IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB, INC. and UCB BIOPHARMA SRL, Plaintiffs, v. ANNORA PHARMA PRIVATE LIMITED, *et al.*, Defendants.	Civil Action No. 20-987-CFC

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OPINION

August 16, 2023
Wilmington, Delaware

COLM F. CONNOLLY
CHIEF JUDGE

This patent infringement case arises out of separate filings of Abbreviated New Drug Applications (ANDAs) by Defendants Annora Pharma Private Limited, Defendants Apotex Inc. and Apotex Corp. (collectively, Apotex), and Defendants MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited (collectively, MSN) with the U.S. Food and Drug Administration (FDA) for approval to market generic versions of Briviact®, a brand name drug made and sold by Plaintiffs UCB, Inc. and UCB Biopharma SRL (collectively, UCB).

The FDA has approved Briviact® for the treatment of partial-onset seizures in epilepsy patients one month of age or older. UCB sells Briviact® in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets, a 50 mg/5 mL single-dose intravenous solution, and a 10 mg/mL oral solution.

UCB alleges that Defendants' ANDA submissions to the FDA each constitute infringement of claim 5 of U.S. Patent No. 6,911,461 (the #461 patent) under 35 U.S.C. § 271(e)(2)(A). Claim 5 covers the compound brivaracetam, the active ingredient of Briviact®.

I held a four-day bench trial on November 14–17, 2022. Defendants did not dispute at trial that they infringe claim 5 but asserted in their defense that claim 5 is invalid as obvious under § 103. As required by Federal Rule of Civil Procedure

52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

I. THE STATUTORY AND REGULATORY FRAMEWORK

The ANDA procedures out of which this case arises were established by FDA regulations promulgated pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, and specifically by the so-called Hatch-Waxman Amendments to the FDCA. Justice Kagan provided in *Caraco Pharmaceutical Laboratories, Ltd. V. Novo Nordisk A/S*, 566 U.S. 399 (2012), this helpful summary of the provisions of the Amendments and the FDA regulations that bear on this case:

> The FDA regulates the manufacture, sale, and labeling of prescription drugs under a complex statutory scheme. To begin at the beginning: When a brand manufacturer wishes to market a novel drug, it must submit a new drug application (NDA) to the FDA for approval. The NDA must include, among other things, a statement of the drug's components, scientific data showing that the drug is safe and effective, and proposed labeling describing the uses for which the drug may be marketed. The FDA may approve a brand-name drug for multiple methods of use—either to treat different conditions or to treat the same condition in different ways.
>
> Once the FDA has approved a brand manufacturer's drug, another company may seek permission to market a generic version pursuant to legislation known as the Hatch-Waxman Amendments. Those amendments allow a generic competitor to file an abbreviated new drug application (ANDA) piggy-

backing on the brand's NDA. Rather than providing independent evidence of safety and efficacy, the typical ANDA shows that the generic drug has the same active ingredients as, and is biologically equivalent to, the brand-name drug. As we have previously recognized, this process is designed to speed the introduction of low-cost generic drugs to market.

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand-name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind . . . gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method-of-use patent even after its patent on the drug compound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch-Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA the patent number and the expiration date of any patent which claims the drug for which the brand submitted the NDA or which claims a method of using such drug. And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method-of-use patent it holds. That description is known as a use code, and the brand submits it on FDA Form 3542. . . . [T]he FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products With Therapeutic Equivalence Evaluations).

> After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.
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> * * * *
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> [One of those ways] is to file a so-called paragraph IV certification, which states that a listed patent "is invalid or will not be infringed by the manufacture, use, or sale of the generic drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve-out label it is willing to adopt cannot avoid the brand's use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of infringement, which gives the brand an immediate right to sue [under 35 U.S.C. § 271(e)(2)(A)]. Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

566 U.S. at 404–08 (irrelevant citations and internal quotation marks omitted).

II. OBVIOUSNESS

Under § 103 of the Patent Act, a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103 (2006).

As the Supreme Court explained in the seminal case *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin

> of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the obviousness analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "might be utilized" and "may have relevancy" is that a district court is permitted—but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts, where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . .

sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan, Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983), for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Id.* at 1538. And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and went on to say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations." *Id.* at 1078.

It is true that less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial

success, long felt need, and the failure of others. *Id.* at 1296. But the safer course for a district court faced with an obviousness challenge (which will be subject to review by the Federal Circuit) is to treat *Graham*'s invitation to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Lab'ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court

must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[ ] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also

be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

III. DEFENDANTS' INVALIDITY THEORY AND THE PARTIES' POSTTRIAL STIPULATION

It is undisputed that brivaracetam is an analogue of the compound levetiracetam, a predecessor compound patented by UCB in 1987 and approved by the FDA in 1999 for the treatment of epilepsy-related seizures. *See* JTX-20001 at 3; PTX-101; D.I. 217-1, Ex. 1 ¶ 49. An analogue is a compound in which one or more individual atoms have been added to or substituted for atoms in a predecessor compound. Brivaracetam and levetiracetam share the same chemical formula in all but one respect: Brivaracetam has a propyl group at the 4-position of the so-called pyrrolidine ring.

Defendants argue that the #461 patent is invalid because it would have been obvious to a skilled artisan as of the priority date of the #461 patent to select levetiracetam as a lead compound from which to develop new anti-seizure drugs and to modify levetiracetam by increasing its lipophilicity with the addition of a propyl group to the 4-position of its pyrrolidine ring.

UCB argued strenuously at trial that an artisan of ordinary skill in the applicable field of medicinal chemistry would not have selected levetiracetam as a lead compound from which to develop new anti-seizure drugs and that, in any

event, it would not have been obvious to a skilled artisan to increase levetiracetam's lipophilicity or to add to it a propyl group. But after trial, for reasons unclear to me, UCB agreed to the following stipulation:

> 1. [UCB] will not challenge Defendants' assertion that the Person of Ordinary Skill in the Art ("POSA") would have chosen levetiracetam as a lead compound "for further development efforts," *see Otsuka Pharms. Co. Ltd. v. Sandoz Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012), with respect to Defendants' assertion that Claim 5 of U.S. Patent No. 6,911,461 is invalid as obvious, and Defendants need not adduce proof thereof.
>
> 2. Nothing in the preceding paragraph shall prevent any party from citing to any evidence adduced at trial to support facts related to any issue relevant to the validity of Claim 5 of U.S. Patent No. 6,911,461, *including to support facts relating to motivation to modify levetiracetam*, motivation to combine references, reasonable expectations of success, objective indicia, or any other factors considered under *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) or *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

D.I. 235 (emphasis added).

As a matter of logic and common sense, an artisan would not have chosen a lead compound "for further development efforts" (i.e., to engage in further efforts to develop an anti-seizure drug) *unless* the artisan had been motivated to modify that lead compound. Thus, if an artisan of ordinary skill "would have chosen levetiracetam as a lead compound for further development efforts then that artisan necessarily would have had a motivation to modify levetiracetam. Accordingly,

notwithstanding UCB's putative reservation of rights in paragraph 2 of the stipulation (and notwithstanding the compelling evidence adduced at trial that an artisan would *not* have been motivated to select levetiracetam as a lead compound for "further development efforts"), UCB's concession in paragraph 1 of the stipulation that an artisan of ordinary skill would have chosen levetiracetam as a lead compound for development of new anti-seizure drugs is also a concession that an artisan would have been motivated to modify levetiracetam to develop new anti-seizure drugs.

As a result of UCB's concession, the sole issue for me to decide is whether it would have been obvious to an artisan of ordinary skill as of the #461 patent's priority date to modify levetiracetam by increasing its lipophilicity with the addition of a propyl group to the 4-position of its pyrrolidine ring.

IV. FINDINGS OF FACT

A. The Parties

1) UCB, Inc. is a Delaware corporation with its principal place of business in Smyrna, Georgia. D.I. 217-1, Ex. 1 ¶ 1. UCB, Inc. holds the approved NDAs for Briviact® in its tablet, intravenous solution, and oral solution forms. D.I. 217-1, Ex. 1 ¶¶ 16, 18, 20.

2) UCB Biopharma SRL is a Belgian corporation with its principal place of business in Brussels, Belgium. D.I. 217-1, Ex. 1 ¶ 2. UCB Biopharma SRL owns the #461 patent. D.I. 217 ¶ 2.

3) Annora Pharma Private Limited is an Indian corporation with its principal place of business in Hyderabad, India. D.I. 217-1, Ex. 1 ¶ 3.

4) Apotex Inc. is a Canadian corporation with its principal place of business in Ontario, Canada. D.I. 217-1, Ex. 1 ¶ 4.

5) Apotex Corp. is a Delaware corporation with its principal place of business in Florida. D.I. 217-1, Ex. 1 ¶ 5. Apotex Corp. is a wholly-owned subsidiary of Apotex Inc. D.I. 217-1, Ex. 1 ¶ 6.

6) MSN Laboratories Private Limited is an Indian corporation with its principal place of business in Hyderabad, India. D.I. 217-1, Ex. 1 ¶ 8.

7) MSN Pharmaceuticals Inc. is a Delaware Corporation with its principal place of business in New Jersey. D.I. 217-1, Ex. 1 ¶ 7. MSN Pharmaceuticals Inc. is a wholly-owned subsidiary of MSN Laboratories Private Limited. D.I. 217-1, Ex. 1 ¶ 9.

B. The Parties' Witnesses

1. UCB's Witnesses

a. Fact Witnesses

8) Dr. Benoit Kenda, Ph.D. is the head of Early Solution Partnering at UCB and one of the #461 patent's three named inventors. Tr. of Nov. 14 to Nov.

17, 2022 Trial at 337:19–20 (Kenda). He was previously a team leader in medicinal chemistry at UCB. Tr. at 337:21–23 (Kenda).

9) Dr. Henrik Klitgaard was a vice president at UCB. Tr. at 347:16–20 (Klitgaard).

b. Expert Witnesses

10) Dr. Tristan Sands is an Assistant Professor of Neurology and Pediatrics at Columbia University Irving Medical Center and has been treating epilepsy patients since 2010. Tr. at 391:24–392:2, 393:23–394:3 (Sands). He has prescribed brivaracetam to roughly 30 patients since 2018. Tr. at 438:11–12, 442:23–443:6 (Sands). I found at trial and confirm here that Dr. Sands was credible. Tr. at 605:3–5, 923:14–17.

11) Dr. Wolfgang Löscher is the head of the Center for Systems Neuroscience in Hannover, Germany and an emeritus Professor of Pharmacology and Toxicology at the University of Veterinary Medicine in Hannover. Tr. at 469:17–23 (Löscher).

12) Dr. David MacMillan is a medicinal chemist and the James S. McDonnell Distinguished University Professor at Princeton University, where he runs a research lab and teaches. Tr. at 607:17–21, 608:16–24, 704:16–17 (MacMillan). Dr. MacMillan has engaged in drug discovery through Chiromics, a company he co-cofounded. Tr. at 610:14–611:2 (MacMillan). He was inducted

into the Royal Society in 2012, elected into the National Academy of Sciences in 2018, and awarded the Nobel Prize in Chemistry in 2021. Tr. at 609:12–20 (MacMillan). I found at trial and confirm here that Dr. MacMillan was credible. Tr. at 985:13–16.

2. Defendants' Witnesses

a. Fact Witnesses

13) Defendants had no fact witnesses.

b. Expert Witnesses

14) Dr. Salvatore Lepore is a Professor of Chemistry and Biochemistry at Florida Atlantic University. Tr. at 78:23–25 (Lepore). Dr. MacMillan testified that Dr. Lepore is a respected researcher in the field. Tr. at 785:3–5 (MacMillan).

15) Dr. Samuel Pleasure is a clinical neurologist and neuroscientist, and a Professor of Neurology at the University of California-San Francisco. Tr. at 280:15–17 (Pleasure). I found at trial and confirm here that Dr. Pleasure was credible. Tr. at 371:20-23; 381:23-382:17.

