IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB, INC., UCB BIOPHARAMA SPRL, RESEARCH CORPORATION TECHNOLOGIES, INC. and HARRIS FRC CORPORATION,	:	UNSEALED ON AUGUST 15, 2016
Plaintiffs,	:	
v.	:	Civil Action No. 13-1206-LPS CONSOLIDATED
ACCORD HEATLHCARE, INC., et al.,	:	
Defendants.	:	

Jack B. Blumenfeld, Maryellen Noreika, and Derek J. Fahnestock, MORRIS, NICHOLS, ARSHT & TUNNELL, LLP, Wilmington, DE

George F. Pappas, Jeffrey B. Elikan, and Alexa Hansen, COVINGTON & BURLING LLP, Washington, DC

Attorneys for Plaintiffs UCB Inc., Research Corporation Technologies Inc., Harris FRC Corporation, and UCB Biopharma SPRL

John C. Phillips, Jr., David A. Bilson, and Megan C. Haney, PHILLIPS, GOLDMAN, & SPENCE, P.A., Wilmington, DE

George C. Lombardi, Maureen L. Rurka, Samuel S. Park, John R. McNair, and Lesley M. Hamming WINSTON & STRAWN LLP, Chicago, IL.
Charles B. Klein and Eimeric Reig-Plessis, WINSTON & STRAWN, Washington, DC.

Attorneys for Defendants Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York LLC, Aurobindo Pharma Ltd., Aurobindo Pharma USA Inc., Breckenridge Pharmaceutical Inc., MSN Laboratories Pvt. Ltd., Sun Pharma Global FZE, Sun Pharmaceuticals Industries Ltd., Watson Laboratories Inc. - Florida, Watson Pharma Inc., and Actavis, Inc.

John W. Shaw, SHAW KELLER LLP, Wilmington, DE

Karen Bromberg and Gurpreet S. Walia, COHEN & GRESSER LLP, New York, NY

Attorneys for Defendants Accord Healthcare Inc. and Intas Pharmaceuticals Ltd.

Richard D. Kirk, Stephen B. Brauerman, and Vanessa R. Tiradentes, BAYARD, P.A., Wilmington, DE

Jeffer Ali & Sarah M. Stensland, CARLSON, CASPERS, VANDENBURGH, LINDQUIST & SCHUMAN, PA, Minneapolis, MN

Attorneys for Defendant Alembic Pharmaceuticals Ltd.

Kenneth L. Dorsney, MORRIS JAMES LLP, Wilmington, DE

Richard T. Ruzich, Stephen R. Auten, and Ian Scott, TAFT STETTINIUS & HOLLISTER LLP, Chicago, IL

Attorneys for Defendant Apotex Corp. and Apotex Inc.

Adam W. Poff and Pilar G. Kraman, YOUNG, CONAWAY, STARGATT & TAYLOR LLP, Wilmington, DE

Nicole W. Stafford, Eric C. Arnell, and Aden M. Allen, WILSON SONSINI GOODRICH & ROSATI, Austin, TX
David S. Steuer, WILSON SONSINI GOODRICH & ROSATI, Palo Alto, CA
Yongdan Li, WILSON SONSINI GOODRICH & ROSATI, Los Angeles, CA

Attorneys for Defendants Mylan Pharmaceuticals Inc. and Mylan, Inc.

Francis J. Murphy, Jr., MURPHY, SPADARO & LANDON, Wilmington, DE

Michael J. Gaertner, David B. Abromowitz, and Timothy F. Petersen, LOCKE LORD LLP, Chicago, IL
Andrea L. Wayda, LOCKE LORD LLP, New York, NY

Attorney for Defendants Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd.

OPINION

August 12, 2016
Wilmington, Delaware

STARK, U.S. District Judge:

Plaintiffs – UCB, Inc., UCB BioPharma SPRL, Research Corporation Technologies, Inc., and Harris FRC Corporation (collectively, "Plaintiffs") – allege that Defendants – Accord Healthcare, Inc., Intas Pharmaceuticals Ltd., Alembic Pharmaceuticals, Ltd., Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York, LLC, Aurobindo Pharma Ltd., Aurobindo Pharma USA, Inc., Breckenridge Pharmaceutical, Inc., MSN Laboratories Pvt. Ltd., Sun Pharma Global FZE, Sun Pharmaceutical Industries, Ltd., Watson Laboratories, Inc. - Florida (n/k/a Actavis Laboratories FL, Inc.), Watson Pharma, Inc. (n/k/a Actavis Pharma, Inc), Actavis, Inc., Apotex Corp., Apotex, Inc., Mylan Pharmaceuticals Inc., Mylan, Inc., Zydus Pharmaceuticals (USA) Inc., and Cadila Healthcare Limited (collectively, "Defendants") – infringe United States patent No. RE38,551 (JTX-1 ("the '551 patent" or "the patent-in-suit")). (D.I. 1)

The '551 patent generally relates to "anticonvulsant drugs," which "control and prevent[] seizures associated with epilepsy or related central nervous system disorders." ('551 patent at 1:26-29) Each of the Defendants has filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to market generic versions of Plaintiffs' pharmaceutical product Vimpat®, which is an embodiment of claims of the patent-in-suit.

The Court construed the disputed claim terms in May 2015. (D.I. 240) In December 2015, the Court conducted a bench trial. (*See* D.I. 264-267 ("Tr.")) The parties completed post-trial briefing on February 8, 2016. (D.I. 263, 271, 274, 277) In connection with the briefing, the parties submitted proposed findings of fact (D.I. 262, 270, 273) as well as a Stipulation of Uncontested Facts ("SUF") (D.I. 272).

On May 23, 2016, the Patent Trial and Appeal Board ("PTAB") instituted an *inter partes* review of the validity of claims 1-13 of the '551 patent. (*See* D.I. 294, 294-1) On June 16, 2016, the U.S. Patent and Trademark Office ("PTO") instituted an *ex parte* reexamination of the same claims. (*See* D.I. 300, 300-1)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) Defendants have stipulated that their proposed products infringe claims 9, 10, and 13 of the '551 patent, and (2) Defendants have failed to prove that any of claims 9, 10, and 13 of the '551 patent are invalid for obviousness-type double patenting, obviousness, anticipation, indefiniteness, or improper reissue. The Court's findings of fact and conclusions of law are set forth in detail below.

I. FINDINGS OF FACT

This section contains the Court's findings of fact for issues raised by the parties during trial. Certain findings of fact are also provided in connection with the Court's conclusions of law.

