 1002 | Declaration of Dr. Binghe Wang from IPR2016-00204 |
| 1003 | Declaration of Dr. Clayton Heathcock from IPR2014-01126 |
| 1004 | Joint Statement of Uncontested Facts, *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del. Oct. 26, 2015) |
| 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., *Trimethylsilyl Halides: Effective Reagents for the Synthesis of β-Halo Amino Acid Derivatives*, Tet. Lett., Vol. 36(39), pg. 7011 (1995) ("Choi 1995") |
| 1011 | Purdie *et al., The Alkylation of Sugars*, J.A.C.S.Vol. 83, pg. 1021 (1903) ("Purdie") |
| 1012 | Kohn *et al., Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids*, J. Med. Chem. Vol. 34, pg. 2444 (1991) ("Kohn 1991") |
| 1013 | Silverman, R. B., *The Organic Chemistry of Drug Design and Drug Action*, Academic Press (1992) ("Silverman") |
| 1014 | Development of New Stereoisomeric Drugs, U.S. F.D.A., May 1, 1992 |
| 1015 | Cortes *et al., Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity*, J. Med. Chem., Vol. 28, pg. 601 (1985) ("Cortes 1985") |

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| 1016 | LeGall *et al., Synthesis of Functionalized Non-Natural Amino Acid Derivatives via Amidoalkylation Transformations*, Int. J. Peptide Protein Res. Vol. 32, pg. 279 (1988) ("LeGall 1988") |
| 1017 | Kohn *et al., Synthesis and Anticonvulsant Activities of α-Heterocyclic α-Acetamido-N-benzylacetamide Derivatives*, J. Med. Chem. Vol. 36, pg. 3350 (1993) |
| 1018 | Kohn *et al., Preparation and Anticonvulsant Activity of a Series of Functionalized α-Aromatic and α-Heteroaromatic Amino Acids*, 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., *Dose-Finding Studies in Clinical Drug Development*, Eur. J. Clin. Pharmacol, Vol. 34, pg. 15 (1988) |
| 1023 | Isbell, H. S., *The Optical Rotation of the Various Asymmetric Carbon Atoms in the Hexose and Pentose Sugars*, 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 | Thornber, C. W., *Isosterism and Molecular Modification in Drug Design*, 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 *et al., Decisions under Uncertainty: the Fuzzy Compromise Decision Support Problem*, Eng. Opt. Vol. 20, pg. 21 (1992) |
| 1030 | Mistree *et al., A Decsion-Based Perspective for the Design of Methods for Systems Design*, (1989) |
| 1031 | Mistree *et al., A Decision-based Approach to Concurrent Design, Concurrent Engineering: Contemporary Issues and Modern Design Tools*, (Parsaei, H. R. & Sullivan W. G. Eds. 1993) |

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| 1032 | Ingram W. T., *Concerning Periodic Points in Mappings of Continua*, J. Am. Math. Soc., Vol. 104(2) (1988) |
| 1033 | Mattson, *Current Challenges in the Treatment of Epilepsy*, Neurology, Vol. 44(suppl. 5), pg. 84 (1994) |
| 1034 | Löscher *et al.*, *New Avenues for Anti-Epileptic Drug Discovery and Development*, Nature Reviews: Drug Discovery, Vol. 12, pg. 12 (2013) |
| 1035 | Cohen authorized amendment in U.S. Patent Application No. 08/818,688 |
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| 1038 | Excerpts from Trial Transcript of Dr. Harold Kohn Testimony, *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del. Nov. 10, 2015) |
| 1039 | Excerpts from Trial Transcript of Dr. William Roush Testimony, *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del. Nov. 10 and 12, 2015) |
| 1040 | Excerpts from Trial Transcript of Defendants' Opening Statement, *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del. Nov. 9, 2015) |
| 1041 | Excerpts from Trial Transcript of Dr. Clayton Heathcock, *UCB, Inc. v. Accord Healthcare Inc.*, 1:13-cv-01206 (D. Del. Nov. 9, 2015) |

Third Party Requester ("Requester") requests *ex parte* reexamination under 35 U.S.C. §§ 301-307 of all claims (claims 1-13) of U.S. Patent No. RE 38,551 ("the '551 patent") (Ex. 1001). The Patent Owner is purportedly Research Corporation Technologies, Inc. ("RCT").

## I. RELATED PROCEEDINGS

A proceeding involving the '551 patent is currently pending in the Office. On November 23, 2015, a petition for *inter partes* review of the '551 patent was filed with the Patent Trial and Appeal Board ("PTAB"). The petition was accorded case number IPR2016-00204. Patent Owner filed a preliminary response on February 25, 2016. A decision from the PTAB on whether to institute the IPR is due no later than May 25, 2015 (i.e., 3 months from the preliminary response).

## II. SUMMARY OF '551 PATENT

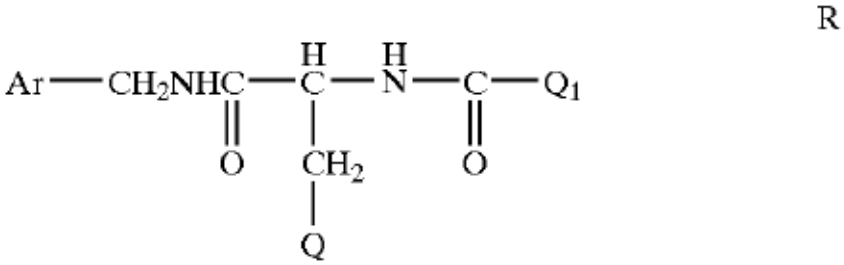
The '551 patent is the third in a series of patents owned by RCT and naming Dr. Harold Kohn as an inventor, each patent expiring later than the last, whose claims cover lacosamide: **U.S. Patent No. 5,378,729** ("the '729 patent") (Ex. 1009); **U.S. Patent No. 5,654,301** ("the '301 patent") (Ex. 1019); and **the '551 patent** (Ex. 1001).

The '551 patent is a reissue of U.S. Patent No. 5,773,475 ("the '475 patent") (Ex. 1005), which issued from U.S. Patent Application No.

08/818,688 ("the '688 application") filed on March 17, 1997, and which claims priority to U.S. Provisional Application No. 60/013,522 filed on March 15, 1996 (the earliest possible effective date).

Claim 1 is the sole independent claim in the '551 patent. Claim 1 reads:

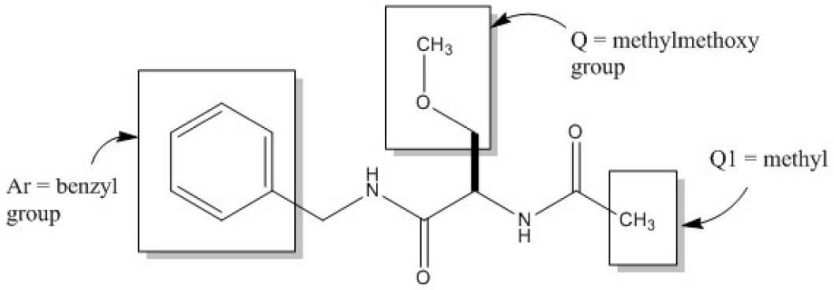
> 1. A compound in the R configuration having the formula:




> wherein
>
> Ar is phenyl which is unsubstituted or substituted with at least one halo group;
>
> Q is lower alkoxy, and
>
> 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-methoxypropion-amide." The structure of lacosamide is shown below (wherein Ar is benzyl, Q is methoxymethyl, and Q1 is methyl):




**Lacosamide**

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."

## III. SUMMARY OF PRIOR AND PENDING PROCEEDINGS INVOLVING THE '551 PATENT

The '551 patent issued as a result of an Examiner's chemistry mistake, which the Patent Owner failed to correct during original prosecution. Later, when seeking a patent term extension from the PTO under 35 U.S.C. § 156,

the Patent Owner made statements to the PTO that were directly contrary to the Examiner's earlier mistaken understanding and reasons for allowing the '551 patent. During litigation before a Federal District Court, the Patent Owner again made statements that confirm that the Examiner's understanding was a mistake. This history is explained below.

### A. Original Prosecution – Examiner's Mistake Regarding "Ether" Group Disclosed in the '301 Patent

The '551 patent and '301 patent are commonly owned by RCT. The '301 patent is an earlier-filed, earlier-expiring patent. Accordingly, under the doctrine of obviousness-type double patenting, the Examiner should have considered whether the term of the '301 patent would be improperly extended by RCT's later-filed, later-expiring patent claims in the '688 application (which issued as the '551 patent).

The prosecution history of the '688 application reveals that the Examiner allowed the claims to issue over the '301 patent due to a chemistry mistake. In her Notice of Allowability for the '688 application, the Examiner identified the '301 patent (referred to as "Cohen," presumably misspelling the first inventor, "Kohn") as one of two "closest prior arts." (Ex. 1036, File History 08/818,688, at p. 158.) The Examiner nonetheless allowed the claims to issue because she concluded that the '301 patent did not disclose

that the substituents $R_2$ or $R_3$ of claims 39-44 of the '301 patent teach or suggest lacosamide's "ether" group (i.e., the methoxymethyl group):

> "The following is an examiner's statement of reasons for allowance: Instant claims are directed [to] anticonvulsant enantiomeric amino acid derivatives in the method of treating CNS disorders. ***The closest prior arts are Cohen (US 5,654,301)*** and Anderson et al. (J. Am. Chem. Soc., 1967). Cohen teach [sic] structurally similar compounds as claimed herein for similar pharmaceutical method. The difference between the reference and herein claimed compounds is the definition of $R_2$, $R_3$ in the reference. ***The reference never teach or suggest [sic] $R_2$, $R_3$ to be an ether***, as against ether in herein claims."

(Ex. 1036, File History 08/818,688, p. 158.)[1]

This was a mistake. Specifically, independent claim 39 of the '301 patent provides that $R_2$ or $R_3$ can be a "lower alkyl which is substituted with an electron donating group" (Ex. 1019, '301 patent, 1:54-60); dependent claim 42 specifies that $R_2$ or $R_3$ is "methyl substituted with an electron donating group" (*id.* at 3:40); and, dependent claim 44 further specifies that the electron donating group is "methoxy" (*id.* at 4:30). Thus, claim 44 of the '301 patent discloses that one of $R_2$ and $R_3$ is hydrogen, and the other is

[1] Emphasis is added to all quotes throughout this request, unless otherwise noted.

***methoxymethyl***. Furthermore, claim 45 specifies that n is 1. This combination of substituents results in the following structure:


'301 Claim 45

Methoxymethyl, shown above in red, is an ***ether***. An ether is a functional group characterized by a C-O-C linkage, an oxygen bonded to two carbons. (Ex. 1003, Heathcock, ¶ 68.) Claim 44 of the '301 patent defines methoxymethyl as the substituent at $R_2$ or $R_3$, which is an ether. (Ex. 1003, Heathcock, ¶ 68.) Therefore, the Examiner made a mistake in concluding that the '301 patent did not disclose "$R_2$, $R_3$ to be an ether." The original patent issued as a result of this mistake.

### B. PTE Request – Patent Owner Admits that Claims 39-45 of the '301 Patent's Read on Lacosamide

In 2008, after the '551 patent issued, Patent Owner filed a request with the PTO, under 35 U.S.C. § 156, for an extension of patent term of the '301 patent. (Ex. 1020, PTE Request.) In that request for patent term extension, Patent Owner affirmatively told 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, PTE Request, p. 5.) Specifically, the Patent Owner stated:

> "U.S. Patent No. 5,654,301 claims the approved product, VIMPAT® injection. More specifically, ***claims 39-45 read on*** the approved product and ***claim the active ingredient of the final approved product lacosamide****, claim 46 reads on the approved product and claims a composition comprising lacosamide, and claim 47 reads on methods that comprise using lacosamide for treatment of CNS (i.e. central nervous system) disorders*."

(*Id*.)

The Patent Owner's statement above confirms that the methoxymethyl group of lacosamide is an "ether" because claims 39-45 of the '301 patent could not otherwise "read on" the approved product lacosamide. Patent Owner submitted a claim chart to support this assertion. (Ex. 1020, PTE Request, pp. 5-7.) That claim chart is consistent with the analysis above. In the claim chart, Patent Owner represented that lacosamide's "central chiral carbon atom is bonded to a hydrogen and a ***-$CH_2OCH_3$ group (a lower alkyl substituted with a methoxy group)***, thus satisfying the ['301 patent] claim's requirement that one of $R_2$ and $R_3$ be a hydrogen while the other of $R_2$ and $R_3$ is a lower alkyl substituted with an electron donating group." (Ex. 1020, PTE Request, p. 6.) This admission confirms that the methoxymethyl group

of lacosamide is an ether (having a C-O-C linkage) and that lacosamide is covered by claims 39-45 of the '301 patent.