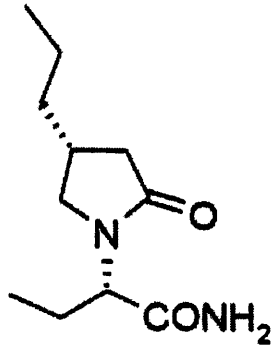
C. The #461 Patent

16) The #461 patent, titled "2-oxo-1-pyrrolidine Derivatives, Processes for Preparing Them and Their Uses," has a priority date of February 23, 2000. D.I. 217-1, Ex. 1 ¶¶ 24–25.

17) Claim 5 of the #461 patent teaches the compound brivaracetam and reads as follows: "(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide or a pharmaceutically acceptable salt thereof." JTX-20001 at 46.

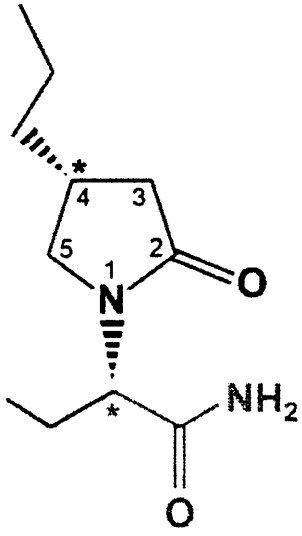
18) Brivaracetam is an analogue of the compound levetiracetam, which has been found to be effective in treating epilepsy. JTX-20001 at 3.

19) Brivaracetam has the following chemical structure:



D.I. 217-1, Ex. 1 ¶ 14.

20) Brivaracetam has the following constituent parts:



4-n-Propyl
chiral carbon with R stereochemistry
2-pyrrolidone ring

butanamide/butyramide chain
ethyl side chain
acetamide moiety
chiral carbon with S stereochemistry

Tr. at 612:11–613:17 (MacMillan) (discussing PDX-5 at 14).

D. Defendants' ANDAs

21) Brivaracetam is the active pharmaceutical ingredient in UCB's Briviact® drug product and in each of Defendants' ANDA products. D.I. 217-1, Ex. 1 ¶¶ 12, 32, 36, 40–41.

22) The Briviact® label states that "[t]he precise mechanism by which BRIVIACT exerts its anticonvulsant activity is not known." D.I. 217-1, Ex. 1 ¶ 22; JTX-20066 at 10.

23) Annora filed ANDA No. 214831 with the FDA seeking approval for the commercial manufacture, use, and sale of brivaracetam tablets in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg dosage strengths (Annora's ANDA Product) prior to the expiration of the #461 patent. D.I. 217-1, Ex.1 ¶ 33.

24) Annora delivered a letter to UCB notifying UCB of Annora's ANDA submission. D.I. 217-1, Ex.1 ¶ 32.

25) Annora has stipulated that its submission of ANDA No. 214831 constitutes infringement of claim 5 of the #461 patent, if that claim is found not invalid or unenforceable, and that the commercial manufacture, use, sale, offer to sell, and/or importation of Annora's ANDA Product as currently described would infringe claim 5 of the #461 patent, if that claim is found not invalid or unenforceable. D.I. 217-1, Ex. 1 ¶¶ 34–35.

26) Apotex filed ANDA No. 214875 with the FDA seeking approval for the commercial manufacture, use, and sale of brivaracetam tablets in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg dosage strengths (Apotex's ANDA Product) prior to the expiration of the #461 patent. D.I. 217-1, Ex.1 ¶ 37.

27) Apotex delivered a letter to UCB notifying UCB of Apotex's ANDA submission. D.I. 217-1, Ex.1 ¶ 36.

28) Apotex has stipulated that its submission of ANDA No. 214875 constitutes infringement of claim 5 of the #461 patent, if that claim is found not invalid or unenforceable, and that the commercial manufacture, use, sale, offer to sell, and/or importation of Apotex's ANDA Product as currently described would infringe claim 5 of the #461 patent, if that claim is found not invalid or unenforceable. D.I. 217-1, Ex. 1 ¶¶ 38–39.

29) MSN filed ANDA Nos. 214921, 214922, and 214924 with the FDA seeking approval for the commercial manufacture, use, and sale of brivaracetam oral solution, intravenous solution, and tablets in 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg dosage strengths (MSN's ANDA Product) prior to the expiration of the #461 patent. D.I. 217-1, Ex.1 ¶ 42.

30) MSN delivered letters to UCB notifying UCB of MSN's ANDA submissions. D.I. 217-1, Ex.1 ¶¶ 40–41.

31) MSN has stipulated that its submissions of ANDA Nos. 214921, 214922, and 214924 each constitutes infringement of claim 5 of the #461 patent if that claim is found not invalid or unenforceable, and that the commercial manufacture, use, sale, offer to sell, and/or importation of MSN's ANDA Products as currently described would infringe claim 5 of the #461 patent if that claim is found not invalid or unenforceable. D.I. 217-1, Ex. 1 ¶¶ 43–44.

E. The Artisan of Ordinary Skill

32) The parties agreed that the artisan of ordinary skill "would be a person with a doctorate degree in chemistry, medicinal chemistry, organic or synthetic chemistry, or a related discipline, and around 2–3 years of experience in the synthesis, research and development of medicinal compounds, or, alternatively, a person with a lesser post-graduate degree in those fields, with at least four or more years of experience in the same areas." D.I. 217-1, Ex. 1 ¶ 54.

33) The parties similarly agreed that the artisan of ordinary skill "would have had knowledge and experience and/or worked with a collaborative team of ordinarily skilled artisans, including a medical doctor, and those with advanced degrees and/or experience in clinical medicine, pharmacology, biochemistry, chemistry, medicinal chemistry, organic or synthetic chemistry, related to research and development of drug products and formulations, including preclinical and clinical research." D.I. 217-1, Ex. 1 ¶ 55.

F. Epilepsy

34) Epilepsy is a collection of neurological disorders characterized by the risk for recurrent, unprovoked seizures. Tr. at 399:13–16 (Sands); *see also* Tr. at 289:10–17 (Pleasure).

35) A seizure is an excessive electrical discharge in the brain that disrupts normal brain activity and typically leads to a behavioral change in a person. Tr. at 399:23–25 (Sands); *see also* Tr. at 289:18–25 (Pleasure).

36) Epilepsy is a heterogeneous disorder, meaning it presents differently in every patient. Tr. at 399:17–21 (Sands); D.I. 217-1, Ex. 1 ¶ 45.

37) Epilepsy is a dynamic disorder: Seizure frequency can wax and wane within an individual patient. Tr. at 423:9–25 (Sands).

38) Epileptic seizures are broadly characterized as either focal onset or generalized onset. Focal onset seizures start in one part of the brain and can spread; generalized onset seizures appear to start everywhere all at once. Tr. at 400:18–25 (Sands); *see also* Tr. at 291:1–17 (Pleasure).

39) Focal onset seizures are also called partial-onset seizures. Tr. at 291:1–17 (Pleasure).

40) Types of generalized onset seizures include absence seizures, myoclonic seizures, atonic seizures, tonic seizures, and generalized tonic-clonic seizures. Tr. at 401:9–20 (Sands).

41) Tonic seizures are characterized by whole-body stiffening. Tr. at 401:9–20 (Sands).

42) Epilepsy affects approximately 3.4 million people in the United States and 65 million people worldwide. Tr. at 400:12–16 (Sands).

43) Epilepsy patients live under the constant threat of an unexpected seizure and must take numerous precautions when engaging in common, everyday activities. Tr. at 401:21-402:24 (Sands); PTX-193.

44) Epilepsy patients have increased mortality. Tr. at 404:13–22 (Sands).

45) Epilepsy affects children differently than adults in part because children are undergoing a period of intense brain development, which can be derailed by uncontrolled seizure activity. Tr. at 403:6-19 (Sands).

46) The precise cause of epilepsy in a particular person is often unknown, but there are many potential causes that tend to correlate to age of onset. D.I. 217-1, Ex. 1 ¶ 46.

G. Treatment of Epilepsy

47) Drug therapy with anti-seizure drugs is the most common method of treating epilepsy. Tr. at 291:18–21 (Pleasure).

48) Epilepsy patients often need to take anti-seizure drugs every day for their entire lives. Tr. at 405:24–406:5 (Sands).

49) The goals of anti-seizure drug treatment are the elimination of all seizures and the absence of unacceptable side effects. Tr. at 406:10–16 (Sands). Both goals are critical. Tr. at 406:17–407:1 (Sands).

50) As of February 2000, no anti-seizure drug adequately controlled all seizures for all patients. Tr. at 407:23–408:1 (Sands).

H. Refractory Epilepsy

51) A patient is deemed to have "refractory epilepsy" if the patient has been treated with two or more appropriate antiepileptic medications to a maximum tolerated dose without full efficacy. Tr. at 293:6–15 (Pleasure).

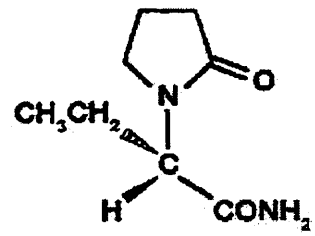
52) As of February 2000, approximately 25–30% of patients had refractory epilepsy. Tr. at 411:5–12 (Sands); PTX-162 at 1.

53) The percentage of patients with refractory epilepsy has consistently been between 20 and 33 percent for the last several decades. Tr. at 293:16–294:1 (Pleasure); Tr. at 354:4-15 (Klitgaard); Tr. at 437:20–438:7 (Sands); Tr. at 567:25–568:17 (Löscher); Tr. at 804:19–805:2 (Pleasure).

54) If seizure elimination cannot be achieved, seizure reduction is still a meaningful clinical outcome because the fewer the seizures, the better the patient's quality of life. Tr. at 409:10–18 (Sands).

I. Levetiracetam

55) Levetiracetam has the following chemical structure:



D.I. 217-1, Ex. 1 ¶ 51; Tr. at 107:5–9 (Lepore).

56) Levetiracetam was first synthesized by chemists at UCB in 1977. D.I. 217-1, Ex. 1 ¶ 48.

57) Levetiracetam was patented in 1987. Tr. at 501:22–24 (Löscher); PTX-101.

58) Levetiracetam was approved by the FDA on November 30, 1999 for the treatment of epilepsy under the trade name Keppra®. D.I. 217-1, Ex. 1 ¶ 49.

59) Levetiracetam was the first piracetam-based compound approved by the FDA for antiepileptic activity. Tr. at 112:18–21 (Lepore).

60) UCB Inc. holds approved NDA No. 021035 for Keppra® (levetiracetam) tablets in 250 mg, 500 mg, 750 mg, and 1000 mg dosage strengths. D.I. 217-1, Ex. 1 ¶ 50.

61) In February 2000, Keppra® was only available for patients in clinical trials; it did not launch in the United States until April 2000. Tr. at 498:20–22 (Löscher); PTX-106 at 2.

62) A skilled artisan would have understood in February 2000 that levetiracetam had been approved by the FDA before the priority date of the #461 patent. Tr. at 711:12–24 (MacMillan); *see also* Tr. at 332:12–333:2 (Pleasure).

63) A skilled artisan would have understood that levetiracetam was safe and effective based on its FDA approval. Tr. at 173:20–174:2 (Lepore).[1]

64) A skilled artisan would have considered levetiracetam to have many exceptional qualities and be a good drug with few problems. Tr. at 711:25–712:9 (MacMillan).

65) The precise mechanism of action of levetiracetam was unknown as of February 2000. Tr. at 315:22–317:3 (Pleasure); Tr. at 489:2–490:13 (Löscher); PTX-110 at 6.

66) Levetiracetam is a central nervous system drug, which means it needs to reach and bind to a receptor in the brain to prevent seizures. Tr. at 635:5–636:8, 642:1–15, 714:1–21 (MacMillan); DTX-10067 at 3.

67) A skilled artisan would have understood that levetiracetam was known only to bind to a receptor at a unique site known as the "levetiracetam

[1] Whenever I say that a skilled artisan "would have" or "would not have" had a particular state of mind (such as knowledge, understanding, motivation, and expectation), I am discussing the artisan's state of mind as of the priority date.

binding site" or "LBS." Tr. at 114:2–8 (Lepore); Tr. at 309:3–310:21, 315:22–317:3 (Pleasure); Tr. at 489:2–490:13 (Löscher).

68) A binding site is considered "well-characterized" if its molecular structure or shape are known. Tr. at 625:3–8; 625:11–626:6 (MacMillan).