A. The Parties

1. Plaintiff UCB, Inc. is a corporation organized and existing under the laws of Delaware, having a principal place of business at 1950 Lake Park Drive, Smyrna, Georgia 30080. (SUF ¶ 1)

2. Plaintiff UCB BioPharma SPRL (together with UCB, Inc., "UCB"), is a corporation organized and existing under the laws of Belgium, having a principal place of business at Allée de la Recherche 60, Brussels, 1070, Belgium. (SUF ¶ 2)

3. Plaintiff Research Corporation Technologies, Inc. ("RCT") is a corporation organized and existing under the laws of Delaware, having a principal place of business at 5210 East Williams Circle, Suite 240, Tucson, Arizona 85711-4410. (SUF ¶ 3)

4. Plaintiff Harris FRC Corporation ("Harris") is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 2137 State Highway 35, Holmdel, New Jersey 07733. (SUF ¶ 4)

5. Defendant Accord Healthcare, Inc. is a corporation organized and existing under the laws of North Carolina, having a principal place of business at 1009 Slater Road, Ste. 210-B, Durham, North Carolina 27703. (SUF ¶ 5)

6. Defendant Intas Pharmaceuticals Ltd. is a corporation organized and existing under the laws of India, having a principal place of business at Chinubhai Centre, off Nehru Bridge, Ashram Road, Ahmedabad 380009, Gujarat, India. (SUF ¶ 6)

7. Defendant Alembic Pharmaceuticals Ltd. is a corporation organized and existing under the laws of India, having a principal place of business at Alembic Road, Vadodara-390 003, Gujarat, India. (SUF ¶ 7)

8. Defendant Amneal Pharmaceuticals, LLC is a corporation organized and existing under the laws of Delaware, having a principal place of business at 400 Crossing Boulevard, 3rd Floor, Bridgewater, New Jersey 08807. (SUF ¶ 8)

9. Defendant Amneal Pharmaceuticals of New York, LLC is a corporation organized and existing under the laws of Delaware, having a principal place of business at 85 Adams Avenue, Hauppauge, New York 11788. (SUF ¶ 9)

10. Defendant Aurobindo Pharma Ltd. is a corporation organized and existing under the laws of India, having a principal place of business at Plot # 2, Maitrivihar, Ameerpet, Hyderabad - 500038, Telagana, India. (SUF ¶ 10)

11. Defendant Aurobindo Pharma USA, Inc. is a corporation organized and existing under the laws of Delaware, having a principal place of business at 6 Wheeling Road, Dayton, New Jersey 08810. (SUF ¶ 11)

12. Defendant Breckenridge Pharmaceutical, Inc. is a corporation organized and existing under the laws of Florida, having a principal place of business at 6111 Broken Sound Parkway NW, Suite 170, Boca Raton, Florida 33487. (SUF ¶ 12)

13. Defendant Vennoot Pharmaceuticals, LLC is a corporation organized and existing under the laws of Georgia, having a principal place of business at 11009 Estates Circle, Alpharetta, Georgia 30022. (SUF ¶ 13) On August 1, 2016, the Court granted the parties' stipulation to substitute MSN Laboratories Ptv. Ltd. for Vennoot. (D.I. 311)

14. Defendant Sun Pharma Global FZE is a corporation organized and existing under the laws of the United Arab Emirates, having a principal place of business at Executive Suite #43, Block Y, SAIF-Zone, P.O. Box 122304, Sharjah, U.A.E. (SUF ¶ 14)

15. Defendant Sun Pharmaceutical Industries, Ltd., is a corporation organized and existing under the laws of India, having a principal place of business at SUN HOUSE, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063, India. (SUF ¶ 15)

16. Defendant Watson Laboratories, Inc. - Florida (n/k/a Actavis Laboratories FL, Inc) is a corporation organized and existing under the laws of Florida, having a principal place of business at 4955 Orange Drive, Fort Lauderdale, Florida 33314. (SUF ¶ 16)

17. Defendant Watson Pharma, Inc. (n/k/a Actavis Pharma, Inc) is a corporation organized and existing under the laws of Delaware, having a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054. (SUF ¶ 17)

18. Defendant Actavis, Inc. is a corporation organized and existing under the laws of Nevada, having a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054. (SUF ¶ 18)

19. Defendant Apotex Corp. is a corporation organized and existing under the laws of Delaware, having a principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326. (SUF ¶ 19)

20. Defendant Apotex, Inc. is a corporation organized and existing under the laws of Canada, having a principal place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9. (SUF ¶ 20)

21. Defendant Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of West Virginia, having a principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. (SUF ¶ 21)

22. Defendant Mylan, Inc. is a corporation organized and existing under the laws of Pennsylvania, having a principal place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317. (SUF ¶ 22)

23. Defendant Zydus Pharmaceuticals (USA) Inc. is a corporation organized and existing under the laws of New Jersey, having a principal place of business at 73 Route 31 North, Pennington, New Jersey 08534. (SUF ¶ 23)

24. Defendant Cadila Healthcare Limited is a corporation organized and existing under the laws of India, having a principal place of business at Zydus Tower, Satellite Cross Roads, Ahmedabad, 380015, Gujarat, India. (SUF ¶ 24)[1]

B. Testifying Witnesses[2]

25. Dr. Clayton Heathcock testified on behalf of Defendants. Dr. Heathcock is an Emeritus Professor of Chemistry at the University of California, Berkeley. He has more than 50 years of experience in organic and medicinal chemistry, and has evaluated antiepileptic drugs for the National Institutes of Health. (Heathcock Tr. at 68-69, 71-72; DTX-2184)[3] Dr. Heathcock has never been involved in the development of anticonvulsant drugs generally or for epilepsy specifically. (Heathcock Tr. at 169)

26. Dr. Samuel J. Pleasure testified on behalf of Defendants. Dr. Pleasure is a Professor of Neurology at the University of California, San Francisco ("UCSF"), School of Medicine and is a practicing physician with over 20 years of experience treating epilepsy patients. (Pleasure Tr. at 220-25, 316; DTX-2455) Dr. Pleasure is neither board certified in epilepsy nor focused on epilepsy in his research or clinical practice. (Pleasure Tr. at 291-93, 1012) He does not see patients at UCSF's Epilepsy Center, nor is he listed as an epileptologist on the UCSF Epilepsy Center website. (Pleasure Tr. at 292-93) He has not been an investigator in any trials for approval of an epilepsy drug. (Pleasure Tr. at 1013)

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[1] The following parties are no longer part of the case: UCB Pharma GmbH, Alembic Limited, Hetero USA Inc., Hetero Labs Limited, Glenmark Generics Inc. USA, Glenmark Generics Ltd., Ranbaxy Laboratories Ltd., Ranbaxy Pharmaceuticals Inc., Ranbaxy Inc., and Sandoz Inc.

[2] The Court here identifies each of the witnesses who testified live at trial. Both sides also called additional witnesses who testified via deposition.

[3] References to the trial transcript are in the form: "([Witness last name] Tr. at [page])."