The above admissions by the Patent Owner can be used in this reexamination. *See* MPEP § 2258 "([***a***]***dmission by the patent owner of record in the file***" can used "to determine the scope and content of the prior art ***in conjunction with patents and printed publications*** in a prior art rejection, whether such admissions result from patents or printed publications or from some other source").

### C. District Court Litigation – Patent Owner Admits that $R_3$ Group of Claim 44 of '301 Patent is Methoxymethyl

Patent Owner is a party in co-pending Federal District Court litigation styled *UCB, Inc., et al. v. Accord Healthcare, Inc., et al.*, Civil Action No. 13-1206-LPS (D. Del.). In that litigation, the Patent Owner made the following admission: "For purposes of this litigation, claim 44 of U.S. Patent No. 5,654,301 (the ''301 patent') defines a genus of compounds with a ***methoxymethyl group at $R_3$***." (Ex. 1004, Joint Statement, ¶ 88.)

The above statement by the Patent Owner again confirms, this time explicitly, that the $R_3$ group of claim 44 of the '301 patent is methoxymethyl. This admission by the Patent Owner can be used in this reexamination. *See* MPEP § 2258: ("[a]n admission by the patent owner of

record in the file or in a ***court record*** may be utilized in combination with a patent or printed publication"). Such admissions may be utilized to "determine the scope and content of the prior art in conjunction with patents and printed publications in a prior art rejection, whether such admissions result from patents or printed publications or from some other source." *Id.*

### D. IPR2014-01126 – Obviousness-Type Double Patenting over the '301 Patent Was Never Presented or Considered

On July 10, 2014, a petition for *inter partes* review IPR2014-01126 ("First IPR Petition") was filed against the '551 patent. The First IPR Petition presented three grounds of unpatentability, none of which involved obviousness-type double patenting over the '301 patent. Instead, the three grounds presented in the First IPR Petition were: (1) statutory anticipation under 35 U.S.C. § 102 by the '301 patent, (2) statutory anticipation under 35 U.S.C. § 102 by LeGall,[2] and (3) statutory obviousness under 35 U.S.C. § 103 over LeGall and the '729 patent. The PTAB denied the First IPR Petition on January 9, 2015. For the first ground (anticipation by the '301 patent), the PTAB denied the petition because a person of ordinary skill would not have "at once envisage[d]" each species with the genus of

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

compounds in the '301 patent sufficient to "anticipate" lacosamide. (Decision, pp. 8-9.) The Board arrived at this conclusion "without deciding" whether the '301 patent disclosed all the substituents of lacosamide, including methoxymethyl, and did not address whether methoxymethyl is an ether. (*Id.* at p. 7.) For the second ground (anticipation by LeGall), the Board found that LeGall was not shown to be a "printed publication" under § 102(b) because no evidence was presented that LeGall was publicly accessible more than 1 year before the effective filing date of the '551 patent. (*Id.* at pp. 12-13.)[3] Likewise, the third ground (obviousness over LeGall and the '729 patent) was denied for the same reason as the second ground. (*Id.* at p. 14.) Accordingly, in IPR2014-01126, the Board never addressed whether the claims of the '301 patent define a methoxymethyl at the $R_2$ or $R_3$ position, nor whether methoxymethyl is an ether, nor whether those claims render obvious (under either statutory § 103 obviousness or obviousness-type double patenting) the claims of the '551 patent.

In any event, even if the same exact double-patenting question were presented in the *inter partes* review (which it was not), the Director does not

[3] Subsequent to this decision, Patent Owner admitted in the District Court litigation that "the LeGall thesis was publicly accessible more than one year before the earliest priority date for the '551 patent and constitutes a 'printed publication' within the meaning of 35 U.S.C. § 102(b)." (Ex. 1004, Statement of Uncontested Facts, at ¶ 87.)

regard an *inter partes* review petition as a basis to deny the existence of a SNQ for purposes of reexamination. *See* Control No. 96/000,071, SNQ Determination mailed Aug. 14, 2014 (finding SNQ based on exact same art and claim charts taken directly from a prior IPR).

### E. IPR2016-00204 – Obviousness-Type Double Patenting over the '301 Patent Was Never Presented or Considered

On November 23, 2015, a petition for *inter partes* review IPR2016-00204 ("Second IPR Petition") was filed against the '551 patent. The Second IPR Petition also does not present any double patenting ground whatsoever, much less a double patenting ground over the '301 patent. Instead, the Second IPR Petition presents only statutory anticipation under 35 U.S.C. § 102 by LeGall, and statutory obviousness under § 103 over combinations of LeGall, the '729 patent, Choi,[4] Kohn 1991,[5] Silverman,[6]

[4] Choi et al., *Trimethylsilyl Halides: Effective Reagents for the Synthesis of β-Halo Amino Acid Derivatives*, Tet. Lett., Vol. 36(39), pg. 7011 (1995) ("Choi") (Ex. 1010).

[5] Kohn et al., *Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids*, J. Med. Chem. Vol. 34, pg. 2444 (1991) ("Kohn 1991") (Ex. 1012).

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

and Cortes.[7] Accordingly, in IPR2016-00204, the question of double patenting over the '301 patent was never presented to the Board. The Board has not yet decided whether to institute IPR2016-00204 based on the grounds presented in the Second IPR Petition.

In any event, even if the same exact double-patenting question were presented in the *inter partes* review (which it was not), the Director does not regard an *inter partes* review petition as a basis to deny the existence of a SNQ for purposes of reexamination. *See* Control No. 96/000,071, SNQ Determination mailed Aug. 14, 2014 (finding SNQ based on exact same art and claim charts taken directly from a prior IPR).

[7] Cortes et al., *Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity*, J. Med. Chem., Vol. 28, pg. 601 (1985) ("Cortes") (Ex. 1015).

## IV. SUMMARY OF SUBSTANTIAL NEW QUESTION OF PATENTABILITY AND PROPOSED REJECTIONS

The instant request sets forth the following Substantial New Question of Patentability ("SNQ") for claims 1-13 of the '551 patent:

| SNQ Reference | SNQ Reference is Presented in a "New Light" | New Technological Teaching |
|---|---|---|
| **'301 patent** (Ex. 1019) raises an SNQ for claims 1-13, alone or as evidenced by **LeGall** (Ex. 1008). | Although the **'301 patent** was considered during original examination, Patent Owner's later admissions to both the PTO (Ex. 1020) and District Court (Ex. 1004) confirm that the Examiner misunderstood that Claim 44 of the '301 Patent does indeed contain an ether (methoxymethyl) at the $R_3$ position.<br><br>**LeGall** was never considered during examination or reissue. LeGall discloses a compound with an ether (methoxymethyl) at the $R_3$ position, as Dr. Kohn admitted under oath to the District Court (Ex. 1038). Moreover, Patent Owner has admitted that LeGall is prior art (Ex. 1004, Joint Statement of Uncontested Facts, ¶86(ee) and ¶87.). | The compound of Claim 44 of the '301 Patent contains an ether (methoxymethyl) at the $R_3$ position. |

Based on the above SNQ, Requester proposes two grounds of rejection, each of which asserts unpatentability of claims 1-13 under the doctrine of obviousness-type double patenting ("OTDP")[8]:

| Ground | Claims | Basis | Reference(s) |
|---|---|---|---|
| 1 | 1-13 | OTDP | '301 patent in view of '729 patent and Kohn 1991 |
| 2 | 1-13 | OTDP | '301 patent in view of '729 patent and LeGall |

## V. DETAILED EXPLANATION OF SUBSTANTIAL NEW QUESTION OF PATENTABILITY

### A. The '301 patent (Claim 44) contains an ether (methoxymethyl)

The '301 patent raises a SNQ for claims 1-13 of the '551 patent. The '301 patent is an earlier-filed, earlier-expiring patent than the '551 patent, both of which are owned by RCT. Specifically, the '301 patent is a pre-GATT patent that enjoyed a 17-year term, expiring on August 5, 2014. By contrast, the '551 patent will not expire until ***March 17, 2022***. (Ex. 1037, FDA Orange Book.) Accordingly, unless the claims of the '551 patent are novel and nonobvious over the claims of the '301 patent, then RCT will have received an "unjustified timewise extension" of the '301 patent of

[8] *See* MPEP § 2258 ("[T]he issue of double patenting, over prior art patents or non-prior art patents, is appropriate for consideration in reexamination under 35 U.S.C. 302, both as a basis for ordering reexamination under 35 U.S.C. 304 and during subsequent examination on the merits.").

approximately ***7 ½ years***. *See* MPEP § 804 (citing *In re Schneller*, 397 F.2d 350, 354 (CCPA 1968)).

The '301 patent raises a SNQ for claims 1-13 of the '551 patent because, contrary to the Examiner's misunderstanding during prosecution, claims 39-45 of the '301 patent do indeed contain an "ether" (a methoxymethyl group) at the $R_2$ or $R_3$ position. Specifically, an "ether" is characterized by a C-O-C linkage (an oxygen bonded to two carbons); and methoxymethyl ($-CH_2OCH_3$) contains such a C-O-C linkage. (Ex. 1003, Heathcock, ¶ 68.) The expert declaration of Dr. Heathcock, submitted herewith as an exhibit, explains in more detail the Examiner's mistake and why methoxymethyl is indeed an ether. (Ex. 1003, Heathcock, ¶¶ 65-73.)

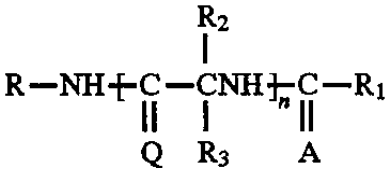
Furthermore, Patent Owner's admissions, both to the PTO and to the District Court, confirm that the claims of the '301 patent cover lacosamide and contain a methoxymethyl group. These admissions by the Patent Owner present the '301 patent in a "new light." *See* MPEP § 2258 (discussing appropriate use of patent owner admissions in reexamination). Specifically, the Patent Owner told the PTO, when requesting a patent term extension of the '301 patent, that "claims 39-45 [of the '301 patent] read on the approved product and claim the active ingredient … lacosamide," and that lacosamide contains a "$-CH_2OCH_3$ group" which is a "lower alkyl substituted with a

methoxy group" in accordance with claim 39 of the '301 patent. (Ex. 1020, PTE Request, pp. 5-6.) Second, in the pending District Court litigation, the Patent Owner admitted that "claim 44" of the '301 patent "defines a genus of compounds with a methoxymethyl group at $R_3$." (Ex. 1004, Statement of Uncontested Facts, ¶ 88.) Together, the above statements by the Patent Owner regarding the '301 patent confirm that the Examiner's reason for allowing the '551 patent was a mistake.

The following discussion maps the disclosures of the '301 patent against the single element of claim 1 of the '551 patent that the Examiner apparently believed was missing in the prior art:

**"<u>Q is lower alkoxy</u>" as recited in Claim 1 of the '551 patent**

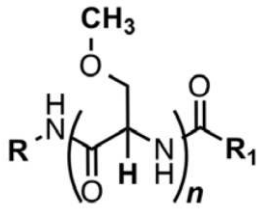
Like claim 1 of the '551 patent which recites "Q is lower alkoxy" at the stereocenter (the α-carbon) of an amino acid, claims 39-45 of the '301 patent define a substituent attached to an amino acid's stereocenter (the α-carbon) wherein the substituent is a lower alkoxy. Specifically, claim 39 of the '301 patent is an independent claim that recites the general formula:




(Ex. 1019, '301 patent, Claim 39.)

Dependent claim 40 specifies that "one of $R_2$ and $R_3$ is hydrogen and the other is lower alkyl substituted with an electron donating group." (Ex. 1019, '301 patent, Claim 40.) Through additional dependency, claim 42 further specifies that "one of $R_2$ and $R_3$ is methyl substituted with an electron donating group." (Ex. 1019, '301 patent, Claim 42.) Claim 43 specifies that the "electron donating group" at $R_2$ and $R_3$ "is ***lower alkoxy***" (Ex. 1019, '301 patent, Claim 43.) Thus, claim 43 of the '301 patent explicitly recites a "lower alkoxy" as per claim 1 of the '551 patent.