69) If a binding site is well-characterized, a skilled artisan can modify a lead compound in ways that attempt to make modified compounds that interact with the binding site more efficaciously. Tr. at 625:11–626:6 (MacMillan).

70) Many different features of a compound and a binding site—including shape, size, volume, electronics, electrostatics, dispersion forces, and conformations—affect how the compound binds to the binding site. Tr. at 626:7–627:9 (MacMillan).

71) A binding site is considered "poorly characterized" if its molecular structure and shape are not known. Tr. at 114:2–16, 115:10–22 (Lepore); Tr. at 627:13–628:3 (MacMillan).

72) If a binding site is poorly characterized, a skilled artisan cannot definitively determine without testing how a compound will interact with the site. Tr. at 627:13–628:3 (MacMillan).

73) LBS was poorly characterized as of the #461 patent's priority date. A skilled artisan would have understood that the LBS was in the brain but would not have known its structure. Tr. at 114:2–116:10 (Lepore); Tr. at 309:3–310:21,

319:1–7, 319:17–19 (Pleasure); Tr. at 489:2–25 (Löscher); Tr. at 625:3–8 (MacMillan); DTX-10068 at 6.

J. Defendants Did Not Establish by Clear and Convincing Evidence that a Skilled Artisan Would Have Had a Reasonable Expectation of Success that Modifying any Compound to Increase Lipophilicity Would Result in a Compound with Increased Antiepileptic Activity.

1. Defendants Did Not Establish a Direct Relationship Between Lipophilicity and Antiepileptic Activity.

74) As used by the parties, the term "lipophilicity" refers to the ability of a chemical compound to dissolve in fats or oils as opposed to water. Alyn William Johnson, *Invitation to Organic Chemistry* 283 (1999); *see also* Tr. at 94:6–16 (Lepore); Tr. at 638:18–639:1 (MacMillan).

75) Lipophilicity is a necessary, but not sufficient, factor to achieve central nervous system activity. Tr. at 252:9–12 (Lepore); Tr. at 509:24–510:13 (Löscher); 642:1-13 (MacMillan); DTX-10067 at 12.

76) Lipophilicity is measured by log *P*, which is equivalent to log *D* for the relevant compounds. Tr. at 96:3–13, 122:12–15 (Lepore); Tr. at 638:11–14 (MacMillan).

77) Log *P* is an inherent property of a compound. Tr. at 729:10–12 (MacMillan).

78) A compound with a higher log *P* is more lipophilic, while a lower log *P* means that a compound is less lipophilic and thus is more water soluble. Tr. at 98:22–99:3 (Lepore).

79) A skilled artisan would not have pursued lipophilicity as an end goal in designing a new drug. Tr. at 794:16–795:11 (MacMillan); Tr. at 341:21–342:15 (Kenda).

2. Lipophilicity and Blood-Brain Barrier Permeability

80) As used by the parties, the term "blood-brain barrier" refers to a protective layer of cells that lines the inner surfaces of the blood vessels inside the brain. Tr. at 95:2–6 (Lepore).

81) As used by the parties, "blood-brain barrier permeability" refers to a drug's ability to penetrate the blood-brain barrier. Tr. at 92:25–93:6, 95:2–6 (Lepore).

82) A skilled artisan would have been aware of tools to analyze the brain permeating ability of compounds. Tr. at 150:12–15 (Lepore).

83) Lipophilicity is a key characteristic in a drug's ability to penetrate the blood-brain barrier. Tr. at 588:6–9 (Löscher); Tr. at 93:20–95:6 (Lepore).

84) A compound's log *P* alone will not tell a skilled artisan whether the compound will pass through the blood-brain barrier. Tr. at 639:12–18 (MacMillan).

85) A skilled artisan would have understood that there are several competing mechanisms associated with increased lipophilicity that could ultimately reduce a compound's blood-brain barrier permeability. Tr. at 693:21–694:12 (MacMillan).

86) For example, it's possible for a more lipophilic compound to have increased permeability for other cells in the body; if the compound enters those cells, the compound is prevented from going into the brain and thus brain permeability is decreased. Tr. at 695:18–696:2 (MacMillan).

87) As another example, it's possible for a more lipophilic compound to stick to blood plasma, making less of the compound available to get into the brain. Tr. at 696:5–13 (MacMillan).

88) As another example, it's possible for a more lipophilic compound with more methylene groups to show increased metabolism, which may affect how much of the compound gets into the brain. Tr. at 693:4–13, 696:14–16, 789:13–20 (MacMillan).

89) As another example, it's possible for a more lipophilic compound to have a decreased ability to partition into the brain's interstitial fluid, which may limit the amount of the compound that gets into the brain. Tr. at 696:17–697:4 (MacMillan).

a. Relevant Prior Art

1) Pardridge

90) Pardridge is a scientific article titled "CNS Drug Design Based in Principles of Blood-Brain Barrier Transport." DTX-10112.

91) Pardridge was published in 1998 and therefore qualifies as prior art to the #461 patent. DTX-10112.

92) Pardridge advises two potential approaches to increase the lipophilicity of a compound: (a) blocking hydrogen bond-forming functional groups, e.g., hydroxyls, or (b) increasing the number of methylene groups. DTX-10112 at 3; Tr. at 100:12–101:10 (Lepore).

93) Pardridge states that, for molecules in a certain molecular weight range, "[blood-brain barrier] transport of the drug may be increased in direct proportion to lipid solubility," another term for lipophilicity. Tr. at 95:18–96:2 (Lepore); DTX-10112 at 5–6.

94) But Pardridge acknowledges that it has not been demonstrated that increasing lipid solubility always translates into proportionate increases in blood-brain barrier permeability. DTX-10112 at 3; Tr. at 683:11–20 (MacMillan).

95) Pardridge also acknowledges that any "benefits from lipidizing a drug and increasing [blood-brain barrier] permeability may be offset by the unfavorable effects of lipidization." DTX-10112 at 6.

96) A skilled artisan would have understood that the prior art teaches that blood-brain barrier transport of a drug may be increased in direct proportion to lipophilicity for molecules in a certain molecular weight range. Tr. at 95:18–96:2 (Lepore); DTX-10112 at 5–6.

97) Pardridge would not, however, have led a skilled artisan to conclude that the higher a drug's lipophilicity, the higher the antiepileptic drug activity. DTX-10112 at 3, 5–6; *see also* Tr. at 509:24–510:21 (Löscher); Tr. at 653:5–18 (MacMillan).

2) Levin

98) Levin is a scientific article titled "Relationship of Octanol/Water Partition Coefficient and Molecular Weight to Rat Brain Capillary Permeability." DTX-10115.

99) Levin was published in 1980 and therefore qualifies as prior art to the #461 patent. DTX-10115.

100) Based on 22 compounds, Levin developed an equation for calculating a compound's predicted permeability coefficient. Tr. at 150:22–25, 151:11–20, 201:19–202:25 (Lepore); Tr. 717:19–22 (MacMillan); DTX-10115 at 2–3.

101) Levin found that the relationship between permeability and log *P* and molecular weight was predictable for a certain class of compounds with molecular weights under 400. Tr. at 718:5–15 (MacMillan).

102) Levin's equation has two variables, log *P* and molecular weight; it does not account for structure. Tr. at 201:19–202:25 (Lepore); DTX-10115 at 3.

103) In Levin's equation, increasing log *P* while keeping molecular weight constant will necessarily result in an increased permeability coefficient. Tr. at 151:11-20, 202:9-15 (Lepore); DTX-10115 at 3.

104) The compounds of Levin are structurally different from the compounds at issue here. Tr. at 701:6–702:14, 718:5–10 (MacMillan).

105) Levin does not correlate log *P* with central nervous system activity. Tr. at 203:17-20 (Lepore).

106) Levin would nonetheless have motivated a skilled artisan with a goal of increasing blood-brain barrier permeability to develop a compound with increased lipophilicity. Tr. at 150:18–154:10 (Lepore); Tr. at 718:1–4, 718:11–15 (MacMillan).

3. Defendants Did Not Establish a Direct Relationship Between Blood-Brain Barrier Permeability and Antiepileptic Activity.

107) Defendants did not establish at trial a direct relationship between blood-brain barrier permeability and antiepileptic activity.

108) Defendants argue in their post-trial briefing that "brain permeability could result in a number of therapeutic advantages. For example, the prior art reported good correlations between brain permeability and relative potency." D.I.

242 at 10. They cite in support of this assertion DFF82, which states: "The prior art reported good correlations between lipophilicity and relative potency." The sources Defendants and UCB cite for and against DFF82 all accordingly focus on the existence or lack thereof of a relationship between lipophilicity (not blood-brain barrier permeability) and antiepileptic activity.

109) Defendants similarly argue that "the prior art taught that increasing lipophilicity, and hence brain permeability, could increase antiepileptic drug activity." D.I. 242 at 10. They cite DFF77 and DFF81 in support of this assertion. Those sources similarly deal with a purported relationship between lipophilicity and antiepileptic drug activity, not between blood-brain barrier permeability and antiepileptic drug activity.

4. Defendants Did Not Establish a Direct Relationship Between Lipophilicity and Brain Uptake.

110) As used by the parties, the term "brain uptake" refers to the steady-state equilibrium of how much of any given molecule is in the brain at any given time. Tr. at 641:20–25 (MacMillan).

111) There is not a strictly linear relationship between log *P* and brain uptake. Tr. at 694:17–23 (MacMillan).

5. Defendants Did Not Establish a Direct Relationship Between Brain Uptake and Antiepileptic Activity.

112) Brain uptake is a necessary, but not sufficient, factor to achieve central nervous system activity. Tr. at 252:9–12 (Lepore); Tr. at 509:24–510:13 (Löscher); 642:1-13 (MacMillan); DTX-10067 at 12.

113) In addition to brain uptake, central nervous system activity depends on dose, receptor affinity, receptor concentration, protein binding in the periphery, and metabolism. Tr. at 176:25–177:16 (Lepore); Tr. at 642:1–13 (MacMillan); DTX-10067 at 3.

114) Metabolism refers to the breaking down of a compound in the body as the body attempts to excrete it. Tr. at 177:14–16 (Lepore); Tr. at 634:2–10 (MacMillan).

K. Defendants Did Not Establish by Clear and Convincing Evidence a Motivation to Increase Levetiracetam's Lipophilicity.

1. Defendants Did Not Establish a Skilled Artisan Would Have Considered Levetiracetam's Brain Uptake Deficient.

115) A skilled artisan would have known that drowsiness, tiredness, asthenia, and headache "are a result of receptors . . . in [the] brain or on the [central nervous system]." Tr. at 659:17–24; DTX-10063 at 43.

116) Increasing brain uptake of an already successful central nervous system drug risks increasing the side effects of drowsiness, tiredness, asthenia, and headache. Tr. at 659:9–660:10 (MacMillan); DTX-10063 at 43.

117) A skilled artisan would have understood that levetiracetam was generally well-tolerated but at high doses was known to cause drowsiness, tiredness, asthenia, and headache. Tr. at 111:18–22 (Lepore); DTX-10063 at 43; *see also* Tr. at 300:13–25, 305:12–16, 307:15–18, 326:8–15 (Pleasure).

118) A skilled artisan would not have been motivated to improve levetiracetam's brain uptake, because levetiracetam was already a successful central nervous system drug and increasing brain uptake would risk increasing its side effects. Tr. at 642:22–643:9, 659:9–660:10 (MacMillan).

2. Defendants Did Not Establish that a Skilled Artisan Would Have Considered Levetiracetam's Blood-Brain Barrier Permeability Deficient.

119) A skilled artisan would have understood that an effective amount of levetiracetam was crossing the blood-brain barrier. Tr. at 589:11–590:5 (Löscher); Tr. at 660:17–25 (MacMillan); *see also* Tr. at 212:9–11 (Lepore); Tr. at 311:12–22 (Pleasure).

120) Dr. Lepore was not aware of anyone, as of February 2000, questioning, expressing criticism, or expressing negative thoughts about the blood-brain barrier permeability of levetiracetam. Tr. at 275:17–276:1, 276:11–20 (Lepore).