27. Dr. Harold Kohn testified on behalf of Plaintiffs. Dr. Kohn is the inventor of the '551 patent. (*See* JTX-1) He possesses a Ph.D. in chemistry and worked as a professor at the University of Houston for over 20 years. (Kohn Tr. at 370-71) Dr. Kohn later worked as a professor at the University of North Carolina at Chapel Hill. (Kohn Tr. at 371) Over the course of his career, Dr. Kohn's research focused on functionalized amino acids. (*See, e.g.*, JTX-7; JTX-9; JTX-10; JTX-11; JTX-40)[4]

28. Dr. Roush was called at trial by Plaintiffs. Dr. William Roush is a professor at the Scripps Institute in Jupiter, Florida, and the Executive Director of the Scripps Institute's internal drug discovery program. (Roush Tr. at 550-51; JTX-71) For the past ten years he has focused on drug development. (Roush Tr. at 550-53) Dr. Roush has authored over 330 peer-reviewed papers, is an associate editor for the *Journal of the American Chemical Society*, and has received numerous honors for his work. (Roush Tr. at 553-54; *see also* JTX-71)

29. Dr. Carl Bazil testified on behalf of Plaintiffs. Dr. Bazil is a Professor of Neurology and the Director of the Comprehensive Epilepsy Center at Columbia University New York Presbyterian Hospital. (JTX-59; Bazil Tr. at 753-63) He is board certified in epilepsy, has treated epilepsy patients for more than 30 years, and has overseen the care of thousands of epilepsy patients. (Bazil Tr. at 758-60) Dr. Bazil has overseen FDA-required phase III and IV trials for three anti-epileptic drugs. (Bazil Tr. at 755-56)[5]

30. Dr. Christopher Vellturo is an economist who has performed a wide variety of economic and econometric analyses in the context of mergers and acquisitions, intellectual property, antitrust litigation, and regulatory disputes. (*See* JTX-73) Dr. Vellturo has expertise in

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[4] The Court found Dr. Kohn to be a particularly credible witness.

[5] The Court found Dr. Bazil to be a particularly credible witness.

pharmaceutical economics based on consulting for clients in the pharmaceutical industry for more than 20 years. (*See id.*; *see also* Vellturo Tr. at 898-901) Dr. Vellturo was called at trial by Plaintiffs.

31. Dr. DeForest McDuff is an economist with more than ten years of experience in consulting, finance, and economic research. (DTX-2188) He has performed economic analyses on more than 100 professional engagements and in a wide variety of subject matters, including pharmaceuticals, biotechnology, diagnostics, consumer electronics, semiconductors, and finance. (*See id.*) Dr. McDuff was called at trial by Defendants.

32. Dr. Henrik Klitgaard is a vice president and research fellow in the Neurosciences Therapeutic Area at UCB. (Klitgaard Tr. at 873) Dr. Klitgaard has been involved in drug development for over 25 years and has published several papers on epilepsy and epilepsy drug development. (*Id.* at 874-75) Dr. Klitgaard conducted UCB's assessment of lacosamide in 1997. (*Id.* at 879-81)

C. Person Having Ordinary Skill in the Art

33. As concerns the '551 patent, the parties agree that a person having ordinary skill in the art ("POSA") would have had knowledge and experience both in medicinal or organic chemistry and in the development of potential drug candidates. (Heathcock Tr. at 95-96; Roush Tr. at 562-63) This includes knowledge and experience in assessing the toxicology, pharmacology, and clinical utility of such candidates. (Heathcock Tr. at 95-96; Roush Tr. at 562-63)

34. "A medicinal chemist is someone who has been trained in organic or medicinal chemistry . . . ." (Heathcock Tr. at 95) This person would "[u]sually" have "at least a master's or bachelor's degree" but, "[m]ore likely . . . a Ph.D. degree and then a few years of actually

doing medicinal chemistry and learning how medicinal chemistry does drug discovery" – "including developing drug candidates." (Heathcock Tr. at 95-96)

35. "[B]ecause drug discovery involves a multi-disciplinary approach, a medicinal chemist may interface or consult with individuals having [other] specialized expertise, for example, a physician with experience in the administration of dosing and efficacy of drugs for the treatment of epilepsy or other central nervous system disorders." (Pleasure Tr. at 315)

D. Epilepsy and Its Treatment

36. Epilepsy is a chronic neurological disorder that afflicts about one percent of the population. (Bazil Tr. at 765-66) It is characterized by uncontrolled seizures that can be life-threatening or life-limiting, impacting the patient's quality of life. (*See* Pleasure Tr. at 226, 228, 255; Bazil Tr. at 769-72)

37. Epilepsy is a heterogeneous disorder. (Bazil Tr. 766-68) The cause of most cases of epilepsy is unknown, making the development of antiepileptic drugs ("AEDs") challenging and unpredictable. (Bazil Tr. 767-69; *see* DTX-2249 at DEF_7606; JTX-63 at PLS_VIM667)

38. The manifestations of epilepsy also vary greatly, as seen in the different types of seizures that patients suffer, which can involve the whole brain (generalized seizure) or a part of the brain (partial seizure). (Bazil Tr. at 766-67; Pleasure Tr. at 255-56)

39. As a result, epilepsy treatments must be individualized to the specific patient. (Bazil Tr. at 768-69) Although a particular treatment may be effective for one patient, it may not work for another and may "be completely absurd to try" as a treatment choice for some patients. (Bazil Tr. at 768-69; *see also id.* at 772-73)

40. Before March 15, 1996, more than 20 AEDs had been marketed to patients in the United States, including phenobarbital, mephobarbital, phenytoin, trimethadione, mephenytoin,

paramethadione, phenythenylate, phenacemide, metharbital, benzchloropropionamide, aminoglutethimide, acetazolamide, phensuximide, primidone, methsuximide, ethotoin, methazolamide, ethosuximide, diazepam, carbamazepine, clonazepam, lorazepam, valproic acid, clorazepate, felbamate, gabapentin, and lamotrigine. (SUF ¶ 83)

E. UCB's Vimpat®

41. UCB is the holder of New Drug Application ("NDA") Nos. 022-253, 022-254, and 022-255, which cover an anti-epileptic drug known by the trade name Vimpat®. (SUF ¶ 25)

42. The active ingredient of Vimpat® is a compound called lacosamide. (SUF ¶ 26)

43. On October 28, 2008, NDA Nos. 022-253, and 022-254 were approved by the FDA to authorize the commercial marketing of Vimpat® tablets and injections as an adjunctive (i.e., add-on AED to be used with other AEDs) therapy in patients ages 17 years or older for partial on-set seizures. (SUF ¶ 28) Injection is indicated as a short-term replacement when oral administration is not feasible in these patients. (SUF ¶ 27)