Furthermore, claim 44 of the '301 patent specifies that the "lower alkoxy" of claim 43 "is methoxy" (Ex. 1019, '301 patent, Claim 43). Thus, claim 44 of the '301 patent discloses that one of $R_2$ and $R_3$ is hydrogen, and the other is methoxymethyl, as depicted below:

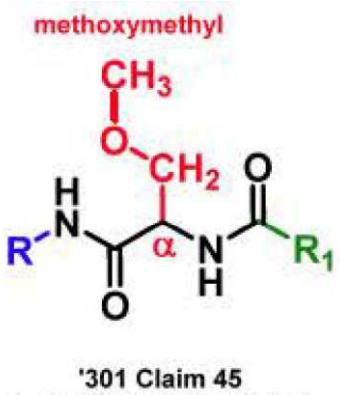



**Kohn '301 Claim 44**

As seen above, the methoxymethyl substituent has the chemical formula $-CH_2OCH_3$. Methoxymethyl thus contains 2 carbon atoms (one carbon atom in addition to the one carbon atom in the methylene bridge $-CH_2-$). This meets the limitation of claim 3 of the '551 patent that

the alkoxy contain ***1-3 carbon atoms***, and it meets the requirement of claim 4 of the '551 that Q is ***methoxy***. *See also* Ex. 1020, PTE Request, p. 6 (Patent Owner admitting that a "-$CH_2OCH_3$ group" is "a lower alkyl substituted with a methoxy group").

Dependent claim 45 of the '301 patent further specifies that n is 1. The resulting structure is depicted below:




'301 Claim 45

The selection of the R and $R_1$ substituents of claim 45 of the '301 patent is addressed in the proposed grounds of rejection below. For purposes of the SNQ here, the Examiner did not base her reasons for allowing the '551 patent claims over the '301 patent due to any supposed novelty or nonobviousness of the R and $R_1$ substituents. Instead the Examiner allowed the '551 patent because of the "definition of $R_2$, $R_3$ in the ['301 patent] reference." (Ex. 1036, File History 08/818,688, at p.158.). As shown above, however, the Examiner was mistaken with respect to the $R_2$, $R_3$ groups in the '301 patent, which clearly do define a methoxymethyl group, exactly as

claimed in the ’551 patent. Therefore, the Director should find that a SNQ has been raised by the ’301 patent.

### B. LeGall confirms that the ’301 patent’s methoxymethyl is an ether

The SNQ discussed above with respect to the ’301 patent is further evidenced by LeGall (Ex. 1008). The status of LeGall as prior art is discussed in detail in Proposed Ground 2 below. For purposes of this SNQ, however, it suffices to simply point out that ***Patent Owner has admitted*** in District Court litigation that “the LeGall thesis was publicly accessible more than one year before the earliest priority date for the ’551 patent and constitutes a ‘printed publication’ within the meaning of 35 U.S.C. § 102(b).” (Ex. 1004, Joint Statement of Uncontested Facts, p. 19, ¶87.) This explicit admission was made by Patent Owner “***in a court record***” and therefore may be “utilized in combination with a patent or printed publication” when ordering reexamination. MPEP § 2258.

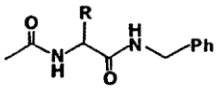
Moreover this admission by the Patent Owner was made ***after*** the PTAB denied an earlier IPR petition (the First IPR Petition, filed in IPR2014-01126) finding insufficient evidence presented in that petition to show that LeGall was publicly accessible in order to constitute a “printed publication” under § 102(b). Whereas Patent Owner during IPR2014-01126 disputed

whether LeGall was prior art, Patent Owner later admitted otherwise during the District Court litigation.

The reason for Patent Owner's about-face is that new evidence of LeGall's public availability was discovered in the District Court litigation that forced Patent Owner to admit that LeGall in fact is prior art. *See* Ex. 1040, Trial Transcript Def.'s Opening, p. 44 (defendants' lawyer explaining "plaintiffs denied that [LeGall] was prior art in the IPR [IPR2014-01126], at least said we didn't have proof that it was. ***In the course of this case, we got the proof, and they now stipulate that it's prior art***.")

Patent Owner's binding admission in court that "LeGall … constitutes a 'printed publication' within the meaning of 35 U.S.C. § 102(b)" (Ex. 1004, Joint Statement, p. 19, ¶87), together with additional evidence presented below in Proposed Ground 2 that LeGall was publicly accessible more than one year before the earliest effective date, is new information relative to any prior examination of the '551 patent which a "reasonable examiner would consider important" in deciding whether or not the claims are patentable.

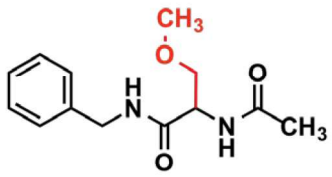
Importantly, LeGall confirms that the ***methoxymethyl of the '301 patent is an ether***. LeGall discloses a compound (107e) that contains a methoxymethyl ($-CH_2OCH_3$) at the $R_3$ position of the '301 patent (which is the "R" position of compound 107), shown below in the red box:



107

| No. | R | yield[a] | mp[b] | IR[c] | M+/e[d] |
|---|---|---|---|---|---|
| 107a | CN | 64 | 179 - 180 | 1620,1505 | 231 (4)[e] |
| 107c | $CONH_2$ | 55 | 191 - 192 | 1665, 1635, 1520 | 249 (6)[e] |
| 107b | COOEt | 45 | 142 - 143 | 1740, 1625, 1525 | 278 (6)[e] |
| 107d | $CH_2OH$ | 66 | 201 - 203 | 1605, 1530 | 237 (48) |
| 107e | $CH_2OCH_3$ | 4 | 109-112 | 1610, 1525 | f |

Ex. 1008, LeGall, p. 137, Tbl. 36 (red box added).



**LeGall thesis compound 107e (racemic lacosamide)**

(methoxymethyl colored red)

In the District Court litigation, Dr. Harold Kohn (the named inventor of the '551 patent and thesis advisor to Mr. Philippe LeGall) was asked about compound 107e of LeGall. Under oath, Dr. Kohn admitted that the -$CH_2OCH_3$ group of compound 107e in LeGall is an **ether**:

> Q. Dr. Kohn, you have the LeGall thesis, I think it's DTX-2019 in your binder. Maybe we can put it on the screen.
>
> . . .
>
> Q. And if you could look at page 137 of that thesis, this is the chart of compounds in the 107 series; correct?
>
> A. Let me get that.
>
> . . .
>
> Q. You recognize this as the chart in the LeGall thesis that shows the formulas for the series of compounds labeled 107?
>
> A. It is, yes.

Q. Okay. And you read the thesis, of course, before you approved it; correct?

A. I read the thesis, that's right.

Q. And the chemical formula, let's take 107e, that's the one obviously we're interested in. The methoxy group on that substituent, would that be called an ether group?

A. The methoxy group is not. But ***if you take the $CH_2OCH_3$, that would encompass the ether group.***

Q. ***So the substituent that's listed on the table under R is an ether; is that correct?***

A. ***That's an ether.***

(Ex. 1038, Kohn Trial Transcript, 539:2 – 540:1.)

As shown above, Dr. Kohn admitted that the -$CH_2OCH_3$ group of LeGall's compound 107e is "an ether." Because LeGall's compound 107e has the same -$CH_2OCH_3$ group as claim 44 of the '301 patent, Dr. Kohn's admission regarding LeGall is equally applicable to claim 44 of the '301 patent. The foregoing confirms that the Examiner was incorrect in her understanding of whether the '301 patent discloses an "ether." Therefore, the Director should find that a SNQ has been raised by the '301 patent, alone or as evidenced by LeGall.

# VI. PROPOSED GROUNDS OF REJECTION

Requester proposes two grounds of rejection in this request. Before addressing those grounds, Requester first addresses the construction of claim terms applicable to both grounds. However, the construction of these terms is not dispositive here because claims 1-13 are unpatentable, even if the Office adopts a narrow construction.

## A. Claim Construction

### 1. The term "A compound in the R configuration" should be construed to mean "At least one compound in the R configuration"

The broadest reasonable interpretation ("BRI") of the introductory phrase in claim 1, "A compound in the R configuration," should be construed to cover R-isomer compounds, whether the R-isomer is substantially pure or mixed with the S-isomer, such as a racemic mixture or isomerically enriched compound. 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, Wang, ¶¶ 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 is "substantially enantiopure." The '551

patent explains that "substantially enantiomerically pure" can include at least 10% (w/w) of the S-isomer. (Ex. 1001, '551 patent, 5:11-16.)

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 that it cannot be solely S.

When the Patent Owner wanted to specifically exclude the presence of S-isomers, it did so explicitly in claims 2 and 9. Therefore, to the extent the 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 Director should hold all claims indefinite under 35 U.S.C. § 112(b). *See BlackBerry Corp. v. MobileMedia Ideas LLC*, IPR2013-00036 (Paper 65) (terminating IPR after finding claims indefinite).

Regardless, claims 2 and 9 are unpatentable under each of the proposed rejections, and therefore the construction of claim 1 would not change the outcome of this proceeding.

### 2. The preamble "therapeutic composition" in claim 10 is non-limiting because the body of the claim contains all the required components

Claim 10 is a product claim that recites two limitations: an "anticonvulsant effective amount" of the compound, and a "pharmaceutical carrier."[9] 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

[9] 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."

that term in any special manner, other than introducing the claimed compound in a pharmaceutical carrier. By definition, a compound within the genus, together with a pharmaceutical carrier, is a therapeutic composition within the meaning of claim 10.

Moreover, the BRI cannot be limited to only a composition that is administered "over an extended period of time" and for "chronic administration," as the Patent Owner may argue. Indeed, nothing in the claim limits the composition to "chronic administration" or any duration of a treatment regimen. (Ex. 1001, '551 patent, cols. 9-10 (reciting a litany of acceptable dosage forms and excipients).) The specification merely states that the compound "can" be used in a treatment regimen over extended periods of time, not that they "must" be used in that manner or "only" in such manner. (Ex. 1001, '551 patent, 37:47-51.)

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, '551 patent, 10:52-59.) 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 9:25-26), 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.

Regardless, claim 10 is unpatentable even if construed to require administration to a patient as part of a CNS treatment regimen (because dependent method of treatment claims 11-13 are separately unpatentable), and therefore the construction of claim 10 would not change the outcome of this proceeding.

### B. Law of Obviousness-Type Double Patenting

As the Federal Circuit has explained, "it is a bedrock principle of our patent system that when a patent expires, the public is free to use not only the same invention claimed in the expired patent but also obvious or patentably indistinct modifications of that invention." *Gilead Sci., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1214 (Fed. Cir. 2014). "The double patenting doctrine has always been implemented to effectively uphold that principle," which "is violated when a patent expires and the public is

nevertheless barred from practicing obvious modifications of the invention claimed in that patent because the inventor holds another later-expiring patent with claims for obvious modifications of the invention." *Id*. at 1214. "The ban on double patenting ensures that the public gets the benefit of the invention after the original period of monopoly expires." *Abbvie*, 764 F.3d at 1373.

While "obviousness is not demonstrated merely by showing that an earlier expiring patent dominates a later expiring patent," "not every species of a patented genus is separately patentable." *Id*. at 1379, 1381 (holding that "[t]he [later species] patent would have been obvious over the [earlier genus] patent"). "For example, in *Pfizer, Inc. v. Apotex, Inc*., [the Federal Circuit] invalidated a patent on a species belonging to a previously patented genus." *Id*. at 1379 (citing 480 F.3d at 1361).

"[W]hen analyzing obviousness-type double patenting in cases involving claimed chemical compounds, the ***issue is not whether a skilled artisan would have selected the earlier compound as a lead compound***." *Otsuka*, 678 F.3d at 1297. "That is so because the analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, ***lead compound or not***." *Id*.

The inquiry for obviousness-type double-patenting is "whether the identified difference renders the [later] claims … non-obvious to a person of ordinary skill in the art in light of the prior art." *Amgen Inc. v. F. Hoffman-La Roche Ltd*., 580 F.3d 1340, 1361 (Fed. Cir. 2009). It has long been "well established that in a double patenting situation, prior art may be considered in order to determine whether the application claims a mere obvious variation of the patented invention." *In re Purdy*, 393 F.2d 1010, 1012 (C.C.P.A. 1968).

"[I]t is also well settled that [the Court] may look to a reference patent's disclosures of utility" "to determine whether the utility of the later patent was unexpected at the time of the earlier patent." *Abbvie*, 764 F.3d at 1380-81 (quotation omitted). That disclosure is relevant because "a later expiring patent is not patentably distinct from an earlier expiring patent if it merely claims a disclosed utility of the earlier claimed invention." *Id*. at 1381.