3. Defendants Did Not Establish that a Skilled Artisan Would Have Considered Levetiracetam's Lipophilicity Deficient.

121) A skilled artisan would have known that levetiracetam's log *P* is negative 0.65. Tr. at 710:18–711:1, 725:9–12 (MacMillan); DTX-10072 at 7.

122) A skilled artisan would have understood that levetiracetam's log *P* was a property that could be increased. Tr. at 124:23–125:12, 125:22–126:6 (Lepore).

123) A skilled artisan would not have been aware of anyone, as of February 2000, questioning, expressing criticism, or expressing negative thoughts about the lipophilicity of levetiracetam. Tr. at 275:17–276:1, 276:11–20 (Lepore).

124) For "compounds that don't exist yet," a skilled artisan would have to calculate log *P*. Tr. at 124:11–22 (Lepore); Tr. at 729:13–22 (MacMillan).

125) Dr. Lepore's calculated log *P* of a 4-n-propyl-substituted levetiracetam is 0.90. Tr. at 154:13-20, 252:22-25 (Lepore).

126) The experimental log *P* value of brivaracetam was not known as of February 2000. Tr. at 588:23–589:5 (Löscher); Tr. at 729:2–22 (MacMillan).

127) Brivaracetam's log *P* was experimentally determined to be 1.04 after the priority date. Tr. at 728:23–729:4 (MacMillan); Tr. at 585:7–8, 586:10–587:14, 588:20–589:5 (Löscher); JTX-20025 at 15.

128) A skilled artisan would have understood that the optimal log *P* for a central nervous system drug is between one and four. DTX-10067 at 12; Tr. at 722:1–4 (MacMillan); Tr. at 359:13–360:15 (Klitgaard).

129) But a negative log *P* does not mean that a drug has poor brain uptake. Tr. 643:17–25; 645:1–8 (MacMillan); DTX-10072 at 5–7.

130) A skilled artisan would have known that some central nervous system-active drugs had a negative log *P*. Tr. at 122:16–24 (Lepore); 643:17–25 (MacMillan); DTX-10067 at 5–7, 12; DTX-10072 at 7.

131) A skilled artisan would therefore not have considered levetiracetam's log *P* particularly unusual. Tr. at 509:24–510:21 (Löscher); Tr. at 643:17–25, 644:15–25 (MacMillan); DTX-10072 at 5–7.

132) Because levetiracetam was an approved drug with effective brain penetrating power, a skilled artisan would not have considered its lipophilicity insufficient and would not have thought that levetiracetam did not have an appropriate level of brain penetrating power. Tr. At 173:20–174:6, 275:17–276:1, 276:11–20 (Lepore); Tr. At 589:11–590:5 (Löscher); Tr. At 643:17–25, 644:15–25, 645:1–8, 646:18–647:16, 660:17–25 (MacMillan).

133) Defendants failed to establish that a skilled artisan as of the priority date would have been motivated to use lipophilicity as a guiding principle for

structural modification of levetiracetam. Tr. at 640:3–15, 794:16–795:11 (MacMillan); Tr. at 341:21–342:15 (Kenda).

134) Defendants failed to establish that a skilled artisan as of the priority date would have been motivated to modify levetiracetam's structure to develop a compound that had a log *P* value closer to two. Tr. at 642:22–643:9, 646:18–647:16 (MacMillan).

a. Relevant Prior Art

1) Perucca

135) Perucca is a scientific article titled "Drugs Under Clinical Trial." DTX-10063.

136) Perucca was published in 1999 and therefore qualifies as prior art to the #461 patent. DTX-10063.

2) Silverman

137) Silverman is an entry-level textbook titled "The Organic Chemistry of Drug Design and Drug Action." DTX-10059; Tr. at 102:11–14 (Lepore); Tr. at 684:21–685:2 (MacMillan).

138) Silverman was published in 1992 and therefore qualifies as prior art to the #461 patent. DTX-10059.

139) Silverman states that "it appears that even if one uncovers a lead, it may be a fairly random process to optimize its potency." Tr. at 205:16–20 (Lepore); DTX-10059 at 60.

140) Silverman states that, when using a random screening approach, "less than 1 in 10,000 compounds synthesized in drug companies makes it to the drug market, and, in so doing, it takes about 10 years of research at a cost of $200–250 million." Tr. at 205:21–206:4 (Lepore); DTX-10059 at 60.

141) Silverman contrasts the random screening approach with "more rational approaches to lead discovery and lead optimization based on chemical and biochemical principles." Tr. at 261:9–15.

142) Silverman teaches that "[i]f a lead compound has modest [central nervous system] activity and has a log *P* value of zero, it would be reasonable to synthesize an analog with a higher log *P*." DTX-10059 at 43; Tr. at 726:18–23 (MacMillan).

143) Silverman does not discuss levetiracetam, the LBS, or audiogenic mouse activity. Tr. at 204:14–205:4 (Lepore).

144) Although Silverman says that it "would be reasonable to synthesize an analog with a higher log *P*" for compounds with "modest [central nervous system] activity," Defendants failed to establish that the central nervous system activity of levetiracetam can be classified as "modest." Tr. at 173:20–174:12 (Lepore); Tr. at 302:4–16 (Pleasure); Tr. at 726:18–727:13 (MacMillan); DTX-10059 at 43; DTX-10063 at 43.

145) Defendants failed to establish that Silverman would have motivated a skilled artisan to modify levetiracetam with the express purpose of increasing its lipophilicity as of the priority date.

3) Waterbeemd

146) Waterbeemd is a scientific article titled "Estimation of Blood-Brain Barrier Crossing of Drugs Using Molecular Size and Shape, and H-Bonding Descriptors." DTX-10067.

147) Waterbeemd was published in 1998 and therefore qualifies as prior art to the #461 patent. DTX-10067.

148) Waterbeemd examined 125 compounds—central nervous system drugs and other drugs that got into the brain but were not central nervous system drugs—and plotted their molecular weight against their log *D*, which is interchangeable with log *P*. Tr. at 121:11–122:15 (Lepore); DTX-10067 at 4–7.

149) Waterbeemd reports whether a compound had above some reasonable threshold central nervous system activity, not the degree of central nervous system activity or how active the central nervous system-active compounds were relative to each other. Tr. at 177:20–179:22 (Lepore); 646:5–17 (MacMillan); DTX-10067 at 3, 5–7.

150) Waterbeemd shows that the log *D* of the central nervous system-active drugs involved in the study ranged from approximately negative one to positive four. Tr. at 122:16–24 (Lepore).

151) A skilled artisan would have known that the vast majority of the central nervous system-active compounds in Waterbeemd have a positive log *D*. Tr. at 122:25–123:5 (Lepore); DTX-10067 at 12.

152) Waterbeemd shows two central nervous system-active drugs with a negative log *D*. Tr. at 123:22–134:1 (Lepore); DTX-10067 at 12.

153) Waterbeemd shows that there are central nervous system-inactive compounds with log *D* above one. Tr. at 176:3-21, 252:1-13 (Lepore); DTX-10067 at 5–7, 12.

154) For example, Waterbeemd discloses that while doxepin (log $D = 2.22$) and methadone (log $D = 2.07$) are central nervous system-active, diltiazem (log $D = 2.22$) and verapamil (log $D = 2.07$) are central nervous system-inactive. DTX-10067 at 6–7, 12.

155) Waterbeemd states that "[o]ptimal log *D* values for brain uptake should be in the range of 1–4." DTX-10067 at 12.

156) Since log *D* is equivalent to log *P*, Tr. at 122:12–15 (Lepore), Waterbeemd teaches that the optimal log *P* for a central nervous system drug is

between one and four. DTX-10067 at 12; Tr. at 691:20–692:3, 722:1–4 (MacMillan).

157) Waterbeemd does not contain information on levetiracetam, LBS binding affinity, or audiogenic mouse activity. Tr. at 123:6–8, 179:5–13 (Lepore); 645:20–646:4 (MacMillan).

158) Waterbeemd does not conclude that compounds with higher lipophilicity will have greater central nervous system activity. DTX-10067 at 5–7; Tr. at 178:14–179:22 (Lepore); 646:5–17 (MacMillan).

159) Waterbeemd would not have motivated a skilled artisan to modify levetiracetam with the express purpose of increasing its lipophilicity. Tr. at 646:18– 647:16 (MacMillan).

4) Litina

160) Litina is a scientific article titled "Review, Reevaluation, and New Results in Quantitative Structure-Activity Studies of Anticonvulsants." DTX-10075.

161) Litina was published in 1998 and therefore qualifies as prior art to the #461 patent. DTX-10075.

162) Litina provides a log *P* range of 1.4 to 2.7 for antiepileptic drugs. DTX-10075 at 3; Tr. at 691:20–692:6 (MacMillan).

163) Litina states that a log *P* of 2 was "ideal ... for passive penetration into the [central nervous system]." DTX-10075 at 1, 26; Tr. at 691:20–692:6 (MacMillan).

164) A log *P* of 0.90 is below the "optimal" range of one to four from Waterbeemd, the range of 1.4–2.7 from Litina, and the "ideal" log *P* of 2.0 from Litina. Tr. at 252:22–253:6 (Lepore); Tr. at 692:21–693:1 (MacMillan).

165) A compound with a phenyl group on the levetiracetam scaffold would have a log *P* of 1.266, which is within the range of log *P* values Waterbeemd identified as "optimal." Tr. at 210:24–211:10 (Lepore); DTX-10067 at 12.

166) A compound with a phenyl group on the levetiracetam scaffold would have a higher permeability coefficient and log *P* than Dr. Lepore calculated for a compound with a 4-propyl group. Tr. at 211:11–20 (Lepore).

L. Defendants Did Not Establish by Clear and Convincing Evidence that a Skilled Artisan Focused on Increasing Lipophilicity Would Have Been Motivated to Modify Levetiracetam at the 4-Position of the Pyrrolidine Ring.

1. Modifying Lead Compounds Generally

167) A so-called "structure-activity relationship" is an analysis whereby a chemist tests a compound or group of compounds in biological tests and gathers information about how they perform. Tr. At 622:14–623:3 (MacMillan).

168) Medicinal chemists regularly use structure-activity relationship information, including quantitative structure-activity relationship information, in drug development. Tr. At 742:9–19 (MacMillan); Tr. At 90:20–91:6 (Lepore).

169) Structure-activity relationship provides data from which a skilled artisan can determine a set of substituents and can help a skilled artisan generate hypotheses about potentially beneficial modifications to an existing compound. Tr. at 743:1–8 (MacMillan).

170) After selecting a lead compound in furtherance of developing a new drug, a skilled artisan attempts to improve upon the lead compound's properties by making structural changes to the compound. Tr. at 622:7–13, 707:20–708:3 (MacMillan).

171) A skilled artisan would have selected one part of a lead compound to modify at a time. Tr. at 620:12–621:8, 741:15–19, 741:25–742:3 (MacMillan).

172) A skilled artisan would have then used *in-vitro* or *in-vivo* tests to test modified compounds. Tr. at 478:11–479:21 (Löscher); Tr. at 620:12–621:21 (MacMillan).

173) A skilled artisan would have then repeated, potentially over 10,000 times, the iterative, cyclical process of modifying and testing compounds. Tr. at 620:12–621:8, 622:7–13 (MacMillan).

174) Using "a typical tactic in medicinal chemistry," a skilled artisan may ultimately end up with a compound that has had changes at two different sites. Tr. at 673:21–25 (MacMillan).

175) A skilled artisan must test modified compounds because there is otherwise no way to definitively foresee their activity and determine what they actually can or cannot do when the skilled artisan does not know the detailed structure of the binding site target. Tr. at 622:14–623:3 (MacMillan).

176) A skilled artisan may, however, rely on quantitative structure-activity relationships to develop some level of predictability when doing drug design. Tr. at 90:12–92:3 (Lepore).

2. Potency

177) Higher potency can allow for smaller doses, which can avoid side effects associated with higher doses. Tr. at 707:16–19 (MacMillan).

178) A skilled artisan seeking to modify levetiracetam would have looked to make structural modifications to increase its potency. Tr. at 794:16–795:11 (MacMillan); Tr. at 341:21–342:15 (Kenda).

3. Animal Models of Epilepsy and Seizures

179) More than 100 different animal models have been used by epilepsy researchers to characterize anti-seizure drugs. Tr. at 479:25–480:2 (Löscher).