44. On April 20, 2010, NDA No. 022-255 was approved by the FDA to authorize the commercial marketing of Vimpat® oral solution as an adjunctive therapy in patients ages 17 years or older for partial on-set seizures. (SUF ¶ 27)

45. In August 2014, NDA Nos. 022-253, 022-254, and 022-255 were further approved as a monotherapy in patients ages 17 years or older for partial on-set seizures. (SUF ¶ 29)

46. Vimpat® first launched in the U.S. market in 2008. (SUF ¶ 84)

47. Lacosamide had been formerly identified by or referred to as SPM 927, ADD 234037, or harkoseride. (SUF ¶ 85)

48. Vimpat® has the features needed in an AED for chronic treatment of epilepsy: high anticonvulsant activity, minimal neurological toxicity, and a high margin of safety. (*See* JTX-1 at 3:14–55; Bazil Tr. 788-93) It also causes little to no liver toxicity, making it suitable for chronic administration. (*See* JTX-1 at 3:36–38)

49. In Dr. Bazil's experience, lacosamide is a "very important option" for a "large number of patients," including those whose serious seizures could not be controlled with other AEDs. (Bazil Tr. at 816-17; *see also* Pleasure Tr. at 990 (agreeing with Dr. Bazil))

F. Applicable Principles of Medicinal Chemistry

50. "Enantiomeric compounds," also known as "enantiomers" or "stereoisomers," are molecules that "have the same connectivity" – *i.e.*, the same atoms connected to each other in the same way – but are mirror images of each other in three-dimensional space. (*See* Heathcock Tr. at 82-83) With the exception of three-dimensionality, enantiomers share "the same structure." (Roush Tr. at 714-16) This relationship is called "chirality." (*See id.*) A 50-50 mixture of two enantiomers is called a "racemate" or "racemic mixture." (Heathcock Tr. at 83)

51. Racemic compounds and enantiomers are different compounds having different properties. (*See* Roush Tr. at 624-30; Kohn Tr. at 403–05) Racemic compounds have different crystal forms, melting points, solubilities, optical rotations, spectroscopic properties, and biological effects than do enantiomeric compounds. (Roush Tr. at 625-28; Kohn Tr. at 403-05) Racemates and enantiomers each receive different registration numbers from the Chemical Abstracts Services ("CAS"). (Kohn Tr. at 404–05; Roush Tr. at 627-28)

52. In this case, the two enantiomers that make up a racemic mixture can be called either "R" and "S," or "D" and "L." (Heathcock Tr. at 85-86; *see also* Roush Tr. at 695) "[F]or

... compounds that we are concerned with . . . D is synonymous with R and L is synonymous with S." (Heathcock Tr. at 86)

53. During the relevant period, medicinal chemists evaluated drugs for their anticonvulsant activity based on "ED_{50}" values obtained in the "maximal electroshock seizure" ("MES") animal test. (Kohn Tr. at 382; Heathcock Tr. at 127; *see also* JTX-1 at 21:30-22:27) ED_{50} represents "the dose at which half of the [animals that were tested] did not have [a] convulsion" in response to an electric shock. (Heathcock Tr. at 127) "[T]he lower the number, the more potent the compound is." (*Id.*; *see also* Kohn Tr. at 382-83, 461)

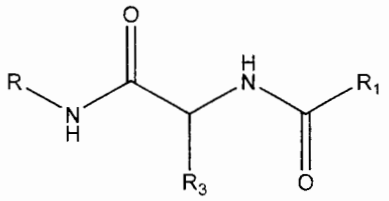
54. The MES test was also used to measure neurotoxicity, which is reported as "TD_{50}" values, representing "the dose at which half of the animals experience ... toxicity" as shown by "loss of balance." (Heathcock Tr. at 128; *see also, e.g.*, JTX-1 at 22:5-13, 26-27) For TD_{50}, "a larger number" – indicating less toxicity – is desirable. (*See* Heathcock Tr. at 128)

55. "[T]he ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50})" is the "protective index" ("PI"). (JTX-1 at 3:19-25; Kohn Tr. at 382) The larger the PI, the safer the drug. (Heathcock Tr. at 382)

56. The '551 patent reports data on anticonvulsant activity in terms of ED_{50}, TD_{50}, and PI values. (*See* '551 patent at 21-24) The '551 patent does not describe any human testing. (Pleasure Tr. at 287)

G. Functionalized Amino Acids

57. The compounds described in the '551 patent belong to a class of compounds called "functionalized amino acids" ("FAAs"). (Kohn Tr. at 372; Heathcock Tr. at 90-91) FAAs have the general structure depicted below:



58. In an FAA, R, R_1, and R_3 are variables, meaning different elements or compounds of elements can be placed at each of these three sites, and each variation for any of these three sites yields a different FAA compound. (*See* Heathcock Tr. at 90-91; Kohn Tr. at 372-73)[6]

H. Aromatic, Heteroaromatic, and Nonaromatic Groups

59. Aromatic groups are two-dimensional and have an electron configuration that confers stability to the unit. Aromatic groups are organized into a ring. (Kohn Tr. at 400-01)

60. Heteroaromatic groups are aromatic groups that contain at least one heteroatom. A heteroatom is any atom other than carbon. In heteroaromatic groups, the heteroatom is most often oxygen, nitrogen, or sulfur. (*Id.* at 411)

61. Non-aromatic groups are compounds that have a three-dimensional structure and no unique stability provided by the electron structure. (Kohn Tr. at 400-01) Non-aromatic groups are not organized into a ring. (*Id.*)

I. Lacosamide's Structure

62. Claim 9 of the '551 patent depends from claim 8 and claims the FAA compound lacosamide, which is the R-enantiomer of N-benzyl-2-acetamido-3-methoxypropionamide. ('551 patent at 38:37-40)

63. Lacosamide has the following structure:

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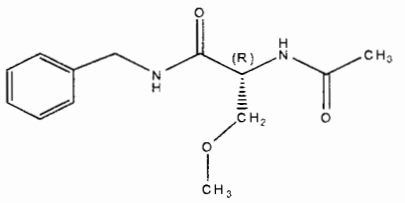
[6] Although all FAAs share the structure depicted and described here, the variables are not always labelled R, R_1, and R_3. Where different nomenclature is used, this Opinion will note it.