"[I]nquiry into secondary considerations is not required in every obviousness-type double patenting analysis." *Lilly*, 689 F.3d at 1381 (citing *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 n.1 (Fed. Cir. 2003) ("The distinctions between obviousness under 35 U.S.C. § 103 and nonstatutory double patenting include: …. Obviousness requires inquiry into objective criteria suggesting non-obviousness; nonstatutory

double patenting does not.")); *see also Procter & Gamble Co. v. Teva Pharm. USA, Inc*., 566 F.3d 989, 999 (Fed. Cir. 2009) ("double patenting does not require inquiry into objective criteria suggesting non-obviousness").

As explained in the MPEP § 804:

> It is important to note that the 'obviousness' analysis for 'obviousness-type' double-patenting is 'similar to, but not necessarily the same as, that undertaken under 35 U.S.C. 103.' *In re Braat*, 937 F.2d 589, 592-93, 19 USPQ2d 1289, 1292 (Fed. Cir. 1991) (citing *In re Longi*, 759 F.2d 887, 892 n.4, 225 USPQ 645, 648 n.4 (Fed. Cir. 1985)); *Geneva Pharmaceuticals*, 349 F.3d 1373, 1378 n.1, 68 USPQ2d 1865, 1869 n.1 (Fed. Cir. 2003). In addition, nonstatutory double patenting also includes rejections based on the equitable principle against permitting an unjustified timewise extension of patent rights. *See In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968).

MPEP § 804.

Finally, any "unexpected results" from the alleged invention of the later patent must be compared to the expected results of the earlier patent. *See Abbvie*, 764 F.3d at 1380 ("To determine whether the [later] patent is directed to a species that yielded unexpected results, we must necessarily look to the [earlier genus] patent's disclosures to assess what results were

expected at the time the [earlier] patent application was filed."); *see also In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985) (comparing alleged unexpected results to subject matter claimed in earlier patent and holding that patentee "fail[ed] to provide the unexpected results necessary to rebut the prima facie case" that "the claim[ed] subject matter [was] unpatentable for double patenting of the obviousness type").

### C. Ground 1: Claims 1-13 are unpatentable for OTDP over the '301 patent in view of the '729 patent and Kohn 1991

Claims 1-13 are unpatentable for obviousness-type double patenting ("OTDP") over the **'301 patent** (Ex. 1019) in view of the **'729 patent** (Ex. 1009), and **Kohn 1991** (Ex. 1017). As explained above, the '301 patent is available as a double-patenting reference against the '551 patent. Likewise, the '729 patent issued to RCT on January 3, 1995 and expired prior to the '551 patent; therefore, the '729 patent is available both as a double-patenting reference and as prior art under § 102(b) against the '551 patent. Finally, Kohn 1991 is a prior art printed publication under § 102(b).

The elements of claims 1-13 of the '551 patent are mapped to the teachings of the above-cited references in the Claim Charts in Part VII below, starting on page 68 of this request. Based on those teachings, and for the reasons explained below, claims 1-13 should be rejected under Ground 1.

### 1. Claims 1-9 of the '551 patent differ from Claims 43-45 of the '301 patent only at the R and $R_1$ substituents and stereochemistry

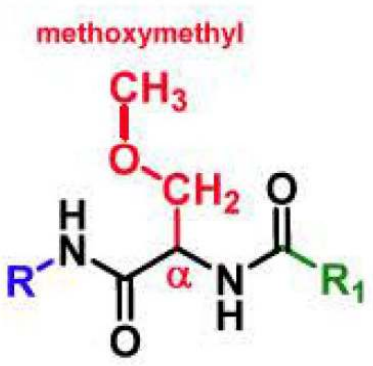
The first step in an obviousness-type double patenting analysis is to "construe[] the claims in the earlier patent and the claims in the later patent and determine[] the differences." *AbbVie*, 764 F.3d at 1374. Unlike in a statutory obviousness analysis, where the initial inquiry is in the selection of a "lead compound," the starting point for double patenting is the compound claimed in the earlier patent itself, regardless whether "a skilled artisan would have selected the earlier compound as a lead compound." *Otsuka*, 678 F.3d at 1297 (double patenting "analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, ***lead compound or not***").

Here, claims 1-9 of the '551 patent differ from claims 43-45 of the '301 patent only at the R and $R_1$ substituents and stereochemistry, explained in detail below.

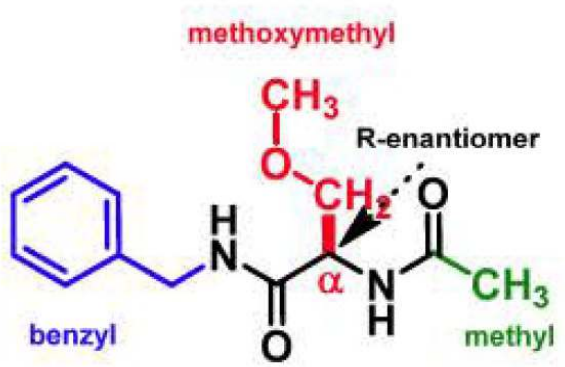
Claim 43 of the '301 patent claims a genus of functionalized amino acids that contains a "**lower alkoxy**" group at $R_3$. Claim 1 of the '551 patent claims a smaller genus of functionalized amino acids that falls within the scope of claim 43 of the '301 patent, and also recites a "**lower alkoxy**" group at that position.

Claim 44 of the ’301 patent defines a methoxymethyl group at $R_3$. (Ex. 1004, Joint Statement, ¶ 88 (Patent Owner admission that “claim 44 … defines a genus of compounds with a methoxymethyl group at $R_3$”)). Methoxymethyl has the chemical formula $-CH_2OCH_3$. Thus, methoxymethyl contains 2 carbon atoms (one carbon atom in addition to the one carbon atom in the methylene bridge $-CH_2-$). This meets the limitation of claim 3 of the ’551 patent that requires the lower alkoxy to contain “**1-3 carbon atoms.**” This also meets the requirement of claim 4 of the ’551 that Q is “**methoxy.**” Thus, claim 4 of the ’551 patent falls within the scope of claim 44 of the ’301 patent.

Claim 45 of the ’301 patent depends from claim 44 and further specifies that the amino acid backbone contains only 1 repeating unit, i.e., n=l. The compounds of the ’551 patent likewise contain only 1 repeating unit. Thus, claim 45 of the ’301 patent recites a genus of compounds, and lacosamide of claim 9 of the ’551 patent is a species of that genus. Claim 45 of the ’301 patent is depicted below on the left, compared with lacosamide, depicted on the right:




'301 Claim 45
(depending on claim 44)




Claim 9 of '551 Patent (i.e. lacosamide)
at least 90% purity

As seen above, the only differences between claim 45 of the ’301 patent and claim 9 of the ’551 patent are: (1) unsubstituted benzyl at R, (2) unsubstituted methyl at $R_1$, and (3) selection of the R- (or D-) enantiomer over the S- (or L-) enantiomer.

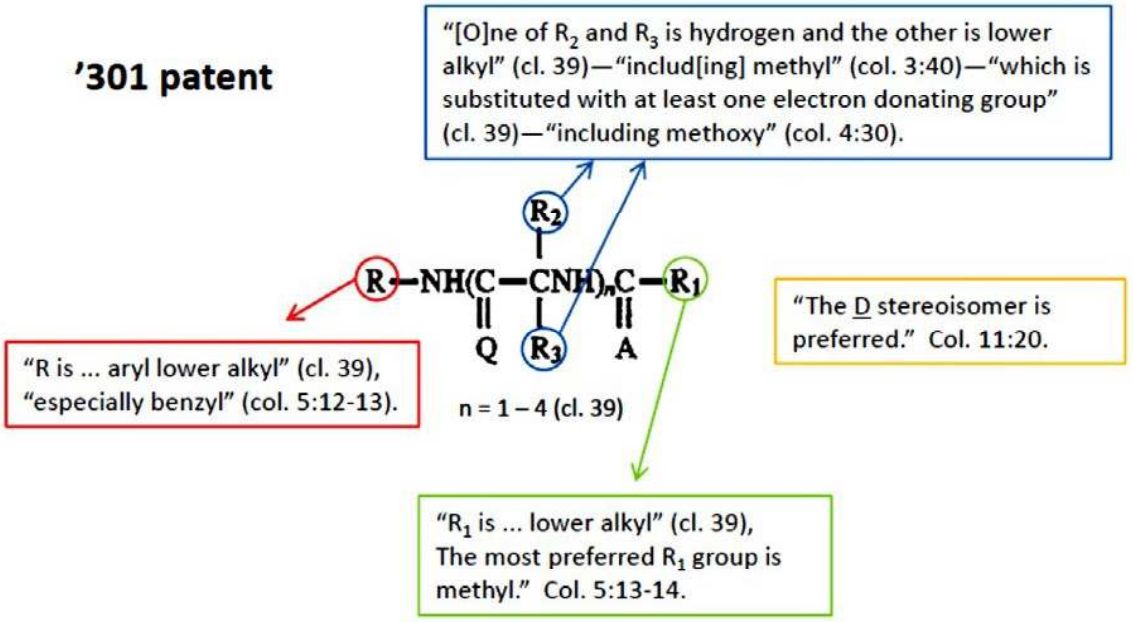
For the reasons explained below, each of the three differences were obvious in view of the prior art as of March 15, 1996.

### 2. The differences between Claims 1-9 of the ’551 patent and Claims 43-45 of the ’301 patent were obvious

The second step of an obviousness-type double patenting analysis is to “determine[] whether those differences [determined in step one] render the claims patentably distinct.” *AbbVie*, 764 F.3d at 1374. As in any obviousness determination, the “question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether ... the combination is the most

desirable combination available." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

As explained below, the '301 patent and the prior art expressed clear and explicit preferences for the selection of each of: (1) benzyl at R, (2) methyl at $R_1$, and (3) the R- (or D-) enantiomer. A POSA would have been directed to those obvious selections based on the '301 patent alone, even before turning to additional prior art discussed below. The '301 patent contains the following express preferences for each of R, $R_1$, and the stereochemistry:




- ***Preference of Benzyl at R***. The '301 patent itself states: "The preferred values of R is aryl lower alkyl, especially **benzyl**…." (Ex. 1019, '301 patent, 5:11-12.) Apart from the '301 patent itself, and further confirming this obvious preference, a POSA would have seen the

identical preference for benzyl in the prior art '729 patent, which states: "The preferred values of R is aryl lower alkyl, especially **benzyl**…." (Ex. 1009, '729 patent, 5:17-18.) Moreover, the '729 patent specifically claims a genus of anticonvulsant compositions that encompass lacosamide (Ex. 1009, '729 patent, Claim 1), further specifying: "wherein **R is benzyl**, $R_1$ is methyl, … and n is 1" (Ex. 1009, '729 patent, Claim 18). A POSA would have been motivating to pursue the above preferences in the '729 patent, because the '729 patent touts: "the compounds of the present invention ***exhibit excellent anticonvulsant activity***." (Ex. 1009, '729 patent, 16:6-7.) Moreover, Table I of the '729 patent provides potency and toxicity data for 54 "representative compounds" of the disclosed inventions, of which 49 of the compounds—over 90%—contain an unsubstituted benzyl at the R position, which further confirms the obvious selection of unsubstituted benzyl at R. (Ex. 1009, '729 patent, 58:1-3 and Tbl. I.) The most potent compounds in Table I have unsubstituted benzyl at R and unsubstituted methyl at $R_1$. (*Id*.) Finally, the inventor of the '551 patent, Dr. Harold Kohn, published an article (Ex. 1012, Kohn 1991) regarding modifications at the R and $R_1$ substituents, explaining: "Potent protection against maximal electroshock seizures (MES) in mice was observed for

functionalized amino acid racemates containing both an ***N-benzylamide moiety*** and an acetylated amino group." (Ex. 1012, Kohn 1991, p. 2444.) This teaches a POSA that potent activity is achieved when a benzyl is on one end of the functionalized amino acid and a methyl is on the other end. Indeed, all 26 compounds reported in Kohn 1991 had ***unsubstituted benzyl at R*** and unsubstituted methyl at $R_1$. (*Id.*, pp. 2444, 2445, Tbl. 1.)