180) Epilepsy researchers have developed different animal models of epilepsy and seizures—including the maximal electroshock, pentylenetetrazole, audiogenic mouse, pilocarpine, and hippocampal kindling models—because there are diverse types of seizures and diverse types of epilepsy. Tr. at 186:7–9 (Lepore); Tr. at 295:17–299:13 (Pleasure); Tr. at 480:3–17 (Löscher).

181) The maximal electroshock test assesses the efficacy of an anti-seizure drug by measuring the extent to which an anti-seizure drug can suppress an electrically-induced seizure in a rodent. Tr. at 295:17–296:3 (Pleasure); Tr. at 481:18–482:3 (Löscher).

182) An anti-seizure drug's efficacy in the maximal electroshock test is thought to be predictive of the anti-seizure drug's potential for efficacy against tonic seizures. Tr. at 481:18–482:3 (Löscher).

183) The pentylenetetrazole test assesses the efficacy of an anti-seizure drug by measuring the extent to which an anti-seizure drug can suppress a chemically-induced seizure in a rodent. Tr. at 296:18–297:7 (Pleasure); Tr. at 482:4–11 (Löscher).

184) An anti-seizure drug's efficacy in the pentylenetetrazole test is thought to be predictive of its potential for efficacy against non-convulsive seizures. Tr. at 482:4–11 (Löscher).

185) The audiogenic mouse model assesses the efficacy of an anti-seizure drug by measuring the extent to which an anti-seizure drug can suppress a sound-induced seizure in a mouse that has a particular genetic mutation. Tr. at 298:1–14 (Pleasure).

186) An anti-seizure drug's efficacy in the audiogenic mouse model is thought to be predictive of the anti-seizure drug's potential for efficacy against generalized seizures. Tr. at 298:1–14 (Pleasure).

187) An anti-seizure drug's potency in an animal model can be denoted by "ED_{50}," which is the effective dose in 50 percent of the animals in a given group. Tr. at 505:23–506:8 (Löscher).

188) An anti-seizure drug's activity in one animal model does not indicate whether, or to what extent, that anti-seizure drug will show activity in another animal model. Tr. at 480:3–17, 508:2–18 (Löscher).

189) Although antiseizure animal models allow a medicinal chemist to see whether the use of a particular compound results in sufficient anticonvulsant activity, they do not reveal how the compound is interacting or what it's doing with respect to all the other biological interactions involved in that biological system. Tr. at 630:2–12 (MacMillan).

190) A medicinal chemist would not use antiseizure animal models to predict whether an untested compound would result in sufficient anticonvulsant

activity; the researcher would instead test the compound to make that determination. Tr. at 630:13–23 (MacMillan).

191) Levetiracetam is inactive in the so-called maximal electroshock and pentylenetetrazole models. Tr. at 180:10– 18 (Lepore); Tr. at 350:3–14 (Klitgaard); Tr. at 508:2–18 (Löscher); Tr. at 629:6–12, 655:7–15 (MacMillan). Levetiracetam is active in the so-called audiogenic mouse model. Tr. at 629:1–12 (MacMillan).

4. Relevant Prior Art

a. Noyer

192) Noyer is a scientific article titled "The Novel Antiepileptic Drug Levetiracetam (UCB L059) Appears to Act via a Specific Binding Site in CNS Membranes." DTX-10068.

193) Noyer was published in 1995 and therefore qualifies as prior art to the #461 patent. DTX-10068.

194) Noyer provides structure-activity relationship information about certain substitutions to levetiracetam. Tr. at 743:9–15 (MacMillan).

195) Noyer contains the only structure-activity relationship data that would have been available to a skilled artisan for levetiracetam and levetiracetam analogues. DTX-10068; Tr. at 743:9–22 (MacMillan).

196) Noyer reports LBS affinity and audiogenic mouse model data for levetiracetam and 23 levetiracetam analogues. DTX-10068 at 5; Tr. at 649:9–650:1, 744:23–745:2 (MacMillan); Tr. at 212:22–213:2 (Lepore).

197) A skilled artisan would have understood that 24 compounds is a "tiny, tiny fraction" of the "between 8,000 to 12,000 compounds" typically assessed in a medicinal chemistry program, even if using a structure-activity relationship approach. Tr. at 667:12–22 (MacMillan); *see also* Tr. at 620:12–621:8, 622:7–623:13 (MacMillan).

198) Noyer's small dataset therefore does not make it a robust structure-activity relationship on an absolute scale. Tr. at 788:21–25 (MacMillan).

199) Noyer includes structure-activity relationship data on levetiracetam analogues with modification at either (1) the pyrrolidine ring, (2) the ethyl side chain of the butanamide group, or (3) the acetamide moiety of the butanamide group. DTX-10068 at 5; Tr. at 744:23–745:9 (MacMillan).

200) Noyer states that "levetiracetam [was] the most active compound (pK_i = 6.1 ± 0.1) among the drugs tested." DTX-10068 at 6; Tr. at 136:21–137:4 (Lepore).

201) But one of the drugs tested in Noyer, compound 10, had higher lipophilicity and binding affinity in the audiogenic mouse model than

levetiracetam. DTX-10068 at 5; Tr. at 216:1–14 (Lepore); Tr. at 668:19–669:1, 674:21–675:1 (MacMillan).

202) Compound 10 has a thiocarbonyl instead of a carbonyl. DTX-10068 at 5; Tr. at 216:1–14 (Lepore).

203) Dr. Lepore did not address compound 10 in his direct testimony. Tr. at 216:1–17 (Lepore).

204) Compound 10 was "potentially toxic" because "thiocarbonyls can have hepatic issues." Tr. 216:9–12 (Lepore); Tr. at 777:24-778:4 (MacMillan).

205) But "[m]any molecules can have hepatic issues" and "there [are] also drugs that have thiocarbonyls which obviously don't have hepatic issues." Tr. at 777:24–778:4 (MacMillan).

206) A skilled artisan would therefore have considered substituting the carbonyl with a thiocarbonyl based on compound 10. Tr. at 668:22–669:9 (MacMillan).

207) Eleven compounds in Noyer modified the ethyl side chain. DTX-10068 at 5; Tr. at 672:2–7 (MacMillan).

208) Noyer compounds 4, 6, and 7 all have more methylenes and are more lipophilic than levetiracetam. DTX-10068 at 5; Tr. at 218:3–12 (Lepore).

209) Noyer compound 7 had an activity of 54.24 mg/kg, which is about four times more potent than a compound with activity of about 200 mg/kg. Tr. at 227:23–228:22 (Lepore).

210) Noyer states, "The methyl homologue (compound 3) and the homologues with the longer alkyl chain displayed intermediate affinities." DTX-10068 at 6; Tr. at 135:6–137:4 (Lepore).

211) Noyer does not provide any data showing that modification of the ethyl side chain of levetiracetam led to an increase in the activity of the compound. DTX-10068 at 5; Tr. at 747:5–8 (MacMillan).

212) A skilled artisan reading the disclosures of Noyer would have understood that levetiracetam was the most potent analogue in the audiogenic mouse model out of the tested analogues with modifications at the ethyl side chain. DTX-10068 at 5–6; Tr. at 136:21–137:4 (Lepore).

213) Noyer shows that the "handful of" tested compounds that resulted from modifications to the ethyl side chain of the butanamide group on levetiracetam had lower lipophilicity and antiepileptic activity. DTX-10068 at 5,6; Tr. at 672:2–673:17, 747:1–4 (MacMillan); Tr. at 136:18–137:4 (Lepore).

214) The results in Noyer, based on "a tiny number of modifications" to create a "small number of compounds," do not definitively discourage a skilled

artisan from pursuing further modifications to the ethyl side chain. Tr. at 672:2–673:17 (MacMillan).

215) Five compounds in Noyer modified the acetamide. DTX-10068 at 5; Tr. at 669:25– 670:7 (MacMillan).

216) Noyer compound 20 adds a benzyl group to the acetamide and is more lipophilic than levetiracetam. DTX-10068 at 5; Tr. at 219:12–15 (Lepore).

217) Noyer discloses that "[m]odifications of the acetamide moiety . . . produced profound reduction of the affinity" and antileptic activity of levetiracetam in the audiogenic mouse model for the tested compounds. DTX-10068 at 6; Tr. at 746:1–10 (MacMillan); Tr. at 139:6–12 (Lepore).

218) Noyer does not provide any data showing that modification of the acetamide group of levetiracetam resulted in an increase of the activity of the compound. DTX-10068 at 5; Tr. at 746:11–15 (MacMillan).

219) The results in Noyer, based on "a small handful" of compounds that "explored replacing the primary amide part of the butanamide chain," do not definitively establish to a skilled artisan that the acetamide portion of the butanamide group of levetiracetam is the optimal functional group at that location of the molecule for the antileptic activity of levetiracetam. Tr. at 669:25–671:21 (MacMillan); Tr. at 213:1–2 (Lepore).

220) Noyer discloses that "[m]odifications" of the "pyrolidinone ring . . . produced profound reduction of the affinity" and antileptic activity of levetiracetam in the audiogenic mouse model for the tested compounds. DTX-10068 at 6; Tr. at 748:2–6 (MacMillan); Tr. at 140:17–22 (Lepore).

221) Noyer only explores one compound that resulted from changing the ring size of the pyrrolidine ring. DTX-10068 at 5; Tr. at 669:10–14 (MacMillan).

222) Noyer only explores one compound that resulted from opening the pyrrolidine ring. DTX-10068 at 5; Tr. at 748:7–11 (MacMillan).

223) Noyer does not provide any data showing that opening or enlarging the pyrrolidine ring on a levetiracetam analogue increases the activity of the compound. DTX-10068 at 5; Tr. at 748:7–11 (MacMillan).

224) From Noyer, a skilled artisan would have understood that levetiracetam's pyrrolidine ring could be modified without changing the ring's size. DTX-10068 at 5, 6; Tr. at 140:25–141:7 (Lepore).

225) Noyer does not disclose any levetiracetam analogues with substituents at the 3-, 4-, or 5-positions of the pyrrolidine ring. Tr. at 668:7–10 (MacMillan).

226) Noyer does not disclose any compound with multiple changes to the levetiracetam scaffold. Tr. at 673:18–20 (MacMillan).

227) Noyer disclosed that the mirror image of levetiracetam had a 1250-fold decrease in LBS affinity. Tr. at 698:17–699:12 (MacMillan).

228) Noyer would provide guidance concerning the precise modifications discussed in the paper, but because the number of modifications in Noyer amount to "a drop in the ocean," Noyer would not discourage a skilled artisan from making any other changes to any specific part of levetiracetam. Tr. at 667:12–673:25 (MacMillan).

b. Bobkov

229) Bobkov is a scientific article titled, when translated into English, "Pharmacological Characteristics of 4-Phenylpiracetam – A New Phenyl Analog of Piracetam." DTX-10073.

230) Bobkov was published in 1983 and therefore qualifies as prior art to the #461 patent. DTX-10073.

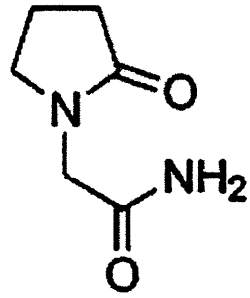
231) Bobkov discloses a piracetam analogue with a substitution at the 4-position. DTX-10073 at 1; Tr. at 751:21–752:1 (MacMillan); Tr. at 143:3–8 (Lepore).

232) Bobkov provides data on four compounds in total: piracetam, 4-phenylpiracetam, 4-phenylpyrrolidone, and morpholep. DTX-10073 at 1; Tr. at 190:11–191:4 (Lepore).

233) Dr. Lepore testified that the ethyl side chain of levetiracetam "should not be modified" to maintain "good antiepileptic activity." Tr. at 133:11–16 (Lepore).

234) Piracetam lacks the ethyl side chain of levetiracetam. DTX-10073 at 1; Tr. at 676:6–21 (MacMillan).

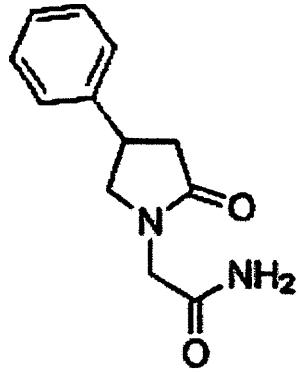
235) Piracetam has the following chemical structure:



PDX-5 at 59.