Lacosamide has a methoxymethyl group at R_3. Methoxymethyl is a carbon-based, non-aromatic group. (Roush Tr. at 603)

J. Drug Development in 1996

64. As of March 1996, a common approach to identify a lead AED was to start with FDA-approved drugs or compounds having proven clinical efficacy. (Roush Tr. at 565)[7] A POSA would also look in the literature to find promising compounds that were either in clinical trials or were viewed as well-advanced preclinical candidates. (Roush Tr. at 565-66, 574) Looking at FDA-approved drugs or promising drugs in clinical or preclinical development yielded hundreds of potential start points. (Roush Tr. at 564-69, 572-74; *see also* JTX-91; JTX-92; PTX-320)

65. As of March 1996, no FAA compound had been approved as an AED by the FDA, nor had any FAA been identified as undergoing clinical evaluation or as a well-advanced preclinical candidate. (Roush Tr. at 570, 575-76) Twenty years later, lacosamide remains the only FAA that has been approved for the treatment of epilepsy. (Kohn Tr. at 373)

66. Drug discovery is, and was as of March 1996, unpredictable. The myriad chemical and biological factors at play made it difficult to predict the effects of a particular compound in the body. (*See* Heathcock Tr. at 187-88; Roush Tr. at 567-68, 611-12; Pleasure Tr.

[7] Sixteen of the 24 AEDs that had been approved as of 1996 shared one of four common chemical cores. (Roush Tr. at 570; *see also* JTX-92 at PLS_VIM 105–06, 113, 120, 123–26; PTX-66 at PLS_VIM 2096-97, 2099-100, 2104–07, 2109, 2111–15; JTX-91 at DEF_8352)

at 1044-46; PTX-4 at 443) Thus, discovery of new drugs was driven by pharmacological data. (Heathcock Tr. at 165-166; Roush Tr. at 566-67; *see also* Kohn Tr. at 521)

67. A POSA would consider a number of factors when seeking to develop a new AED. Among the most important are anticonvulsant activity (Heathcock Tr. at 165-66; Roush Tr. at 566-67), neurotoxicity (Kohn Tr. at 383; Heathcock Tr. at 127-28), and liver toxicity (Heathcock Tr. at 177).

68. Medicinal chemists also use structure-activity relationships ("SARs") to design new drugs. (Heathcock Tr. at 103) This involves starting with a structure and "making changes and observing whether that change . . . improves the potency or whatever biological property you are using as your endpoint, or if it doesn't improve it. And then you continue to make changes of the sort that improve it." (Heathcock Tr. at 103, 134) SARs allow chemists to determine "what areas of a molecule seem promising to continue to change." (Roush Tr. at 586-87)

K. Dr. Kohn's Research Leading to Vimpat®

69. In the early 1980s, Dr. Kohn theorized that FAAs may demonstrate anticonvulsant activity. (Kohn Tr. at 375-77) This was a new theory that was outside the mainstream of AED discovery. (*See id.* at 373; Heathcock Tr. at 103-04, 135 (describing Dr. Kohn's FAAs as "novel"); JTX-9 at DEF_571; JTX-10 at DEF_645)

70. When Dr. Kohn started his research, he had no evidence that any FAA would exhibit anticonvulsant activity, low or no neurological toxicity, a high margin of safety, or minimal adverse effects during long-term chronic administration. (*See* Kohn Tr. at 375-77, 388-89) For many years, Dr. Kohn was working virtually alone in the field. (*See* Heathcock Tr. at 171 (describing prior art as "originat[ing] from Dr. Kohn's laboratory"))

71. Beginning in 1985, Dr. Kohn published a series of papers reporting the results of his work with FAAs. This prior art is discussed in the next section. (*See infra* Findings of Fact ("FF") 85)

72. During the more than ten years from Dr. Kohn's first publication of an FAA compound to the filing of the '551 Patent, there was no pharmacological data published on any compound with a methoxymethyl group – which is a nonaromatic group – at R_3. (Heathcock Tr. at 159-60, 167)

73. Based on the results of his 1987 paper, Dr. Kohn and his students focused on compounds with aromatic, particularly heteroaromatic, groups at R_3. (Kohn Tr. at 402, 409-10)

74. Eventually, Dr. Kohn tested about 130 FAAs, approximately 50 of which had heteroaromatic groups at R_3. (*See* JTX-7 at DEF_566; DTX-2019 at DEF_194–96, DEF_244; JTX-11 at DEF_269–270; JTX-80 at DEF_710; JTX-56 at DEF_278–79; DTX-2012 ("'729 patent"), Tbl.1; JTX-67 at DEF_719; JTX-65 at DEF_723) Fourteen of the 16 FAAs with ED_{50}s under 20 mg/kg had heteroaromatic groups at R_3. (*See* DTX-2019 at DEF_194; JTX-11 at DEF_269; JTX-80 at DEF_710; JTX-56 at DEF_278–79; JTX-65 at DEF_723) Thus, about 30% of the compounds with heteroaromatic groups at R_3 had excellent anticonvulsant activity, compared to approximately only 3% of compounds with non-heteroaromatic groups at R_3.

75. One of the most promising of the heteroaromatic compounds Dr. Kohn developed contained a furan group at R_3. (Kohn Tr. at 436-47)

76. In the mid-1980s, Plaintiff RCT attempted to interest pharmaceutical companies in FAAs; only Eli Lilly & Co. ("Lilly") took a license. (*Id.* at 407-08)

77. Under its license, Lilly evaluated the compound with furan at R_3. (*Id.* at 435-37) Even though this compound exhibited excellent efficacy and relatively low neurotoxicity, it was

found to produce serious liver toxicity. (*Id.* at 437-39; JTX-11 at DEF_270; *see also* PTX-215 at KOHN-VIM44737) In late 1991, after five years, Lilly terminated its license and collaboration with Dr. Kohn. (PTX-215 at KOHN-VIM44737 ("You will note that the compound caused substantial hepatocellular necrosis, which was the basis for our termination of development."); JTX-23; Kohn Tr. at 408, 437-39)

78. After Lilly terminated its license, Dr. Kohn largely focused his research on heteroaromatic compounds. (Kohn Tr. 439-41) But by late 1993, Dr. Kohn was forced to reevaluate. (*Id.* at 441-42) He tested a set of 12 FAAs having different structures – with carbon-based, non-heteroaromatic groups at R_3. (Kohn Tr. at 441-44; *see also* JTX-40 at KOHN_VIM33271) Of those 12 compounds, ten showed only modest or marginal activity, one showed what Dr. Kohn termed "nice" activity, and one, (R,S) N-benzyl-2-acetamido-3-methoxypropionamide ("RS-BAMP"), showed promise. (Kohn Tr. at 445-46)

79. Dr. Kohn provided his findings on FAAs to RCT, which was "in charge to try to find a licensee" for Dr. Kohn's patents. (*See id.* at 407) In November 1993, Dr. Kohn had biological test results of the racemic mixture with methoxymethyl (*i.e.*, what the LeGall Thesis, described below, disclosed as compound 107e), which he sent to RCT and characterized as "impressive phase one results." (DTX-2092 at RCT-VIM 68156; Kohn Tr. at 531-32) Dr. Kohn further indicated that "this data is for the racemate so I suspect that the D-isomer [*i.e.*, lacosamide] will have the highest ED_{50} value reported to date." (DTX-2092 at RCT-VIM 68156; Kirkpatrick Tr. at 323-25; Kohn Tr. at 531-32)