- ***Preference of Methyl at $R_1$***. The '301 patent itself states: "The most preferred $R_1$ group is **methyl**." (Ex. 1019, '301 patent, 5:12-13.) Apart from the '301 patent itself, and further confirming this obvious preference, a POSA would have seen the identical preference for methyl in the prior art '729 patent, which states: "The most preferred $R_1$ group is **methyl**." (Ex. 1009, '729 patent, 5:19.) Moreover, the '729 patent specifically claims a genus of anticonvulsant compositions that encompass lacosamide (Ex. 1009, '729 patent, Claim 1), further specifying: "wherein R is benzyl, **$R_1$ is methyl**, … and n is 1" (Ex. 1009, '729 patent, Claim 18). A POSA would have been motivating to pursue the above preferences in the '729 patent because the '729 patent touts that "the compounds of the present invention ***exhibit excellent anticonvulsant activity***." (Ex. 1009, '729 patent, 16:6-7.) Moreover, Table I of the '729 patent provides potency and toxicity data for 54

"representative compounds" of the disclosed inventions, with all 54 of the compounds—100%—containing an unsubstituted benzyl at the R position, which further confirms the obvious selection of unsubstituted benzyl at R. (Ex. 1009, '729 patent, 58:1-3, Tbl. I.) The most potent compounds in Table I have unsubstituted benzyl at R and unsubstituted methyl at $R_1$. (*Id*.) Finally, the inventor of the '551 patent, Dr. Harold Kohn, published an article (Ex. 1012, Kohn 1991) regarding modifications at the R and $R_1$ substituents, explaining: "Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an N-benzylamide moiety and an ***acetylated amino group***." (Ex. 1012, Kohn 1991, p. 2444.) This teaches a POSA that potent activity is achieved when a benzyl is on one end of the functionalized amino acid and a methyl is on the other end. As noted above, all 26 compounds reported in Kohn 1991 had unsubstituted benzyl at R and ***unsubstituted methyl*** at $R_1$. (*Id.*, pp. 2444, 2445, Tbl. 1.)

- ***Preference of R- (or D-) enantiomer***. Both the '301 patent and '729 patent recognize that the claimed compounds exist as pairs of stereoisomers (D or R on the one hand, versus S or L on the other hand), and that between these two stereoisomers, "[t]he **D [R] stereoisomer** is

preferred." (Ex. 1019, '301 patent, 11:20; Ex. 1009, '729 patent, 10:28.) 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. (Ex. 1009, '729 patent, col. 58-61, Tbl. I.) 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.*) Likewise, Kohn 1991 expressly teaches that, with respect to this class of compounds, "in each case the ***anticonvulsant activity resided primarily in the R stereoisomer***." (Ex. 1012, Kohn 1991, p. 2444.) Finally, POSA would have known how to resolve the claimed compounds into the R-isomer using standard techniques known in the art, because the '551 patent admits as much: "[t]he racemic mixture . . . can be resolved into the R-isomer by ***standard techniques known in the art*** such as chiral chromatography." (Ex. 1001, '551 patent, 8:59-61.) The '729 patent likewise confirms this: "Diastereomers can then be separated by ***recognized techniques known in the art***, such as fractional recrystallization and the like." (Ex. 1009, '729 patent, 15:31-16:4.)

***Summary regarding Claims 1-9:*** As shown above for claims 1-9 of the '551 patent, it would have been obvious to select benzyl and methyl at R and

$R_1$, and to select the R-isomer over the S-isomer. These selections fall within even the most specific claims, such as claims 2 and 9 directed to "substantially" or "at least 90%" enantiopure compounds, given that the above disclosures would have motivated a POSA to select and isolate the R-isomer up to 100% enantiopurity. *See Spectrum Pharms., Inc. v. Sandoz Inc*., 802 F. 3d 1326, 1335 (Fed. Cir. 2015) (explaining that 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"); *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.").

### 3. Claim 10 of the '551 patent is not patentably distinct over Claim 46 of the '301 patent

Claim 10 of the '551 patent and claim 46 of the '301 patent are identical except for (1) the compound claims they refer to, and (2) "anticonvulsant

composition" is replaced in claim 10 with "therapeutic composition." Neither difference renders claim 10 patentably distinct over claim 46 of the '301 patent.

The compound limitation of claim 10 of the '551 patent includes the compounds of claims 1-9, and thus for the reasons discussed above regarding claims 1-9, the compound limitation of claim 10 of the '551 patent is obvious over claim 44 or claim 45 of the '301 patent.

The "therapeutic composition" term in claim 10 of the '551 patent has the same meaning as the "anticonvulsant composition" term in claim 46 of the '301 patent. The '301 patent's description of an "anticonvulsant composition" clearly indicates that it is the same as the "therapeutic composition" in claim 10 of the '551 patent, and Patent Owner itself represented to the PTO that "[c]laim 46 [of the '301 patent] cover[s] a "***therapeutic composition***." (Ex. 1007, PTE Request, p.6.) Moreover, the '301 patent specification states that (1) its claimed "compositions … are useful in the treatment of epilepsy and other CNS disorders;" (2) "[t]he mainstay of treatment for such disorders has been the ***long-term and consistent administration*** of anticonvulsant drugs;" and (3) the claimed "***therapeutic compositions***" may be administered "***daily***." (Ex. 1019, '301 patent, 1:29-33, 2:36-38, 18:33-52.) Therefore, claim 46 of the '301 patent

meets the term "therapeutic composition" in the preamble of claim 10 of the '551 patent, even if the Office were to construe the preamble to be limiting (which it should not) and even if the Office were to adopt a narrow construction for that term (which it should not).

Aside from the '301 patent, the disclosures of the '729 patent render the therapeutic composition obvious. Claim 1 of the '729 patent recites: "An anticonvulsant composition comprising an ***anti-convulsant effective amount*** … and a ***pharmaceutically acceptable carrier***." The '729 patent teaches: "[T]he 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, '729 patent, 3:35-40, 16:5-8 (compounds "exhibit excellent anticonvulsant activity").)

The '729 patent teaches ranges of ***anticonvulsant effective amounts*** that are identical to the ranges described in the '551 patent. The '729 patent states that the compounds "exhibit excellent anticonvulsant activity," (Ex. 1009, '729 patent, 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—"about 5 to about 1000 mg." (Ex. 1001, '551 patent, 10:52-59.) Therefore, the '729 patent teaches the limitation "anticonvulsant effective amount."

Regarding a "pharmaceutically acceptable carrier," the '729 patent teaches that the genus of claimed compounds, which encompasses lacosamide, can be "compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier." (Ex. 1009, '729 patent, 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." (Ex. 1009, '729 patent, 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." (Ex. 1009, '729 patent, 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, Wang, ¶ 76.) Therefore, the '729 patent teaches the limitation "pharmaceutically acceptable carrier."

A POSA would have had a reasonable expectation of success in making and using the therapeutic composition of claim 10 of the '551 patent. (Ex. 1002, Wang, ¶¶ 78-79.) Like the '301 patent, the '729 patent claims cover lacosamide. Like the '301 patent, the '729 patent states that the claimed amino acid compounds are useful to treat CNS disorders, including epilepsy. And like the '301 patent, the '729 patent is presumed enabled. *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."). Furthermore, 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, Wang, ¶ 75.) A POSA could have successfully used established FDA guidelines and known dose-finding studies for determining an effective amount of a drug. (Ex. 1002, Wang, ¶ 74; Ex. 1021, FDA Guideline, pp. 9, 13 (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, Schmidt, pp. 15-19 (describing "dose-finding studies" for determining the effective amount of a drug)).

### 4. Claims 11-13 of the '551 patent are not patentably distinct over Claim 47 of the '301 patent

Method claims 11-13 of the '551 patent are directed to "treating central nervous system disorders" by administering an "anticonvulsant effective amount" of the compound. Those claims are obvious.

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, Wang, ¶ 81.) 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 read the prior references as discussing the treatment of CNS disorders in humans, not merely in rodents. (Ex. 1002, Wang, ¶ 81.)

Second, the preclinical data disclosed in each of the '301 patent, the '729 patent, and Kohn 1991 is the same type of preclinical data disclosed in the '551 patent as support for its method of treatment claims. (Ex. 1001, '551 patent, 21:27-22:22; Ex. 1002, Wang, ¶ 81.) Indeed, the '551 patent itself does not contain data on *human* subjects but instead relies on screening tests performed on *rodents*. (Ex. 1001'551 patent, 21:27-22:22.) The rodent tests were deemed enabling for claim 13 of the '551 patent, 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").

Third, the '301 patent discloses the utility of treating CNS disorders in humans. It discloses that its "compositions … are useful in the treatment of epilepsy and other CNS disorders," and are directed to addressing the problem that "a significant ***percentage of the population [i.e., humans]*** with epilepsy or related disorders are poorly managed," and teaches the utility of treating CNS disorders in "mammalian subjects" by administering an anticonvulsant effective amount of lacosamide. (Ex. 1019, '301 patent, 1:29-32, 2-26-38, 3:4-5, 20:21.)

Fourth, the '729 patent provides an additional reason for a POSA to expect racemic lacosamide and R-lacosamide 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, '729 patent, 3:9-17.) The '729 patent also specifically claims the compounds in a "method of

treating central nervous system disorders in animals." (Ex. 1009, '729 patent, Claim 132.) A POSA would reasonably expect that compounds falling within claim 132 of the '729 patent, such as lacosamide, would be useful for treating CNS disorders, and would have a reasonable expectation of success in using them for this purpose. (Ex. 1002, Wang, ¶ 80); *see Amgen*, 314 F.3d at 1355.

Fifth, and as noted above, the '729 patent discloses the same ranges of an "anticonvulsant effective amount"—about ***5 mg to about 1000 mg***—that the '551 teaches as an anticonvulsant effective amount. (*Compare* Ex. 1009, '729 patent, 16:44-47; *with* Ex. 1001, '551 patent, 10:52-59.) Thus, a POSA would reasonably expect that the amounts disclosed in the prior art is an "anticonvulsant effective amount," as required by claims 11-13 of the '551 patent.

### D. Ground 2: Claims 1-13 are unpatentable for OTDP over the '301 patent in view of the '729 patent and LeGall

Claims 1-13 are unpatentable for obviousness-type double patenting ("OTDP") over the **'301 patent** (Ex. 1019) in view of the **'729 patent** (Ex. 1009) and **LeGall** (Ex. 1008). The elements of claims 1-13 of the '551 patent are mapped to the teachings of the above-cited references in the Claim Charts in Part VII below, starting on page 68 of this request. Based

on those teachings, and for the reasons explained below, claims 1-13 should be rejected under Ground 1.

**1. LeGall is prior art under 35 U.S.C. § 102(b)**

LeGall is a University of Houston master's thesis that bears the date "***December, 1987***" on its first page. (Ex. 1008, LeGall, p. *i*.) The author of the thesis, Mr. Philippe LeGall, was a master's student in Dr. Kohn's research group, and Dr. Kohn's signature appears on the second page as one of the faculty members who signed and approved the thesis. (Ex. 1008, LeGall, p. *ii*.) The LeGall thesis was deposited in the University of Houston library on or around 1987, as Patent Owner's own expert Dr. William Roush admitted under oath in District Court litigation:

> Q. So LeGall is out there in the art back in 1987; correct?
>
> A. ***The LeGall thesis was deposited in the University of Houston library***. I mean, it's signed in December, I don't recall what date it actually appeared in the library, but ***I'll give you 1987 time***.
>
> Q. And I'm not meaning to be fuzzy about the precise date. ***Sometime long before 1996***, that's true, isn't it, Doctor, we can say that?
>
> A. ***I would agree with that***.

(Ex. 1039, Roush Trial Transcript, p. 683.)

Additional sworn testimony by defendants' expert Dr. Clayton Heathcock in the District Court litigation states:

> Q. And ***when was the thesis published***?
>
> A. ***December 1987***.
>
> Q. And where was it published?
>
> A. It was submitted to the Faculty of Chemistry at the University of Houston.
>
> Q. Who was the first person to approve the thesis?
>
> A. This was Dr. Harold Kohn.

(Ex. 1041, Heathcock Trial Transcript, p. 102.)

Dr. Harold Kohn—the sole named inventor on the '551 patent and thesis advisor who read, signed, and approved LeGall—had a duty to disclose LeGall to the PTO, both during original prosecution in 1997-1999 and again when the patent was reissued in 2002-2004. *See* 37 C.F.R. § 1.56(c) (1997–2004) (duty to disclose applies to "[e]ach inventor named in the application"). However, on both occasions before the PTO, LeGall was never disclosed to any Examiner.[10]

[10] Dr. Kohn has admitted that he "read" the LeGall thesis "before" he approved it, and that he has personally received "about $25 million" in royalties to date from his '551, '301, and '729 patents, and that these royalties "will continue through 2022" when the '301 patent expires. (Ex. 1038, Kohn Trial Transcript, pp. 535-536, 539.)