236) 4-phenylpiracetam lacks the ethyl side chain of levetiracetam and has a phenyl substituent at the 4-position. Tr. at 676:6–21 (MacMillan).

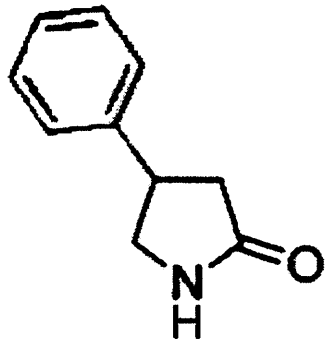
237) 4-phenylpiracetam has the following chemical structure:



PDX-5 at 59.

238) 4-phenylpyrrolidone lacks the ethyl side chain and acetamide of levetiracetam and has a phenyl substituent at the 4-position. Tr. at 676:6–21 (MacMillan).

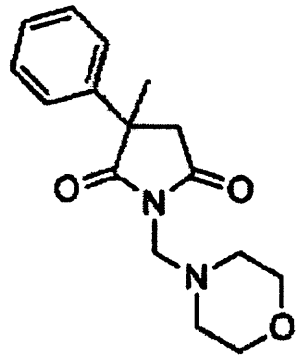
239) 4-phenylpyrrolidone has the following chemical structure:



PDX-5 at 59.

240) Morpholep lacks the ethyl side chain of levetiracetam, has two carbonyl groups, a methyl and phenyl at the 4-position, and a morpholine ring instead of an acetamide. Tr. at 676:6–21 (MacMillan).

241) Morpholep has the following chemical structure:



PDX-5 at 59.

242) Bobkov reports on the antiepileptic activity of piracetam and a 4-substituted piracetam in the maximal electroshock, pentylenetetrazole, and epileptiform tests. DTX-10073 at 1–3; Tr. at 143:3–19, 190:1–3 (Lepore).

243) Bobkov discloses that "[t]he most active of the compounds studied was found to be the amide of 4-phenylpyrrolidone-2-acetic acid, known as 4-phenylpiracetam." DTX-10073 at 1; Tr. at 143:12-19 (Lepore); Tr. at 752:5–7 (MacMillan).

244) Bobkov teaches that making a substitution at the 4-position of piracetam—namely, adding a 4-phenyl group—resulted in a compound with activity in the maximal electroshock, pentylenetetrazole, and epileptiform tests. DTX-10073 at 1; Tr. at 755:17–24 (MacMillan); Tr. at 143:12–19, 190:1–3 (Lepore).

245) Bobkov compares the anticonvulsant activity of 4-phenylpiracetam with morpholep, which was known as of February 2000 as an antiepileptic agent, in the maximal electroshock, pentylenetetrazole, and epileptiform tests. DTX-10073 at 1; Tr. at 752:25–753:3 (MacMillan); Tr. at 190:1–3 (Lepore).

246) Bobkov discloses that 4-phenylpiracetam had better antiepileptic activity than morpholep in the maximal electroshock and epileptiform tests. DTX-10073 at 1–3.

247) Bobkov discloses that morpholep's maximal electroshock activity is 55 mg/kg, similar to 4-phenylpiracetam's maximal electroshock activity of 50 mg/kg. DTX-10073 at 1; Tr. at 191:18–22 (Lepore).

248) Bobkov discloses that morpholep's pentylenetetrazole activity is 65 mg/kg, more potent than 4-phenylpiracetam's pentylenetetrazole activity of 300 mg/kg. DTX-10073 at 1; Tr. at 191:18–22 (Lepore); *see also* DTX-10074 at 3.

249) Bobkov discloses that the addition of a 4-phenyl substituent to piracetam to make 4-phenylpiracetam increased toxicity in the rotating rod and acute 24-hour toxicity tests. Tr. at 195:1–198:20 (Lepore); DTX-10073 at 1; DTX-10074 at 3.

250) Bobkov discloses that the toxicity of 4-phenylpiracetam is better than the toxicity of morpholep in the maximal electroshock model. Tr. at 755:2–5 (MacMillan).

251) Neither Bobkov nor any other prior art would have provided a skilled artisan with experimental data about what would happen to anticonvulsant activity if the 3- or 5-positions on the pyrrolidine ring of piracetam analogues alone were substituted. Tr. at 144:16–23 (Lepore).

252) Defendants failed to establish that a skilled artisan as of the priority date would have treated Bobkov as showing positive design information about the 4-position on the pyrrolidine ring of a piracetam analogue. DTX-10073 at 1; DTX-10074 at 3; Tr. at 195:1–198:20 (Lepore); Tr. at 677:13–678:8, 750:20–25 (MacMillan).

253) Bobkov does not discuss levetiracetam. Tr. at 189:16–23 (Lepore).

254) Bobkov does not discuss LBS affinity or audiogenic mouse activity. Tr. at 189:24–190:3 (Lepore); Tr. at 675:22–676:3 (MacMillan).

255) Bobkov would not have motivated a skilled artisan to make changes to levetiracetam at the 4-position of the pyrrolidine ring. Tr. at 189:16–23, 195:1–198:20 (Lepore); Tr. at 675:4–13, 677:5–678:8, 701:6–20, 750:20–25 (MacMillan).

c. The Relevant Teachings and Suggestions of Noyer and Bobkov

256) A skilled artisan would have understood based on Noyer that the LBS was sensitive to small structural changes, thereby making it difficult to predict the impact of adding a 4-propyl group to levetiracetam on LBS affinity and audiogenic mouse activity. Tr. at 699:15–21 (MacMillan).

257) Dr. Lepore testified there is "some expectation that putting a propyl would be tolerated, but going into four, five, six, seven, now you're—we don't know what the outcome will be." Tr. at 155:17–156:3 (Lepore).

258) Bobkov does not provide an artisan of ordinary skill with a reasonable expectation that a propyl at the 4-position would be "tolerated" or lead to a therapeutically useful anti-seizure drug. Tr. at 144:7–15, 158:12–159:1 (Lepore); Tr. at 675:14–676:3, 701:6–20 (MacMillan).

259) A skilled artisan would have understood that modifying levetiracetam at position 1 of the pyrrolidine ring would diminish the ring's integrity; it would stop the ring from being a pyrrolidine ring. Tr. at 141:8–16 (Lepore).

260) A skilled artisan would not have believed that modifying levetiracetam at position 2 of the pyrrolidine ring would stop the ring from being a pyrrolidine ring. Tr. at 748:22–749:6 (MacMillan).

261) A skilled artisan would therefore not have limited a search for new compounds to changes at the 3-, 4-, or 5-positions of the pyrrolidine ring. Tr. at 668:19–669:1, 669:10–673:17 (MacMillan).

262) Because levetiracetam is a piracetam derivative, a skilled artisan would have searched the piracetam literature to find any teachings about substitutions on the pyrrolidine ring. Tr. at 142:10–19 (Lepore); Tr. at 752:2–4 (MacMillan).

263) But Defendants did not establish that the prior art would have motivated a skilled artisan seeking to improve levetiracetam's lipophilicity to focus on the pyrrolidine ring. Tr. at 669:10-671:21, 672:2-673:25 (MacMillan).

264) Defendants also failed to establish that a skilled artisan would have prioritized the 4-position on the pyrrolidine ring for modification relative to the other available positions based on the prior art. Tr. at 230:13–231:16, 250:6–251:9 (Lepore); Tr. at 664:24–666:4, 668:7–10, 677:8–678:8, 701:6–17 (MacMillan).

265) Defendants therefore also failed to establish that a skilled artisan pursuing a lipidization strategy would have prioritized adding a straight chain alkyl group specifically at the 4-position of the pyrrolidine ring. Tr. at 663:23–667:5, 685:3–686:20 (MacMillan).

266) Defendants therefore also failed to establish that a skilled artisan would have been motivated add a propyl group specifically at the 4-position of the pyrrolidine ring on levetiracetam. Tr. at 664:8–667:5, 693:4–18 (MacMillan).

M. Defendants Did Not Establish by Clear and Convincing Evidence that a Skilled Artisan Looking to Develop a New Antiseizure Drug Would Have Been Motivated to Use a Propyl Group.

1. Lipophilicity and Alkyl Groups

267) There are many structural changes that one can make to a compound that will result in a more lipophilic compound. Tr. at 199:5–8 (Lepore).

268) There are many substituents, such as branched alkyls, cyclic alkyls, and aromatics, that, if added to a chemical structure, will result in a compound with increased lipophilicity. Tr. at 200:2–201:9, 255:7–15 (Lepore); Tr. at 664:8–667:5 (MacMillan).

269) The carbons in a molecule are generally the reason why the compound dissolves in an oil layer. Tr. at 101:11–20 (Lepore).

270) Adding carbons increases a compound's lipophilicity. Tr. at 101:11–20 (Lepore). And the prior art taught that one approach to increasing lipophilicity

was to increase the number of carbon groups (also referred to as "methylene groups" or "alkyl groups"). DTX-10112 at 3; Tr. at 730:4–16 (MacMillan); Tr. at 89:18–90:11, 100:12–19, 217:15–17, 101:5–10 (Lepore).

271) Accordingly, a skilled artisan would have understood as of the priority date that adding alkyl groups to a compound would increase the lipophilicity of the compound. Tr. at 730:4–15 (MacMillan); DTX-10059 at 42.

272) A skilled artisan would also have understood that increasing alkyl chain length would increase the lipophilicity of the compound. Tr. at 733:8–12 (MacMillan); DTX-10059 at 42.

273) A skilled artisan would therefore have understood that modifying levetiracetam at the 4-position with an alkyl group would lead to a more lipophilic compound. Tr. at 106:15–106:20 (Lepore). But, to use Dr. Lepore's words, it is "not a good thing" "if you put a group on the ring in order to increase its lipophilicity, but the result is that adding that group would diminish its ability to bind" to its biological target. Tr. at 148:25–149:15 (Lepore).

274) It was unknown in February 2000 how adding a 4-n-propyl group to the levetiracetam scaffold would affect the resulting compound's ability to get into the brain. Tr. at 697:11–18 (MacMillan).

275) Although a skilled artisan seeking to enhance the lipophilicity of a compound might have considered adding a straight-chain alkyl, Defendants failed

to establish clearly and convincingly that a skilled artisan seeking to enhance the lipophilicity of levetiracetam would have prioritized adding a straight-chain alkyl to it. Tr. at 684:9-16, 685:11–686:20, 693:4–18, 763:5–13, 763:19–764:4 (MacMillan); Tr. at 256:15–20, 267:10–14 (Lepore).

276) A skilled artisan adding a 4-n-propyl group to a compound would consider both resulting diastereomers, which "is another level of complexity" regarding the impact "on biologic interactions." Tr. at 156:22–157:9 (Lepore); Tr. at 700:16–701:3 (MacMillan).[2]

277) A skilled artisan would have known that the 4-propyl substituted analogue of levetiracetam exists in both the 4R and 4S form. Tr. at 156:22–157:9 (Lepore).

278) In the 4R diastereomer, "the propyl goes behind the plane of the page," and in the 4S diastereomer, "the propyl group com[es] out of the plane of the page." Tr. at 156:22–157:9 (Lepore).

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[2] "Diastereomers are two molecules which are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are not enantiomers. Unlike enantiomers which are mirror images of each other and non-superimposable, diastereomers are not mirror images of each other and non-superimposable. Diastereomers can have different physical properties and reactivity. They have different melting points and boiling points and different densities." Layne Morsch, *Organic Chemistry* 5.6.1 (2023), https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Organic_Chemistry_(Morsch_et_al.)/05%3A_Stereochemistry_at_Tetrahedral_Centers/5.06%3A_Diastereomers.

279) A skilled artisan would have known that the 4R and 4S diastereomers are different compounds with different physical properties that likely have different antiepileptic activity. Tr. at 768:6–9 (MacMillan); Tr. at 156:22–157:15 (Lepore).

280) A skilled artisan would have known how to prepare and test diastereomers; it was routine in medicinal chemistry. Tr. at 767:4–21 (MacMillan); Tr. at 157:16–158:9 (Lepore).