80. Dr. Kohn was "ecstatic" when he received the biological data for the R-enantiomer (also known as the "D isomer"), lacosamide, "around the end of '94" from the NIH. (Kohn Tr. at 448-49, 533; JTX-50) In October 1994, Dr. Kohn sent RCT what he called "neat

test results" for lacosamide. (JTX-051; Kohn Tr. at 534; Kirkpatrick Tr. at 323) Dr. Kohn also wrote that "[a]ll of the pieces are in place for RCT to move forward taking actions that will lead to licensing within the next 6 to 9 months." (JTX-051; Kohn Tr. at 534) "[S]hortly after that," RCT "had a license agreement with [Plaintiff] Harris." (Kohn Tr. at 534)

81. In June 1995, Harris "tentatively selected the methoxymethyl (d) as [its] lead candidate for further evaluation." (DTX-2075; Harris Tr. at 331) That compound, ADD Number 234037 is lacosamide. (DTX-2075; Harris Tr. at 332; Kohn Tr. at 450)

82. In 1996, the mode of action for anticonvulsant activity of FAAs was unknown. (Roush Tr. at 567-69; Kohn Tr. at 451) Mode of action was an important factor in determining whether to investigate a particular class of compounds. (*See* JTX-142) Without knowing the mode of action, a POSA could not have predicted how structural modifications to a compound would affect its pharmacological properties. (*See* Roush Tr. at 567-68)

83. As of March 1996, there was limited data regarding the structure-activity relationships of FAAs, which concerned only the compounds' anticonvulsant activity and neurotoxicity. (*See id.* at 575-76) There was no data available on other potential side effects of FAAs, such as liver toxicity. (Heathcock Tr. at 129, 178; Roush Tr. at 561-62)

L. Prior Art

84. None of the prior art documents relied on by Defendants described lacosamide or provided any pharmacological data on either lacosamide or any FAA having a methoxymethyl group at R_3 (which lacosamide has). (*See* Heathcock Tr. at 167, 177-78; *see also* JTX-9; JTX-10; JTX-11; JTX-80; JTX-56; JTX-65; JTX-67 (Kohn publications, none of which discusses LeGall Thesis compound 107e or any compound having a methoxymethyl at R_3))

i. Dr. Kohn's Prior Art Publications

85. In 1985, Dr. Kohn published the anticonvulsant activity of his first FAA compound, "the alanine compound," or "AAB." (Kohn Tr. at 387-88; JTX-57 at Tbl.4 (compound 6d); *see also* Heathcock Tr. at 98-99) According to Dr. Kohn, AAB demonstrated the "proof of concept" for FAAs. (Kohn Tr. at 389) AAB contains a methyl (CH_3) at the α-carbon substituent R_3 (Heathcock Tr. at 100), a benzyl at R, and a methyl substitution at R_1 (Kohn Tr. at 457-58; *see also* Heathcock 100:9-11; DDX-105).

86. In 1987, Dr. Kohn and one of his graduate students, Judith Conley, reported on the anticonvulsant activity of 16 structural analogues of the "parent compound," AAB. (JTX-7 at Abstract; Heathcock Tr. at 100)

87. Dr. Kohn reported that each of the groups at the different positions of his FAAs affected the properties of the molecule. (*See* JTX-7 at DEF_567 ("The specific activities of these compounds in the MES, sc Met, and toxicity tests can be independently modulated by alteration of the substitution pattern at the α-carbon atom, the N-acyl, and the N-amido moieties."); Roush Tr. at 578, 619)

88. The 1987 paper also contained data relating to FAAs having a non-aromatic group at the R_3 position. (*See* JTX-7 at DEF_563 (describing non-aromatic compounds); Roush Tr. at 579 (same); JTX-7 at DEF_566 (describing aromatic compound); Kohn Tr. at 401 (same)) The use of the aromatic group at R_3 greatly improved the anticonvulsant activity. (*See* Roush Tr. at 579 ("[T]he important take-home message from the R_3 analysis . . . is that compounds that have an aromatic residue see a large jump in activity."))

89. The 1987 paper used unsubstituted[8] benzyl at R and unsubstituted methyl at R_1 as a reference point. (*See* JTX-7 at Tbls.2, 3; Heathcock Tr. at 100; Kohn Tr. at 467-68) The paper considered five possible modifications of the benzyl at R. (JTX-7 at Tbl.2) One of these modifications showed activity comparable to the base case (which had unsubstituted benzyl at R). (*Id.*; *see also* Kohn Tr. at 468) Each of the three modifications made at the R_1 position decreased anticonvulsant activity when compared to the placement of unsubstituted methyl at R_1. (*See* JTX-7 at Tbl.3)

90. In 1988, Dr. Kohn reported data on the "enantiomers and racemates" of certain FAAs – particularly AAB (containing methyl at R_3, benzyl at R, and methyl at R_1) and APB (containing phenyl at R_3, rather than methyl, but otherwise the same as AAB). (JTX-10; Kohn Tr. at 473, 475) In two articles, Kohn published that the R enantiomers of AAB and APB were about 10 times more potent than the S enantiomers. (JTX-10 at DEF_646-47; JTX-9 at DEF_573; Kohn Tr. at 476, 481) Indeed, "[f]or both compounds, the anticonvulsant activity is due to the D[/R]-stereoisomer, and the L[/S]-stereoisomer is virtually inactive as an anticonvulsant." (JTX-10 at abstract; Heathcock Tr. at 108) As Dr. Kohn concluded, "the anticonvulsant activity observed resided primarily in the D-stereoisomers and represents the greatest pharmacological stereochemical differentiation reported to date among antiepileptic agents." (JTX-9 at DEF_273)

91. The relative potency of the R enantiomer was demonstrated again in a paper published by Dr. Kohn in 1990. (JTX-11 at DEF_272; Heathcock Tr. at 109)

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[8] A substituted molecule replaces one of the hydrogen atoms of the parent molecule with another atom or structure. For example, unsubstituted benzyl has the formula $C_6H_5CH_2$, while a fluoro-substituted benzyl would replace one of the hydrogens with a fluorine. (*See* Kohn Tr. at 396)

92. In the 1990 paper, in which Dr. Kohn applied the teachings of his 1987 paper, Dr. Kohn kept "R_1 constant and R constant" as methyl and benzyl, respectively. (*See* Kohn Tr. at 485-86; JTX-11 at 919 Tbl.1) He reported that the most potent compound was 2g, which had 2-furanyl at R_3, benzyl at R, and methyl at R_1. (Kohn Tr. at 486; DDX-726) Compound 2g "was found to be significantly more potent than APB, and at the time in 1990 when this paper was published this was the most potent compound in the FAA family." (Heathcock Tr. at 109)