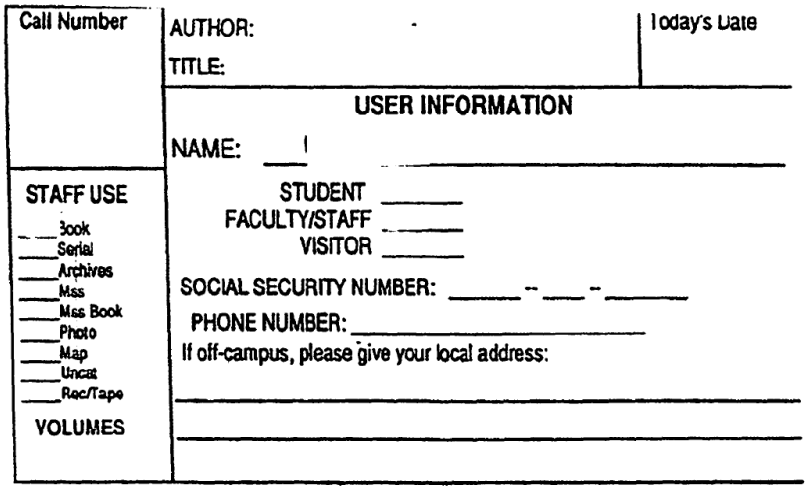
For the following reasons, there is sufficient evidence that LeGall was publicly accessible in the University of Houston library before March 15, 1995, to establish a *prima facie* case that LeGall constitutes a "printed publication" under 35 U.S.C. § 102(b):

*a. Patent Owner admitted that LeGall is prior art*. In the Federal District Court litigation, Patent Owner filed a "Statement of Uncontested Facts" in which the Patent Owner admitted "the LeGall thesis was publicly accessible more than one year before the earliest priority date for the '551 patent and constitutes a 'printed publication' within the meaning of 35 U.S.C. § 102(b)." (Ex. 1004, Joint Statement, p. 19, ¶ 87.) This admission ***made in a court record*** is binding against Patent Owner and can be utilized in this reexamination proceeding, both for purposes of the initial reexamination determination and reexamination on the merits. *See* MPEP § 2258. Moreover, as the MPEP explains, "[a]n admission as to what is in the prior art is simply that, an admission, and ***requires no independent proof***. It is an acknowledged, declared, conceded, or recognized fact or truth." *Id*. Therefore, Patent Owner's admission that LeGall "constitutes a 'printed publication' within the meaning of 35 U.S.C. § 102(b)" is a recognized truth that requires no independent proof. (Nevertheless, additional proof is offered below.)

*b. LeGall is explicitly cited by name and location in three different journal articles*. As explained in MPEP § 2128.01, "Even if access to the library is restricted, a reference will constitute a 'printed publication' as long as a presumption is raised that the portion of the ***public concerned with the art would know of the invention***." Here, members of the public concerned with the art would know of the LeGall thesis because three different journal articles published by Dr. Kohn's research group (articles that scientists interested in LeGall's functionalized amino acids would read) explicitly cite to the thesis by the author's name (Philippe LeGall) and location (University of Houston). (Ex. 1016, LeGall 1988, p. 279 (citing "Masters dissertation of this author," listed as "**Philippe LeGall**" at "University of Houston"); Ex. 1017, Kohn 1993, p. 3360 n.9b (citing "**LeGall, P. M.S. Thesis, University of Houston, 1987"**); Ex. 1010, Choi 1995, p. 7013 n.16 (citing "**LeGall, P. M.S. Thesis, University of Houston**").) These three explicit citations would lead a POSA to the University of Houston library, where the POSA could request a copy of LeGall by author name (Philippe LeGall).

*c. Visitors to the University of Houston library in 1988-1997 could have requested LeGall by author name*. Requester has obtained from the University of Houston "a blank Special Collections request form from the decade in question," *i.e.*, 1988-1997. (Ex. 1028, University of Houston

response, at p. 0009.) According to the University, "[t]hese forms have not changed significantly over the years except perhaps in formatting." (*Id.*) The Special Collections request form, reproduced below, would have allowed a "VISITOR" in 1988-1997 to request a University of Houston masters thesis by identifying the "AUTHOR" of the document. (*Id.* at p. 0010.) Thus, using the form below, a visitor could have obtained the LeGall thesis by identifying its author, Philippe LeGall, and optionally identifying the document as a M.S. Thesis.


Call Number

AUTHOR:

TITLE:

Today's Date

USER INFORMATION

NAME:

STAFF USE

___Book
___Serial
___Archives
___Mss
___Mss Book
___Photo
___Map
___Uncat
___Rec/Tape

VOLUMES

STUDENT _____
FACULTY/STAFF _____
VISITOR _____

SOCIAL SECURITY NUMBER: _____ -- ___ - _____

PHONE NUMBER: _____

If off-campus, please give your local address:

(Ex. 1028, University of Houston response, at p. 0010.)

*d. University of Houston has a list of dates when LeGall was checked out*. As explained in MPEP § 2128, the "Examiner need not prove anyone actually looked at the document" in order to qualify as a "printed publication." Even so, Requester is aware that the University of Houston possesses a "spread sheet" of the dates when LeGall was "checked out" of

the library. (Ex. 1028, University of Houston response, at p. 0003 (stating "the responsive information is enclosed" with the University's letter).)[11] Therefore, not only was LeGall ***accessible*** by the public, LeGall was ***actually accessed*** in the library, which is more than is required to prove LeGall is a "printed publication" under 35 U.S.C. § 102(b).

*e. Numerous publications before the '551 patent's critical date cited to other University of Houston masters theses from the 1980s*. As MPEP § 2128.02 explains, "Evidence showing ***routine business practices*** can be used to establish the date on which a publication became accessible to the public." Here, numerous other publications (besides the three that cite directly to LeGall) contain citations to *other* University of Houston masters theses from the mid-1980s to early-1990s (before the '551 patent's critical date). This evidence establishes a "routine business practice" by the University of Houston library, prior to 1995, in making the University's

[11] The University withheld this spread sheet from Requester, claiming that "the dates when [the LeGall] thesis was checked out of the University library" is "critical" and "crucial" information, the release of which would jeopardize the University's "financial interest in royalties received from the patent." (*Id.* at pp. 0005, 0006.) Because the University is Patent Owner's licensee and identifies this information as "critical" and "crucial" to patentability, the information is, at the very least, "material" to patentability under 37 C.F.R § 1.56. In this proceeding, Patent Owner will have a duty to disclose all information pertaining to the public accessibility of LeGall of which it is aware. Such information includes "the proof" discovered in litigation which required Patent Owner to stipulate that LeGall is prior art. (Ex. 1040, Trial Transcript Def.'s Opening, p. 44.)

1980s-90s masters theses available to the public. *See* Ex. 1029, Zhou, pp. 42-43 nn.8, 11, 20 (article published in 1992 citing three University of Houston theses from ***1988-1991***); Ex. 1030, Mistree 1989, p. 1135 nn.21, 28 (article published in 1989 citing two University of Houston theses from ***1985*** and ***1988***); Ex. 1031, Mistree 1993, pp. 157-158 (article from 1993 citing four University of Houston theses from ***1985-1990***); Ex. 1032, Ingram, p. 649 n.9 (article from 1988 citing a "Master's Thesis, University of Houston, ***1987***"). As previously mentioned, any "VISITOR" to the library could have accessed any of these masters theses using the Special Collections request form reproduced above. (Ex. 1028, University of Houston response, at p. 0010.)

### 2. Claims 1-9 of the '551 patent differ from Claims 43-45 of the '301 patent only at the R and $R_1$ substituents and stereochemistry

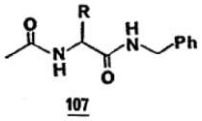
Requester realleges and incorporates by reference the assertions of Part VI.C.1 above, beginning on page 38. For the reasons set forth therein, the only differences between claims 1-9 of the '551 patent claims 43-45 of the '301 patent are: (1) unsubstituted benzyl at R, (2) unsubstituted methyl at $R_1$, and (3) selection of the R- (or D-) enantiomer over the S- (or L-) enantiomer. As will be explained next, those differences were trivially obvious.

### 3. The differences between Claims 1-9 of the '551 patent and Claims 43-45 of the '301 patent were obvious in view of LeGall

Requester realleges and incorporates by reference the assertions of Part VI.C.2 above, beginning on page 40. In addition to the teachings of the '301 patent and '729 patent incorporated herein, LeGall provides further reasons why the differences between claims 1-9 of the '551 patent and claims 43-45 of the '301 patent were obvious:

- ***Preference of Benzyl at R***. LeGall provides additional reasons to select unsubstituted benzyl at R. Like claims 44-45 of the '301 patent, LeGall's compound 107e contains a methoxymethyl at the $R_3$ position. (Ex. 1008, LeGall, p. 133, Tbl. 35.) And consistent with the'301 patent and '729 patent's preferences that the "preferred values of R is … especially benzyl" (Ex. 1019, '301 patent, 5:11-12; Ex. 1009, '729 patent, 5:17-18), LeGall's compound 107e contains both an ***unsubstituted benzyl at R*** and an unsubstituted methyl at $R_1$ (Ex. 1008, LeGall, p. 133, Tbl. 35.) Moreover, a POSA would have been motivated to follow LeGall's selections for R and $R_1$, because LeGall expressly states: "The close structural analogy of this compound [107e] with 86b suggest[s] that this adduct [107e] may have ***good anticonvulsant activity***." (Ex. 1008, LeGall, p. 155.) This statement in LeGall is an

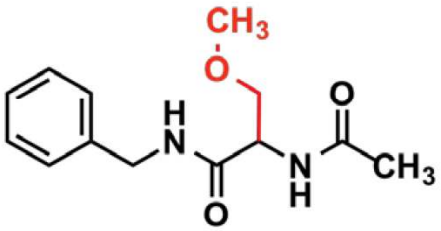
express teaching, suggestion, or motivation to select LeGall's compound 107e. Compound 107e of LeGall is depicted below, showing both an unsubstituted benzyl and unsubstituted methyl on each of the two ends:



107

| No. | R |
|---|---|
| 68a | $CH_3$ |
| 107a | CN |
| 107b | $CONH_2$ |
| 107c | $COOCH_2CH_3$ |
| 107d | $CH_2OH$ |
| 107e | $CH_2OCH_3$ |

Ex. 1008, LeGall, p. 133, Tbl. 35 (red box added).



**LeGall thesis compound 107e (racemic lacosamide)**

(methoxymethyl colored red)

- ***Preference of Methyl at $R_1$***. As depicted above in compound 107e, LeGall motivates the selection of an unsubstituted methyl at $R_1$. Like claims 44-45 of the '301 patent, LeGall's compound 107e contains a methoxymethyl at the $R_3$ position. (Ex. 1008, LeGall, p. 133, Tbl. 35.) And consistent with the'301 patent and '729 patent's preferences that the "most preferred $R_1$ group is methyl" (Ex. 1019, '301 patent, 5:12-13; Ex. 1009, '729 patent, 5:19), LeGall's compound 107e contains both an unsubstituted benzyl at R and an ***unsubstituted methyl at $R_1$*** (Ex. 1008,

LeGall, p. 133, Tbl. 35.) LeGall motivates this selection by predicting that "this adduct [107e] may have ***good anticonvulsant activity***." (Ex. 1008, LeGall, p. 155.)

- ***Preference of R- (or D-) enantiomer***. LeGall teaches a POSA to select the R- (or D-) enantiomer over the L- (or S-) enantiomer. Like claims 44-45 of the '301 patent, LeGall's compound 107e contains a methoxymethyl at the $R_3$ position. (Ex. 1008, LeGall, p. 133, Tbl. 35.) And consistent with the'301 patent and '729 patent's experimental data and explicit preference that "[t]he D [/R] stereoisomer is preferred" (Ex. 1019, '301 patent, 11:20; Ex. 1009, '729 patent, 10:28), LeGall observes that the R-enantiomer of compound 68a was ***thirteen times more active*** than the S-enantiomer, with a comparable difference for the two stereoisomers of 68b. (Ex. 1008, LeGall, p. 42; Ex. 1002, Wang, ¶¶ 70-72.) LeGall further states that R-enantiomers are "***more active and less toxic*** than the corresponding racemates" and therefore suggests that the R-isomers of 69a and 69b "may display even ***improved pharmacological properties***." (Ex. 1008, LeGall, pp. 164-65.) Given the close structural similarity of 68a and 107e, 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 the R-enantiomer of 107e.