281) By separating diastereomers, a skilled artisan could determine if they have different activity and if either form or both forms exhibit toxicity. Tr. at 768:3– 5, 768:13–16 (MacMillan); Tr. at 157:16–158:9 (Lepore).

282) As of February 2000, drug discovery groups were separating racemic mixtures into their R and S forms. Tr. at 767:22–768:2 (MacMillan).

2. Spacers

283) Bioisosterism describes the relationship between two molecules with similar spacing lengths. Tr. at 145:19–146:12; 148:10–24 (Lepore).

284) A skilled artisan can potentially replace a "problem[atic]" substituent with a bioisostere. Tr. at 685:22–686:6 (MacMillan).

285) A skilled artisan cannot predict that use of a bioisostere will result in a useful compound. Tr. at 685:22–686:6 (MacMillan).

286) A skilled artisan would have known that a phenyl group and a propyl group could be interchangeable at the 4-position of a pyrrolidine ring for purposes of their spacer and length qualities. Tr. at 264:9–16 (Lepore).

287) But that does not mean they have any other shared properties. Tr. at 687:10–23 (MacMillan).

288) A skilled artisan would have understood that the phenyl group on the 4-phenylpiracetam compound of Bobkov extends a certain distance from the 4-carbon on the pyrrolidine ring. Tr. at 145:19–146:8 (Lepore).

289) The prior art taught that the distance between two ends of a phenyl ring is similar to the distance between the two ending carbons of a propyl group. Tr. at 765:7–11 (MacMillan); Tr. at 145:19–146:8 (Lepore).

290) The phenyl ring and propyl group are considered nonclassical bioisosteres. Tr. at 148:10–24 (Lepore); Tr. at 765:3–18; DTX-10059 at 32–34.

291) If a propyl or phenyl group were added to the pyrrolidine ring of levetiracetam, the group would be a terminal group, not a spacer. Tr. at 689:24–690:23 (MacMillan).

292) Terminal groups can interact with the active site of a receptor. Tr. 689:24-691:12 (MacMillan).

293) Phenyl and n-propyl groups have different properties, such as size, shape, and electronics, all of which affect receptor binding interactions. Tr. at 209:24–210:23 (Lepore); Tr. at 688:2–689:23, 690:24–691:12 (MacMillan).

294) Phenyl and n-propyl groups are not similar in length when they function as terminal substituents because a terminal n-propyl group is "floppy" and "like a rope" while the phenyl remains "completely rigid" and "flat like a plate." Tr. at 687:24–689:4, 689:24–690:7 (MacMillan).

3. Relevant Prior Art

a. Silverman

295) Silverman teaches several techniques for increasing the lipophilicity of a compound: homologation, chain branching, bioisosterism, and ring-chain transformations. DTX-10059 at 29–36; Tr. at 685:3–21 (MacMillan).

296) Silverman does not prioritize any method for increasing lipophilicity over another. Tr. 685:3-686:20 (MacMillan).

297) Silverman teaches that biological properties of homologous compounds show regularities of increase and decrease. DTX-10059 at 42.

298) Silverman teaches that there is generally a bell-shaped relationship between carbon chain length and drug potency; an increase in the carbon side length leads to an increase in drug potency until a peak, after which point there is a decrease in drug potency as the chain lengthens. DTX-10059 at 29.

299) Silverman teaches that alkyl groups are among the least constitutive functional groups, which means that adding alkyl groups proportionally increases lipophilicity to a better degree than other groups. DTX-10059 at 43; Tr. at 733:8–734:1 (MacMillan).

300) In deciding the appropriate length of alkyl chain to add at the 4-position, a skilled artisan would have known that there is a bell-shaped interplay between the number of carbon units added and how it increases or decreases the compound's potency, such that a skilled artisan would not add carbon units ad infinitum. Tr. at 101:21–102:4, 135:23–136:16 (Lepore).

301) Determining how exactly a compound set exhibits a parabolic relationship—where the peak of the curve is—requires a skilled artisan to decide to make the compounds and then to "determine that experimentally." Tr. at 103:10–17 (Lepore); *see also* Tr. at 739:22–741:2, 788:7–20 (MacMillan).

302) A skilled artisan would not consider homologation a "preferred way" of increasing lipophilicity. Tr. at 684:9–16, 685:3–686:20 (MacMillan).

303) A skilled artisan would not want to add a substituent that forms hydrogen bonds. Tr. at 201:5–9 (Lepore).

304) Neither Silverman nor any other piece of prior art alone explicitly teaches the addition of a 4-n-propyl group to levetiracetam. Tr. at 204:18–205:4 (Lepore); Tr. at 675:14–21, 676:6–24, 683:21–685:7 (MacMillan).

b. Levin

305) Predictive tools such as Levin's equation are routine calculations that a skilled artisan would have used to generate hypotheses and determine a set of substituents that may be more or less beneficial to pursue. Tr. at 151:23–152:5, 154:5–10 (Lepore); Tr. at 743:1–8 (MacMillan).

306) And a skilled artisan seeking to develop a new compound with increased antiepileptic activity would have used certain predictive tools taught in the prior art to synthesize a limited number of compounds, based on the teachings of the prior art and that would reasonably be expected to work, and test them for antiepileptic activity. Tr. at 155:3–16 (Lepore).

307) But a skilled artisan would not have used Levin's equation specifically to predict the impact of adding alkyl groups at the 4-position of levetiracetam, because an increase in lipophilicity does not directly lead to an increase in antiepileptic activity. Tr. at 201:19–202:25 (Lepore); Tr. at 634:2–10, 637:8–638:6, 694:17–698:8, 701:6–20 (MacMillan); DTX-10112 at 6.

308) A skilled artisan who chose to focus on increasing lipophilicity, chose to substitute an alkyl group at the 4-poisition of levetiracetam, and chose to apply Levin's equation to see the effect of such a change would have started with a methyl group at the 4-position of levetiracetam and used Levin's equation to calculate the log *P* and permeability coefficient for that compound, which would

be 0.12 and 0.95 respectively, only a slight increase over levetiracetam. Tr. at 153:19–154:10 (Lepore).

309) A skilled artisan using Levin's equation and motivated to increase lipophilicity would have understood after applying the equation to the addition of a methyl group that the addition of a longer alkyl group would make the compound more lipophilic. Tr. at 154:14–20 (Lepore).

310) A skilled artisan motivated to increase lipophilicity and who had already applied Levin's equation to the addition of a methyl group would have been motivated to try an ethyl, propyl and possibly butyl group at the 4-position and would have expected to obtain a more lipophilic compound. Tr. at 155:3–156:3 (Lepore).

311) A skilled artisan using Levin's equation to evaluate the addition of a propyl group to the 4-position of the pyrrolidine ring of levetiracetam would have calculated that adding a propyl group would result in a log *P* of 0.90 and permeability coefficient of 1.93. Tr. at 154:13–20 (Lepore).

312) Levin's equation predicts that adding a propyl group at the 4-position would increase brain permeability by 250 percent, which a skilled artisan would have considered to be a significant increase. Tr. at 154:21–155:2 (Lepore).

313) But even a skilled artisan motivated to increase lipophilicity and who was applying Levin's equation to compounds resulting from changes to

levetiracetam would not have reasonably expected the resulting compound to lead to a well-tolerated drug with antiepileptic activity. Tr. at 640:3–15, 682:8–12, 693:21–694:12, 697:19–698:8, 699:15–700:8 (MacMillan).

314) After testing these compounds for antiepileptic activity, a skilled artisan would have observed a bell curve relationship between carbon chain length and drug potency, where the propyl substitution was at the peak of the bell curve, demonstrating the greatest potency. Tr. at 740:12–741:2 (MacMillan).

315) But Defendants did not establish clearly or convincingly that a skilled artisan *would have* made those predicate decisions, namely using levetiracetam as a guiding principle, focusing on the 4-position of levetiracetam, and choosing to apply Levin's equation to levetiracetam; they established at most that a skilled artisan *could* make all those decisions. Tr. at Tr. 661:3-14, 664:8–667:5, 788:7–20 (MacMillan).

c. FDA Guidance

316) The FDA Guidance titled "Development of New Stereoisomeric Drugs" was published in 1992. DTX-10132 at 1; Tr. at 769:21–770:1 (MacMillan).

317) A skilled artisan would have been aware of the FDA guidance as of February 2000. Tr. at 770:2–5 (MacMillan).

318) The FDA Guidance sets forth the FDA's recommendations on developing stereoisomeric drugs. Tr. at 770:6–8 (MacMillan).

319) The FDA Guidance discloses that "diastereoisomers . . . should, with the rare exception of cases where in vivo interconversion occurs, be treated as separate drugs and developed accordingly." DTX-10132 at 1; Tr. at 771:16–25 (MacMillan).

320) The FDA Guidance discloses that "[a]ll information developed by the sponsor or available from the literature that is relevant to the chemistry, pharmacology, toxicology, or clinical actions of the stereoisomers should be included in the IND and NDA submissions." DTX-10132 at 3; Tr. at 772:11–23 (MacMillan).

321) The reason FDA tells drug companies to test stereoisomers is because stereochemistry can make or break a drug. Tr. at 772:24–773:4 (MacMillan).

d. GB #692

322) GB #692 is a British patent filed by UCB in 1970 and titled "N-Substituted Lactams." DTX-10069.

323) GB #692 was published in 1973 and therefore qualifies as prior art to the #461 patent. DTX-10069.

324) A skilled artisan would have understood that GB #692 disclosed a set of compounds with numerous options at different positions on the molecule. DTX-10069 at 2; Tr. at 701:23–702:14 (MacMillan).

325) The GB #692 genus encompasses, conservatively, millions of compounds. Tr. at 223:10–18 (Lepore); Tr. at 678:25–679:2, 702:2–14 (MacMillan).

326) GB #692 discloses piracetam derivatives with alkyl substitutions at the 4-position. DTX-10069 at 1, 7; Tr. at 756:11–14 (MacMillan); Tr. at 159:17–160:22 (Lepore).

327) GB #692 claims 32 compounds that it specifically identifies by chemical names. Tr. at 756:18–757:7 (MacMillan); DTX-10069 at 7.

328) For example, claim 19 of GB #692 claims the compound 2-(4-methyl-2- oxo-pyrrolidino)-butyramide. DTX-10069 at 7.

329) Claim 19 does not cover levetiracetam. DTX-10069 at 7; Tr. at 277:22–23 (Lepore); Tr. at 760:2–14 (MacMillan).

330) The compound of claim 19 of GB #692 differs structurally from brivaracetam. For example, whereas the compound of claim 19 has a methyl group at the 4-position of the pyrrolidine ring, brivaracetam has a propyl group at that position. DTX-10069; Tr. at 161:25–162:22 (Lepore); Tr. at 762:5–13 (MacMillan).

331) GB #692 teaches that piracetam derivatives with alkyl substitutions on the pyrrolidine ring, including at the 4-position, can be used for the treatment of epilepsy. DTX-10069 at 1,7; Tr. at 159:17–22 (Lepore).

332) GB #692 states that its compounds "can be used for therapeutic purposes, for example, for the treatment of motion sickness, hyperkinesia, hypertonia and epilepsy." DTX-10069 at 1; Tr. at 757:4–7 (MacMillan).

333) GB #692 also states that "the compounds of the present invention bring about a decrease in cerebral excitability, as demonstrated by the audiogenic seizure test in mice. The compounds of the present invention are active in the tonic phase of the audiogenic seizure at an intraperitoneally administered dose of about 200 mg/kg body weight." DTX-10069 at 2 (citation omitted).

334) Levetiracetam had an activity of 8.5 mg/kg in the audiogenic mouse model, which is over 20 times more potent than a compound with activity of about 200 mg/kg. Tr. at 214:1–6, 224:18–21, 227:15–22 (Lepore).

335) Three of the 32 specifically claimed compounds in GB #692 are mono-substituted at the 4-position. DTX-10069 at 7; Tr. at 229:16–20 (Lepore).

336) Two specifically claimed GB #692 compounds are mono-substituted at the 3-position. DTX-10069 at 7.

337) Five specifically claimed GB #692 compounds are mono-substituted at the 5-position. DTX-10069 at 7.