93. Dr. Kohn's 1990 paper also considered the effect of replacing an unsubstituted benzyl at R with a fluoro-substituted benzyl. (JTX-11 at DEF_272) The 1990 paper found that such a substitution yields a "far superior" protective index and a comparable anti-convulsant effect. (*See id.*; Kohn Tr. at 489) The substitution was made in an FAA with an unsubstituted methyl at R_1 and an aromatic 2-furanyl structure at R_3. (*See* JTX-11 at DEF_269-70)

94. Kohn 1991 summarizes the previous work with FAAs, explaining that that "you get potent protection if you have a benzyl on one end and a methyl on the other." (Kohn Tr. at 493) All 26 compounds reported in Kohn 1991 had unsubstituted benzyl at R and unsubstituted methyl at R_1, with different compounds at the R_3 group attached to the α-carbon.[9] (JTX-80 at DEF_709, Tbl.1)

95. In Kohn 1991, compound 31 – in which R_3 was methoxyamino ($NHOCH_3$) – possessed "the best activity to date" for any FAA racemate. (Kohn Tr. at 494; Heathcock Tr. at 111; JTX-80 at Tbl.1) Another compound in Kohn 1991, compound 3n, in which R_3 is methoxymethylamino (NCH_3OCH_3), was reported to have "essentially equivalent properties" to its "simpler variant," methoxyamino compound 3l. (Heathcock Tr. at 162-63; JTX-80 at Tbl.1)

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[9] Kohn 1991 uses a different depiction of the FAA structure where R_3 is labeled X or R^2. (*See, e.g.*, JTX-80 at Tbl.1)

96. Compound 3l contains a nonaromatic methoxyamino group at R_3. (Heathcock Tr. at 136) Prior to March 1996, Lilly knew about compound 3l and tested it. (Kohn Tr. at 434; PTX-197 at KOHN_VIM1405) But Lilly never expressed any interest in compound 3l. (Kohn Tr. at 435) Lilly instead focused all of its development efforts on a structurally different FAA compound with a heteroaromatic furan group at R_3. (*See* Kohn Tr. at 435-36)

97. Moreover, the ED_{50} data for compound 3l was published in 1991, five years before the priority date of the '551 patent. (Heathcock Tr. at 126-27; Kohn Tr. at 434-35; JTX-80) Yet compound 3l was never pursued nor even suggested as a lead compound by anyone (until this litigation). (*See* Heathcock Tr. at 186-87)

98. Compound 3l possesses chemical properties that a POSA would have wished to avoid. (Roush Tr. at 604-05) Specifically, the compound contains an N-O bond. (*See id.*; Heathcock Tr. at 137-38; JTX-80) Medicinal chemists try to avoid developing compounds containing this bond because it is not sufficiently stable for use in drugs. (*See* Heathcock Tr. at 137-38; Roush Tr. at 604-05)

99. Dr. Kohn continued to explore heteroaromatic groups, publishing data for many other compounds with heteroaromatic groups at R_3 and demonstrating excellent anticonvulsant activity. He reported nine FAAs with heteroaromatic groups with ED_{50}s below 20 mg/kg:

R_3	**ED_{50} (mg/kg, i.p. mice)**	**Reference**
Pyrimidine	8.1	JTX-65 at DEF_723
Furan	10.3	DTX-2019 at DEF_194
Oxazole	10.4	JTX-56 at DEF_278
Pyridine	10.8	JTX-65 at DEF_723
Thiazole	12.1	JTX-56 at DEF_278

Pyrazine	14.8	JTX-65 at DEF_723
Pyrrole	16.1	DTX-2019 at DEF_194
Pyrazole	16.5	JTX-56 at DEF_278
5-CH_3-Furan	19.2	JTX-11 at DEF_269

100. All of the prior art compounds with nonaromatic, carbon-based groups at R_3 had significantly lower anticonvulsant activity and would not have been of any interest. (Roush Tr. at 598)

101. In 1993, Dr. Kohn published the results of an experiment that reinforced the importance of an aromatic group at R_3. (JTX-56; Roush Tr. at 591-92) He showed that when the heteroaromatic furan ring was chemically converted into the nonaromatic tetrahydrofuran ("THF") ring, two THF isomers were produced, which were five and nine times less active than the compound with a furan ring at R_3. (JTX-56 at DEF_279, Tbl.2) A POSA would take away from these data that an aromatic group is the key for good anticonvulsant activity. (Roush Tr. at 591)

102. In Kohn 1993, the "starting point" again was benzyl at R and methyl at R_1. (Kohn Tr. at 497-98) Kohn 1993 first investigated modifications of the 2-furanyl group at R_3 with other heteroaromatic groups.[10] (JTX-56 at Tbl.1; Kohn Tr. at 498) Kohn 1993 did not find any heteroaromatic substitutions with improved activity relative to the 2-furanyl. (JTX-56 at Tbl.1)

[10] In Kohn 1993, R_3 is labeled R_2. (*See, e.g.*, JTX-56 at 3351 Tbl.1)

103. In Bardel 1994, Dr. Kohn once again provided support for his hypothesis "that placement of a substituted heteroatom two atoms removed from the [α-carbon] site provided enhanced protection against MES-induced seizures." (JTX-65 at 4568; Kohn Tr. at 505)

ii. The LeGall Thesis

104. In 1987, Philippe LeGall, a graduate student of Professor Kohn's at the University of Houston, completed work on his master's thesis. (DTX-2019) The LeGall Thesis is a 178-page student thesis that did not undergo formal peer review. (Roush Tr. at 587) However, for purposes of this litigation, the parties agree that the LeGall Thesis was publicly accessible more than one year before the earliest priority date for the '551 patent and constitutes a "printed publication" within the meaning of 35 U.S.C. § 102(b). (SUF ¶ 87)

105. The LeGall Thesis disclosed 15 new FAA compounds and provided anticonvulsant data for all but one of those compounds. (DTX-2019 at DEF_194-96, 223, 244-45)

106. The most active compounds in the LeGall Thesis had heteroaromatic groups at the R_3 position. (*Id.* at DEF_254) Specifically, the two most potent compounds had a furan group (ED_{50} = 10.3 mg/kg) or a pyrrole group (ED_{50} = 16.1 mg/kg) at R_3. (*Id.* at DEF_194)

107. Compound 107e from the LeGall Thesis is a racemate known as (R,S)-N-Benzyl 2-Acetamido-3-methoxypropionamide. (Roush Tr. at 624; DTX-2019 at DEF_223, 250) Compound 107e is similar to lacosamide except that it contains both the R and S enantiomers in a mixture, rather than just the R enantiomer. (Heathcock Tr. at 104-06)

108. The LeGall Thesis contains no pharmacological data for compound 107e. (Heathcock Tr. at 178) Compound 107e is the only one of LeGall's 15 new compounds for which his Thesis provides no data at all. (Roush Tr. at 585, 599-601)