***Summary regarding Claims 1-9:*** As shown above for claims 1-9 of the '551 patent, it would have been obvious to select unsubstituted benzyl and unsubstituted methyl at R and $R_1$, and to select the R-isomer over the S-isomer. These selections fall within even the most specific claims, such as claims 2 and 9 directed to "substantially" or "at least 90%" enantiopure compounds, given that the above disclosures would have motivated a POSA to select and isolate the R-isomer up to 100% enantiopurity. Specifically, a POSA would have had a reason to believe that (a) racemic lacosamide disclosed in LeGall as compound 107e would have "good" to "excellent" anticonvulsant activity, (Ex. 1008, LeGall, p. 166; Ex. 1009, '729 patent, 16:7); (b) R-lacosamide would be "more active and less toxic" than the racemate, (Ex. 1008, LeGall, p. 164); and (c) it would have been routine to isolate or prepare the R-isomer using "standard techniques known in the art," (Ex. 1001, '551 patent, 8:52; Ex. 1009, '729 patent, 15:31-16:4). These express disclosures are sufficient to render claim 2 and 9 obvious under controlling Federal Circuit precedent involving purification or isolation of isomeric compounds. *See Spectrum*, 802 F. 3d at 1335; *Aventis*, 499 F.3d at 1301.

#### 4. Claim 10 of the '551 patent is not patentably distinct over Claim 46 of the '301 patent in view of LeGall

Requester realleges and incorporates by reference the assertions of Part VI.C.3 above, beginning on page 46. In addition to the teachings of the '301 patent and '729 patent incorporated herein, LeGall provides further reasons why the differences between claim 10 of the '551 patent and claim 46 of the '301 patent were obvious.

As explained above, LeGall discloses compound 107e, which contains a methoxymethyl, an unsubstituted benzyl, and an unsubstituted methyl at each of the claimed substituent groups of claims 1-9 of the '551 patent. In its introduction, LeGall reviews the state of the art for treating epilepsy and highlights "the ***anticonvulsant properties*** of several N-benzyl amino acids," which the thesis describes as "a new class of ***anticonvulsant*** drugs." (Ex. 1008, LeGall, p. 42.) LeGall explains that compound 107e—the racemic compound that contains lacosamide—was prepared "[i]n an effort to further delineate the structure-activity relationship of this novel class of ***antiepileptic compounds***." (*Id.* at p. 43.) Although the anticonvulsant activity of 107e was not reported, LeGall expressly states—and accurately predicts—that compound 107e "may have ***good anticonvulsant activity***" in light of the "close structural analogy of this compound with 86b." (Ex.

1008, LeGall, p. 155.) LeGall therefore provides a clear reason for a POSA to select compound 107e as an active ingredient in a therapeutic composition for treatment of epilepsy and other CNS disorders. Ex. 1002, Wang, ¶ 73.

### 5. Claims 11-13 of the '551 patent are not patentably distinct over Claim 47 of the '301 patent in view of LeGall

Requester realleges and incorporates by reference the assertions of Part VI.C.4 above, beginning on page 51. In addition to the teachings of the '301 patent and '729 patent incorporated herein, LeGall provides further reasons why the differences between claims 11-13 of the '551 patent and claim 47 of the '301 patent were obvious.

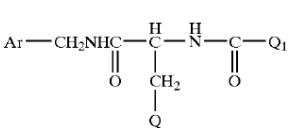
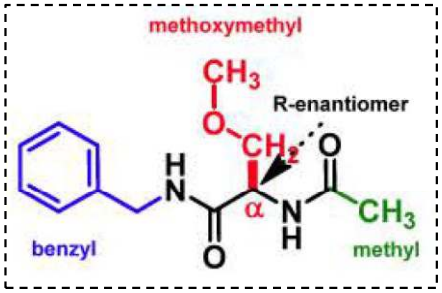
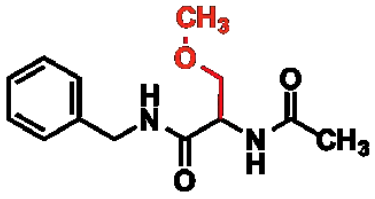
LeGall describes the "***clinical applications***" of anticonvulsant compounds "for the ***treatment of epilepsy***" in humans (Ex. 1008, LeGall, pp. 25-30)—a CNS disorder. LeGall specifically describes how the synthesized compounds were screened for anticonvulsant activity in mice, (*id.* at pp. 102-03, 162-63), using the same preclinical test methods disclosed in the '551 patent as enabling methods of treating CNS disorders, (*e.g.*, Ex. 1001, '551 patent, 21:27-22:22). And, as discussed above, LeGall states that compound 107e is expected to have "***good anticonvulsant activity***." (Ex. 1008, LeGall, p. 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.

Importantly, 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, '551 patent, 21:27-22:22; Ex. 1002, Wang, ¶ 81.) Indeed, the '551 patent itself does not contain data on human subjects but instead relies on screening tests performed on rodents. (Ex. 1001, '551 patent, 21:27-22:22.) The rodent tests were deemed enabling for claim 13, directed to humans. Therefore, LeGall enables a POSA to treat humans to the same extent as claim 13 of 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").

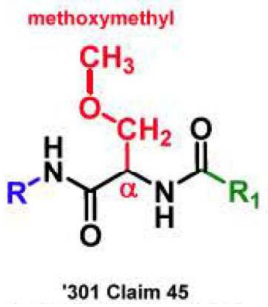
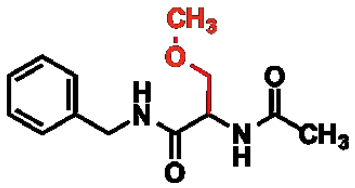
## VII. CLAIM CHARTS IN SUPPORT OF PROPOSED REJECTIONS

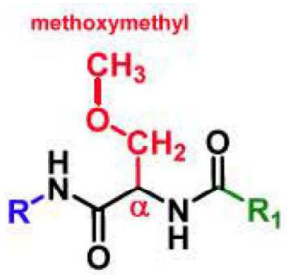
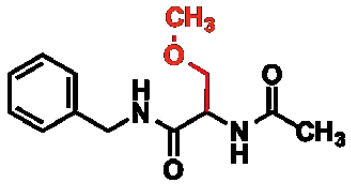
In the following claim charts, each claim of the '551 patent is item-mapped to the disclosures of the patents, printed publications, and Patent Owner admissions discussed above.

| '551 Patent Claims | '301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| 1. A compound in the R configuration having the formula:<br>  <br>wherein<br>**Ar is phenyl which is unsubstituted or substituted with at least one halo group**;<br>**Q is lower alkoxy**, and<br>**Q1 is methyl**.<br>  <br><br>**Lacosamide** | ***Methoxy at Q (Methoxymethyl):***<br>• '301 patent, Claim 43 ($R_2$ or $R_3$ "is **lower alkoxy**").<br>• '301 patent, Claim 45 (depending on Claim 44):<br>  <br><br>'301 Claim 45<br>• Patent Owner's PTE Request, p.6 ("A **lower alkoxy**, such as a **-$OCH_3$ group**, is defined by ['301 patent's] dependent claim 43 and the specification as a suitable electron donating group.").<br>• Patent Owner's Statement of Uncontested Facts, p.19 ¶88 ("[C]laim 44 of U.S. Patent No. 5,654,301 … defines a genus of compounds with a **methoxymethyl** group at $R_3$.")<br>• LeGall, p.133, Tbl. 35 (compound 107e):<br>  <br>**LeGall thesis compound 107e (racemic lacosamide)** |

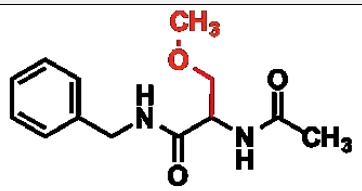
| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | • Patent Owner’s Statement of Uncontested Facts, p.19 ¶87 (“[T]he LeGall thesis was publicly accessible more than one year before the earliest priority date for the ’551 patent and constitutes a ‘printed publication’ within the meaning of 35 U.S.C. § 102(b).”).<br>***Phenyl at Ar (Unsubstituted Benzyl at R):***<br>• ’301 patent, 5:11-12 (“The preferred values of R is aryl lower alkyl, especially **benzyl**.…”).<br>• ’729 patent, Claim 18 (“The composition of claim 1 wherein **R is benzyl**, $R_1$ is methyl, $R_2$ is hydrogen, $R_3$ is methyl and n is 1 or the D or L steroisomer.”).<br>• ’729 patent, 5:17-18 (“The preferred values of R is aryl lower alkyl, especially **benzyl**.…”).<br>• ’729 patent, col. 58:1-3 and Tbl. I (49 of the 54 tested compounds—over 90%—contained an **unsubstituted benzyl** at the R position).<br>• Kohn 1991, p.2444 (“Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an ***N*-benzylamide** moiety and an acetylated amino group.”)<br>• Kohn 1991, Tbl. 1 (all 26 compounds reported in Kohn 1991 had **unsubstituted benzyl** at R and unsubstituted methyl at $R_1$).<br>• LeGall, pp.133, 155 (compound 107e contains an **unsubstituted benzyl** at R and is predicted to “have good anticonvulsant activity”).<br>***Methyl at Q1:***<br>• ’301 patent, 5:12-13 (“The most preferred $R_1$ group is **methyl**.”).<br>• ’729 patent, Claim 18 (“The composition of claim 1 wherein R is benzyl, $R_1$ is **methyl**, $R_2$ is hydrogen, $R_3$ is methyl and n is 1 or the D or L steroisomer.”).<br>• ’729 patent, 5:19 (“The most preferred $R_1$ group |