338) Eighteen specifically claimed GB #692 compounds are di- or tri-substituted at the 3-, 4-, and/or 5-positions. Tr. at 230:15–18 (Lepore); DTX-10069.0007.

339) Only three claimed GB #692 compounds have an unsubstituted butanamide like levetiracetam. DTX-10069 at 7; Tr. at 230:6–10 (Lepore).

340) Eleven claimed GB #692 compounds have a substitution on the acetamide. DTX-10069 at 7; Tr. at 231:20–232:2 (Lepore).

341) None of the compounds specifically claimed by GB #692 have an n-propyl substituent around the pyrrolidine ring. Tr. at 250:3–5 (Lepore); Tr. at 682:8–14 (MacMillan).

342) Twenty-eight claimed GB #692 compounds have methyl substitutions at one or more of the 3-, 4-, and 5-positions on the pyrrolidine ring. DTX-10069 at 7; Tr. at 249:19–251:9 (Lepore).

343) GB #692 only provides compound-specific data for the central nystagmus test (for motion sickness) and the spinal fixation test (for amnesic activity), neither of which is a test for anti-seizure activity. DTX-10069 at 2; Tr. at 679:24–681:5 (MacMillan).

344) GB #692 does not provide specific audiogenic mouse data for any compound. DTX-10069 at 2; Tr. at 230:22–231:16 (Lepore); Tr. at 681:6–20 (MacMillan).

345) A skilled artisan would not reasonably expect that all the compounds in GB #692 would demonstrate audiogenic mouse activity. Tr. at 230:22–231:16 (Lepore); Tr. at 681:13–16 (MacMillan).

346) Although GB #692 covers alkyl substitutions at the 4-position of the pyrrolidine ring, it would not have motivated a skilled artisan to make an alkyl substitution at the 4-position of the pyrrolidine ring. DTX-10069 at 2; Tr. at 640:3–15, 664:8–23, 681:17–682:3, 751:1–20 (MacMillan).

347) GB #692 would similarly not have given a skilled artisan a reasonable expectation of success in adding lower alkyl groups to the 4-position of the pyrrolidine ring to create a new compound with improved antiepileptic activity. Tr. at 227:15–22, 228:2–22 (Lepore); Tr. at 681:6–682:14 (MacMillan).

348) GB #692 therefore would not have motivated a skilled artisan to substitute or have given a skilled artisan a reasonable expectation of success of substituting a propyl group at the 4-position of the pyrrolidine ring of levetiracetam. Tr. at 640:3–15, 664:8–23, 681:6–682:14, 751:1–20 (MacMillan).

N. Reasonable Expectation of Success

349) Dr. MacMillan credibly testified that when starting with an FDA-approved drug like levetiracetam, a skilled artisan is "almost reaching the top of the mountain," but in trying to improve upon that drug, "every step tends to go in the wrong direction," making it harder "to predict if you do something [whether]

it's going to have a net positive [e]ffect." Tr. at 712:10–18, 736:21–737:14 (MacMillan).

350) Dr. MacMillan also credibly testified that a skilled artisan would not have been able to predict the audiogenic mouse activity of a levetiracetam analogue with a seven-carbon side chain based on data from up to six compounds. Tr. at 737:15–738:9 (MacMillan).

351) A skilled artisan would have reasonably expected a propyl substitution at the 4- position of levetiracetam to increase lipophilicity, measured by log *P*, of the compound. Tr. at 783:18–23 (MacMillan).

352) But as previously discussed, a skilled artisan would not have reasonably expected that adding a propyl group at the 4-postion of levetiracetam would significantly increase the brain permeability of the compound. Tr. at 694:17–698:1 (MacMillan).

353) It therefore follows that a skilled artisan would not have reasonably expected a propyl substitution at the 4-position of levetiracetam to improve antiepileptic activity. Tr. at 506:17–21, 507:16–508:23 (Löscher); Tr. at 640:3–15, 661:15–662:3, 681:6–16, 682:4–13, 693:21–694:12, 694:17–698:8, 699:15–700:8 (MacMillan).

O. Alleged Objective Indicia of Nonobviousness

1. Alleged Unexpected Results of Brivaracetam

354) The parties presented competing, conclusory expert testimony about whether brivaracetam's results were unexpected.

355) What brivaracetam's results were and whether those results are good are different questions that whether brivaracetam's results were unexpected.

356) Dr. Löscher testified that brivaracetam demonstrated unexpected results relative to levetiracetam in terms of affinity for the LBS, potency in animal models, and "mechanistic differences." Tr. at 502:9–15 (Löscher).

357) But Dr. Löscher did not identify any published literature in which an author expressed surprise at brivaracetam's increased binding affinity for the LBS compared to levetiracetam, nor at the difference in potency between the two drugs. Tr. 581:13–17, 584:7–11 (Löscher).

358) Dr. Lepore testified "that brivaracetam does not demonstrate unexpected results" and "that there is no evidence of industry skepticism." Tr. at 163:10–16 (Lepore).

359) Dr. Sands testified that Briviact®'s side-effect profile with respect to psychiatric and behavioral side effects was unexpectedly milder than levetiracetam's. Tr. at 424:18–25, 429:24–430:8 (Sands); JTX-20045 at 4; JTX-20061 at 5.

360) Dr. Pleasure testified that he did not agree that "Briviact's . . . side-effect profile as compared to levetiracetam was unexpected," because he did not "think that that's been established." Tr. at 825:9–20 (Pleasure).

361) I found Drs. Lepore and Pleasure to be credible witnesses, and I find that the testimony of Drs. Löscher and Sands did not establish by a preponderance of the evidence that brivaracetam's results were unexpected.

2. Alleged Long-Felt Unmet Need for Brivaracetam

362) As of February 2000, there was a need for anti-seizure drugs effective in reducing or eliminating seizures in patients with refractory epilepsy. Tr. at 408:14–19, 410:16–411:12 (Sands); Tr. at 833:17–22 (Pleasure); PTX-162 at 1.

363) Dr. Sands testified, based on his personal experience of treating patients, that brivaracetam is effective for some number of patients with refractory epilepsy in reducing or eliminating those patients' seizures. Tr. at 408:13–19, 411:13–412:3, 431:22–432:10, 444:13–445:10, 454:23–455:6 (Sands).

364) Briviact®'s efficacy in some patients who previously tried and failed other anti-seizure drugs has been recognized in the medical literature. Tr. at 412:14–414:24, 415:13–417:21, 418:6–420:12, 421:15–24 (Sands); JTX-20046 at 2, 4; JTX20059 at 5; PTX-202 at 3.

365) In 2000, approximately 30% of patients with epilepsy suffered

from refractory epilepsy. That percentage has not changed as of today. Tr. 567:25–568:10 (Loscher).

366) UCB did not establish by a preponderance of the evidence that brivaracetam resolved a long-felt unmet need for anti-seizure drugs effective in reducing or eliminating seizures in patients with refractory epilepsy.

3. Alleged Failure of Others to Develop Antiepileptic Drugs That Achieve Approval by the FDA for Use in Humans

367) Dr. Löscher contended that there have been failures of others to develop antiepileptic drugs that achieve approval by FDA for use in humans. Tr. at 569:17–571:18 (Löscher).

368) One source of information regarding anti-seizure drugs that have failed in preclinical development is the National Institutes of Health (NIH) Epilepsy Therapy Screening Program (ETSP). Tr. at 515:11–24 (Löscher).

369) The NIH started the ETSP in 1975 to bring more anti-seizure drugs to market by offering free compound screening for both the pharmaceutical industry and academic institutions in a battery of seizure models, including the maximal electroshock and pentylenetetrazole tests. Tr. at 515:11–24, 516:8–13 (Löscher).

370) By 2002, the ETSP had screened approximately 23,000 compounds. Tr. at 516:5–7 (Löscher).

371) By 2002, only six of the compounds screened by the ETSP had

become approved anti-seizure drugs. Tr. at 517:10–12 (Löscher).

372) Carabersat, irampanel, talampanel, isovaleramide, valrocemide, remacemide, and fluorofelbamate are examples of potential anti-seizure drugs that were in clinical development at or around February 2000 that failed to achieve regulatory approval. Tr. at 517:20–521:14 (Löscher).

373) Carabersat, irampanel, talampanel, isovaleramide, valrocemide, remacemide, and fluorofelbamate had all been (1) characterized in preclinical tests and (2) the subject of at least one clinical trial. Tr. at 518:3–12 (Löscher).

374) The development of talampanel was stopped because clinical trials showed that the compound had poor pharmacokinetic behavior and poor tolerability. Tr. at 519:14–20 (Löscher).

375) The development of remacemide was stopped after a meta-analysis of several clinical trials showed poor tolerability. Tr. at 520:23–521:3 (Löscher).

376) Drs. Lepore and Pleasure did not offer any opinions regarding failures of others. Tr. at 837:24–838:3 (Pleasure); *see generally* Tr. (Lepore).

377) UCB established by a preponderance of the evidence that others tried but failed to develop antiepileptic drugs that achieve approval by FDA for use in humans.

4. Alleged Industry Praise for Brivaracetam

378) In arguing that Briviact®'s efficacy has been praised in the medical

literature, UCB relies on studies (1) with authors employed by UCB and (2) in which UCB was involved. JTX-20040 at 1, 6; Tr. at 830:15–25 (Pleasure).

379) In arguing that Briviact®'s tolerability has been praised in the medical literature, UCB relies in part on a study (1) based on Phase 2 clinical trials, (2) with authors employed by UCB, or (3) in which UCB was involved. Tr. at 828:20–830:1, 830:15–25 (Pleasure); JTX-20036 at 1–2; JTX-20062 at 9; JTX-20040 at 1, 6.

380) UCB demonstrated that there was some industry praise for Briviact®'s tolerability. Tr. at 434:14–18 (Sands); JTX-20062 at 9.

381) Briviact®'s clinical profile as compared to levetiracetam has received some praise in the medical literature. Tr. at 434:23–435:6 (Sands); JTX-20046 at 3.

382) UCB established by a preponderance of the evidence that there was a mild amount of industry praise for brivaracetam to support a finding of nonobviouness. Tr. at 361:10–13 (Klitgaard).

V. CONCLUSIONS OF LAW

A. Claim 5 of the #461 Patent

I agree with UCB that Defendants failed to prove by clear and convincing evidence that claim 5 of the #461 patent is invalid for obviousness. The parties have stipulated that a skilled artisan would have chosen levetiracetam as a lead

compound for further development. But as I have found above as a factual matter, Defendants failed to prove that a skilled artisan would have used lipophilicity as a guiding principle when modifying levetiracetam, because a skilled artisan would not have been motivated to create a compound with greater lipophilicity than levetiracetam and because a skilled artisan would not have had a reasonable expectation that doing so would have resulted in a successful anti-seizure drug. Defendants further failed to establish that a skilled artisan seeking to modify levetiracetam to create a compound with increased lipophilicity would have been motivated to do so by adding a 4-n-propyl to the levetiracetam scaffold and that a skilled artisan would have reasonably expected that alteration to yield a compound with similar or better performance as an anti-seizure drug. Defendants therefore failed to prove that it would have been obvious to a skilled artisan to alter levetiracetam by adding a 4-n-propyl to the levetiracetam scaffold. Accordingly, I conclude as a matter of law that claim 5 of the #461 patent is not invalid.

Because Defendants stipulated to infringement in the event claim 5 of the #461 patent were not invalid, I conclude as a matter of law that Defendants' ANDA products infringe claim 5 of the #461 patent.

VI. CONCLUSION

For the reasons discussed above, I find that Defendants' ANDA products infringe claim 5 of the #461 patent and that claim 5 of the #461 patent is not invalid.

The Court will issue an Order directing the parties to submit a proposed order by which the Court may enter final judgments consistent with this Opinion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB, INC. and UCB BIOPHARMA SRL, Plaintiffs, v. ANNORA PHARMA PRIVATE LIMITED, *et al.*, Defendants.	Civil Action No. 20-987-CFC

ORDER

At Wilmington on this Sixteenth day of August in 2023:

IT IS HEREBY ORDERED that the parties shall submit no later than August 30, 2023, a proposed order by which the Court may enter final judgment consistent with the Opinion issued this day.

CHIEF JUDGE