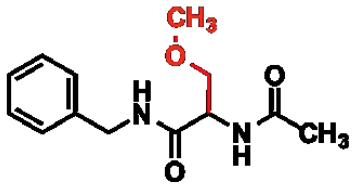
| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | is **methyl**.”).<br>• ’729 patent, col. 58:1-3 and Tbl. I (54 of the 54 tested compounds—100%—contained an **unsubstituted methyl**).<br>• Kohn 1991, p.2444 (“Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an *N*-benzylamide moiety and an **acetylated amino** group.”)<br>• Kohn 1991, Tbl. 1 (all 26 compounds reported in Kohn 1991 had unsubstituted benzyl at R and **unsubstituted methyl** at $R_1$).<br>• LeGall, pp.133, 155 (compound 107e contains an **unsubstituted methyl** at $R_1$ and is predicted to “have good anticonvulsant activity”). |
| 2. The compound according to claim 1 which is substantially enantiopure. | ***Known preference for R (or D) configuration:***<br>• ’301 patent, 11:20 (“The **D [/R] stereoisomer** is preferred.”).<br>• ’729 patent, 10:28 (“The **D [/R] stereoisomer** is preferred.”).<br>• ’729 patent, col.58-61, Tbl. 1 (biological data demonstrating that the **R-isomers** of similar compounds were at least **ten times more active** than their corresponding S-isomers, and 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).<br>• Kohn 1991, p. 2444 (“[I]n each case the anticonvulsant activity resided primarily in the **R stereoisomer**.”)<br>• LeGall, p.42 (**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).<br>• LeGall, pp.164-65 (R-isomer is “**more active** and **less toxic** than the corresponding racemates,” and therefore predicting that that R-isomers of |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | 69a and 69b “may display even **improved pharmacological properties**”).<br><br>***Known isolation techniques:***<br><br>• ’551 patent, 8:59-61 (Patent Owner admission that “the racemic mixture . . . can be resolved into the R-isomer by **standard techniques known in the art** such as chiral chromatography”).<br><br>• ’729 patent, 15:31-16:4 (stereoisomers are “**separated by recognized techniques known in the art**,” including fractional crystallization and chiral chromatography). |
| 3. The compound according to claim 1wherein **Q is lower alkoxy containing 1-3 carbon atoms**. | • ’301 patent, Claim 45 (depending on Claim 44):<br>  <br><br>'301 Claim 45<br><br>• Patent Owner’s PTE Request, p.6 (“A **lower alkoxy, such as a -$OCH_3$ group**, is defined by [’301 patent’s] dependent claim 43 and the specification as a suitable electron donating group.”).<br><br>• Patent Owner’s Statement of Uncontested Facts, p.19 ¶88 (“[C]laim 44 of U.S. Patent No. 5,654,301 … defines a genus of compounds with a **methoxymethyl** group at $R_3$.”)<br><br>• LeGall, p.133, Tbl. 35 (compound 107e):<br>  <br><br>**LeGall thesis compound 107e (racemic lacosamide)** |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| 4. The compound according to claim 3 wherein **Q is methoxy**. | • ’301 patent, Claim 45 (depending on Claim 44):<br>  <br><br>'301 Claim 45<br>• Patent Owner’s PTE Request, p.6 (“The central chiral carbon atom is bonded to a hydrogen and a **-$CH_2OCH_3$ group** (a lower alkyl substituted with a **methoxy group**), thus satisfying the [’301 patent] claim’s requirement that one of $R_2$ and $R_3$ be a hydrogen while the other of $R_2$ and $R_3$ is a lower alkyl substituted with an electron donating group.”)<br>• Patent Owner’s Statement of Uncontested Facts, p.19 ¶88 (“[C]laim 44 of U.S. Patent No. 5,654,301 … defines a genus of compounds with a **methoxymethyl** group at $R_3$.”)<br>• LeGall, p.133, Tbl. 35 (compound 107e):<br>  <br><br>**LeGall thesis compound 107e (racemic lacosamide)** |
| 5. The compound according to claim 1 wherein **Ar is unsubstituted phenyl**. | ***Phenyl at Ar (Unsubstituted Benzyl at R):***<br>• ’301 patent, 5:11-12 (“The preferred values of R is aryl lower alkyl, especially **benzyl**.…”).<br>• ’729 patent, Claim 18 (“The composition of claim 1 wherein **R is benzyl**, $R_1$ is methyl, $R_2$ is hydrogen, $R_3$ is methyl and n is 1 or the D or L steroisomer.”).<br>• ’729 patent, 5:17-18 (“The preferred values of R |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | is aryl lower alkyl, especially **benzyl**.…”).<br>• ’729 patent, col. 58:1-3 and Tbl. I (49 of the 54 tested compounds—over 90%—contained an **unsubstituted benzyl** at the R position).<br>• Kohn 1991, p.2444 (“Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an ***N*-benzylamide** moiety and an acetylated amino group.”)<br>• Kohn 1991, Tbl. 1 (all 26 compounds reported in Kohn 1991 had **unsubstituted benzyl** at R and unsubstituted methyl at $R_1$).<br>• LeGall, pp.133, 155 (compound 107e contains an **unsubstituted benzyl** at R and is predicted to “have good anticonvulsant activity”). |
| 6. The compound according to claim 1 wherein halo is fluoro. | • Same as claim 1. |
| 7. The compound according to claim 1 wherein **Q is alkoxy containing 1-3 carbon atoms** and **Ar is unsubstituted phenyl**. | ***Q is alkoxy containing 1-3 carbon atoms:***<br>• ’301 patent, Claim 45 (depending on Claim 44):<br>  <br><br>'301 Claim 45<br>• Patent Owner’s PTE Request, p.6 (“A **lower alkoxy, such as a -$OCH_3$ group**, is defined by [’301 patent’s] dependent claim 43 and the specification as a suitable electron donating group.”).<br>• Patent Owner’s Statement of Uncontested Facts, p.19 ¶88 (“[C]laim 44 of U.S. Patent No. 5,654,301 … defines a genus of compounds with a **methoxymethyl** group at $R_3$.”)<br>• LeGall, p.133, Tbl. 35 (compound 107e): |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| |  <br>**LeGall thesis compound 107e (racemic lacosamide)**<br>***Phenyl at Ar (Unsubstituted Benzyl at R):***<br>• ’301 patent, 5:11-12 (“The preferred values of R is aryl lower alkyl, especially **benzyl**.…”).<br>• ’729 patent, Claim 18 (“The composition of claim 1 wherein **R is benzyl**, $R_1$ is methyl, $R_2$ is hydrogen, $R_3$ is methyl and n is 1 or the D or L steroisomer.”).<br>• ’729 patent, 5:17-18 (“The preferred values of R is aryl lower alkyl, especially **benzyl**.…”).<br>• ’729 patent, col. 58:1-3 and Tbl. I (49 of the 54 tested compounds—over 90%—contained an **unsubstituted benzyl** at the R position).<br>• Kohn 1991, p.2444 (“Potent protection against maximal electroshock seizures (MES) in mice was observed for functionalized amino acid racemates containing both an ***N*-benzylamide** moiety and an acetylated amino group.”)<br>• Kohn 1991, Tbl. 1 (all 26 compounds reported in Kohn 1991 had **unsubstituted benzyl** at R and unsubstituted methyl at $R_1$).<br>• LeGall, pp.133, 155 (compound 107e contains an **unsubstituted benzyl** at R and is predicted to “have good anticonvulsant activity”). |
| 8. The compound according to claim 1 which is (R)-N-benzyl 2-acetamido-3-methoxypropionamide. | • Patent Owner’s PTE Request, p.5 (“[C]laims 39-45 [of ’301 patent] read on the approved product and claim the active ingredient of the final approved product lacosamide…. The active ingredient of the approved product is lacosamide, which is **(R)-2-acetamido-N-benzyl-3-methoxypropionamide**.”).<br>• ’301 patent, Claim 45 (depending on Claim 44): |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| |  <br>'301 Claim 45<br>• LeGall, p.133, Tbl. 35 (compound 107e):<br>  <br>**LeGall thesis compound 107e (racemic lacosamide)** |
| 9. The compound according to claim 8 which contains at least 90% (w/w) R stereoisomer. | • Same as claim 2. |
| 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. | ***Therapeutic composition:***<br>• Patent Owner’s PTE Request, p.6 (“Claim 46 [of the ’301 patent] cover[s] a “***therapeutic composition***….”)<br>• ’301 patent, 2:36-38 (“The mainstay of treatment for such disorders has been the ***long-term and consistent administration*** of anticonvulsant drugs.”)<br>• ’301 patent, 18:33-52 (the claimed “***therapeutic compositions***” may be administered “***daily***”)<br>***Anticonvulsant effective amount*:**<br>• ’301 patent, Claim 46 (“An anti-convulsant composition comprising an **anticonvulsant effective amount** of a compound from any one of claim 37-42 and a pharmaceutical carrier therefor.”).<br>• Patent Owner’s Statement of Uncontested Facts, p.19 ¶89 (“Claim 46 of the ’301 patent should |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | read as follows: ‘An anti-convulsant composition comprising an **anti-convulsant effective amount** of a compound from any one of claim 39-44 and a pharmaceutical carrier therefor.’”).<br>• ’729 patent, Claim 1 (“An anticonvulsant composition comprising an **anti-convulsant effective amount** … and a pharmaceutically acceptable carrier.”)<br>• ’729 patent, 3:35-40 (“[T]he 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**”).<br>• ’729 patent, 16:5-8 (compounds “exhibit **excellent anticonvulsant activity**”).<br>• ’729 patent, 16:44-47 (“an oral dosage unit form [that] contains between about **5 and 1000 mg** of active compound”), *compare with* ’551 patent, 10:52-59 (effective amount being “about **5 to about 1000 mg**”).<br>• LeGall, p.155 (stating that the “close structural analogy of this compound [107e] with 86b suggests that this adduct [107e] may have **good anticonvulsant activity**”).<br>• LeGall, p. 43 (compounds, including 107e, were prepared “[i]n an effort to further delineate the structure-activity relationship of this novel class of **antiepileptic compounds**.”<br>• FDA Guideline, pp. 9, 13 (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”).<br>• Schmidt, pp. 15-19 (describing “dose-finding studies” for determining the effective amount of a drug). |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | ***Pharmaceutically acceptable carrier:***<br>• ’301 patent, Claim 46 (“An anti-convulsant composition comprising an anticonvulsant effective amount of a compound from any one of claim 37-42 and a **pharmaceutical carrier** therefor.”).<br>• Patent Owner’s Statement of Uncontested Facts, p.19 ¶89 (“Claim 46 of the ’301 patent should read as follows: ‘An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claim 39-44 and a **pharmaceutical carrier** therefor.’”).<br>• ’729 patent, Claim 1 (“An anticonvulsant composition comprising an anti-convulsant effective amount … and a **pharmaceutically acceptable carrier**.”)<br>• ’729 patent, 18:12-16 (active ingredient can be “compounded for convenient and effective administration in effective amounts with a suitable **pharmaceutically acceptable carrier**”).<br>• ’729 patent, 16:33-37, 17:13, 17:53-58 (disclosing numerous “**pharmaceutically acceptable carriers**,” including various “solvents, dispersion media, coatings, . . . absorption delaying agents, and the like,” for formulating compounds into “tablets,” “capsules, elixirs, suspensions, syrups” or “for injectable use”).<br>• LeGall, p. 43 (compounds, including 107e, were prepared “[i]n an effort to further delineate the structure-activity relationship of this novel class of ***antiepileptic compounds***”) |
| 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. | ***Treatment of CNS disorders:***<br>• ’551 patent does not disclose any meaningful distinction between compositions and methods for use in *animals* versus *mammals* versus *humans*.<br>• ’301 patent, Claim 47 (“A method of **treating CNS disorders** in an animal comprising administering to said animal an **anti-convulsant effective amount** of a compound of any one of |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | claims 39-44.”).<br>• ’729 patent, Claim 132 (“A method of **treating central nervous system disorders** in animals comprising the administration to said animal an effective amount of a compound according to claim 1.”).<br>• ’729 patent, 3:9-17 (compounds “useful in the **treatment of epilepsy and other CNS disorders**”).<br>• LeGall, p.155 (predicting “**good anticonvulsant activity**” of compound 107e based on the “close structural analogy of this compound [107e] with 86b”).<br>• LeGall, p. 42 (describing “the **anticonvulsant properties** of several N-benzyl amino acids” that are “a new class of **anticonvulsant drugs**.”).<br>• LeGall, p. 43 (compounds, including 107e, were prepared “[i]n an effort to further delineate the structure-activity relationship of this novel class of **antiepileptic compounds**”)<br>***Anticonvulsant effective amount*:**<br>• ’301 patent, Claim 46 (“An anti-convulsant composition comprising an **anticonvulsant effective amount** of a compound from any one of claim 37-42 and a pharmaceutical carrier therefor.”).<br>• Patent Owner’s Statement of Uncontested Facts, p.19 ¶89 (“Claim 46 of the ’301 patent should read as follows: ‘An anti-convulsant composition comprising an **anti-convulsant effective amount** of a compound from any one of claim 39-44 and a pharmaceutical carrier therefor.’”).<br>• ’729 patent, Claim 1 (“An anticonvulsant composition comprising an **anti-convulsant effective amount** … and a pharmaceutically acceptable carrier.”)<br>• ’729 patent, 3:35-40 (“[T]he administration of an **effective amount** of the present compounds, in |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| | 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**”).<br>• ’729 patent, 16:5-8 (compounds “exhibit **excellent anticonvulsant activity**”).<br>• ’729 patent, 16:44-47 (“an oral dosage unit form [that] contains between about **5 and 1000 mg** of active compound”), *compare with* ’551 patent, 10:52-59 (effective amount being “about **5 to about 1000 mg**”).<br>• LeGall, p.155 (stating that the “close structural analogy of this compound [107e] with 86b suggests that this adduct [107e] may have **good anticonvulsant activity**”).<br>• FDA Guideline, pp. 9, 13 (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”).<br>• Schmidt, pp. 15-19 (describing “dose-finding studies” for determining the effective amount of a drug). |
| 12. The method according to claim 11 wherein the animal is a mammal. | • ’551 patent does not disclose any meaningful distinction between compositions and methods for use in animals versus mammals versus humans.<br>• ’301 patent, 1:29-32, 2-26-38, 3:4-5, 20:21 (“compositions … are useful in the treatment of epilepsy and other CNS disorders,” and are directed to addressing the problem that “a significant ***percentage of the population [i.e., humans]*** with epilepsy or related disorders are poorly managed,” and teaches the utility of treating CNS disorders in “***mammalian subjects***” by administering an anticonvulsant effective amount of lacosamide.) |
| 13. The method according to claim 12 wherein the mammal is | • ’551 patent does not disclose any meaningful distinction between compositions and methods for |

| ’551 Patent Claims | ’301 Patent Combined with Prior Art and Patent Owner Admissions |
|---|---|
| a human. | use in animals versus mammals versus humans.<br>• ’301 patent, 1:29-32, 2-26-38, 3:4-5, 20:21 (“compositions … are useful in the treatment of epilepsy and other CNS disorders,” and are directed to addressing the problem that “a significant ***percentage of the population [i.e., humans]*** with epilepsy or related disorders are poorly managed,” and teaches the utility of treating CNS disorders in “***mammalian subjects***” by administering an anticonvulsant effective amount of lacosamide.)<br>• LeGall, pp. 25-30 (discussing “**clinical applications**” of anticonvulsants used in the late 1980s as a treatment of **epilepsy in humans**). |

## VIII. CONCLUSION

For the foregoing reasons, Requester respectfully submits that reexamination should be ordered and that claims 1-13 of the ’551 patent should be cancelled.

Respectfully submitted,

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*Argentum Pharmaceuticals LLC*

Dated: March 25, 2016

## CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **REQUEST FOR *EX PARTE* REEXAMINATION OF U.S. PATENT NO. RE38,551**, together with all exhibits and other papers filed therewith, was served on March 25, 2016, by sending a copy via FEDERAL EXPRESS or similar overnight service directed to the attorney(s) of record for the patent at the following address:

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