109. In particular, the LeGall Thesis discloses no efficacy or toxicity data for compound 107e, and no liver toxicity data for any compound. (Heathcock Tr. at 167, 178; Pleasure Tr. at 303-04; Roush Tr. at 603)

110. Compound 107e was one of a series of "polar analogue" compounds disclosed in the LeGall Thesis. (Roush Tr. at 583) These compounds all had nonaromatic, carbon-based groups at R_3, instead of heteroaromatic groups. (Roush Tr. at 583-86) As a group, the polar analogues showed little or no potency. (*See* DTX-2019 at DEF_244-45; Roush Tr. at 599-600, 744-45; Kohn Tr. at 422-24) In particular, the ED_{50} results were all greater than 100 and mostly greater than 300, as compared to (for instance) the far more potent results reported for furan and pyrole groups, which were 10 and 16, respectively. The potency results for the "polar analogue" compounds of the LeGall Thesis are shown in the table below:

Compound	**R_3**	**MES ED_{50} (mg/kg)**
cyano (107a)	CN	>300
amido (107b)	$C(O)NH_2$	>300
ethyl ester (107c)	$C(O)OCH_2CH_3$	>300
hydroxymethyl (107d)	CH_2OH	>100, <300
methoxymethyl (107e)	CH_2OCH_3	**not tested**

(*See* DTX-2019 at DEF_244-45)

111. LeGall recognized that heteroaromatic compounds showed the most promise. In the conclusion of his thesis, he emphasized the "highly active" "five-membered ring heteroaromatic" compounds; he did not mention the nonaromatic compound 107e. (DTX-2019 at DEF_254-55; Heathcock Tr. at 184-185; Roush Tr. at 583-85, 601) Dr. Heathcock described

the heteroaromatic furan compound disclosed in the LeGall Thesis as Dr. Kohn's "first big breakthrough," based on its high potency. (Heathcock Tr. at 179-80)

112. Despite the fact that he did not have data for compound 107e, LeGall hypothesized that structural similarities between compound 107e and another compound, 86b, suggested that compound 107e "may have good anticonvulsant activity." (DTX-2019 at DEF_245)

113. Compound 86b contained OCH_2CH_3 at R and had an ED_{50} value of 62.0 mg/kg. (DTX-2019 at DEF_196) While a more potent compound than the "polar analogue" compounds for which data was reported (see table above), by March 1996 a POSA would have found the potency of 86b to be uninteresting. (Heathcock Tr. at 186; Roush Tr. at 602-04)

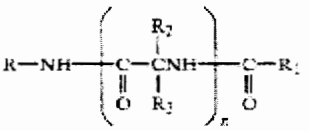
114. "[A]ll fifteen molecules that Mr. LeGall synthesized had a benzyl group at R and a methyl group at R_1," making these "common structural element[s]" in LeGall's work. (Roush Tr. at 676-80) LeGall "didn't consider any other options," "only compounds with unsubstituted benzyls" at R and methyls at R_1. (*Id.* at 677-78)

115. The LeGall Thesis was not before the PTO when it examined the application that became the '551 patent. (*See* Heathcock Tr. at 76-77; JT-4; JTX-2)

116. For nine years after the LeGall Thesis, compound 107e was never mentioned in any article, patent, or other reference. (Heathcock Tr. at 159-61)

iii. U.S. Patent No. 5,378,729 (the "'729 patent")

117. The '729 patent, entitled "Amino Acid Derivative Anticonvulsant," was filed on June 4, 1991 and issued on January 3, 1995 to inventors Dr. Kohn and Dr. Darrell Watson. ('729 Patent (DTX-2012) at cover) The '729 patent discloses a broad genus of millions or billions of compounds of the generic formula:



(*Id.* at 61:40-62:34; Roush Tr. at 749)

118. The '729 patent includes many compounds and groups referred to as "preferred," including a dozen sets of "preferred compounds" or "preferred embodiments," and many preferred groups for each position of each compound or embodiment. ('729 patent at 5-10)

119. The first "[p]referred compounds" of the '729 patent define R as a benzyl group, which can be unsubstituted or substituted (up to 3 groups on the phenyl ring are described as "preferred" R groups of these preferred compounds). ('729 patent at 6:31-45; Roush Tr. at 746-48) A POSA reading the '729 patent would understand this to mean that it is preferred that the benzyl group be either substituted or unsubstituted. (Roush Tr. at 746-47) Other classes of "preferred compounds" in the '729 patent list the R groups as "aryl, aryl lower alkyl, heterocyclic or heterocyclic alkyl which is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group" and the R_1 groups as "hydrogen or lower alkyl which is unsubstituted or substituted with at least one electron withdrawing group or one electron donating group." ('729 patent at 8:50-64, 9:20–22)

120. The '729 patent also lists preferences for groups located at R_3. The parameters for the preferred R_3 groups encompass millions of possible groups. (*See, e.g.*, '729 patent at 6:14-31; Roush Tr. at 748-49) While lacosamide falls within the scope of the preferences of the '729 patent (Heathcock Tr. at 125), neither methoxymethyl nor any alkoxy alyl is explicitly listed as a preferred R_3 group ('729 patent at 6:13-43, 8:65-9:2, 9:22-28).

121. The '729 patent nowhere mentions lacosamide. (*See generally* '729 Patent; Heathcock Tr. at 160)

122. The '729 patent identifies scores of FAAs and provides pharmacological data for 54 FAAs in Table 1. None of these compounds is lacosamide, 107e, or any compound with a methoxymethyl group at R_3. (Heathcock Tr. at 160, 197; Roush Tr. at 594-95, 741-42)

123. All 54 compounds for which data is provided have methyl at R_1. (Heathcock Tr. at 117; '729 patent at Tbl.1) Forty-nine of these compounds have an unsubstituted benzyl at R; the other five have fluoro-substituted benzyls at R. ('729 patent at Tbl.1) The pharmacological results for the compounds vary greatly. (*See id.*)

124. The ED_{50}s of compounds in Table 1 with unsubstituted benzyl at R and unsubstituted methyl at R_1 range from 3.3 mg/kg to inactive. (*Id.*) Ten of the compounds with these substitutions showed no activity, while many others exhibited only weak activity. (*Id.*)

125. Of the 10 compounds with the best ED_{50} values, eight had heteroaromatic groups at R_3; the other two had nitrogen-based groups. (Heathcock Tr. at 198; Roush Tr. at 742-43; '729 patent at Tbl.1 (10 compounds with heteroaromatic groups at R_3 shown as entries 9, 10, 13, 18, 30, 32, 37, 45, 48, and 51)) The four compounds in Table 1 that had nonaromatic, carbon-based groups at R_3 (the RS-, R-, and S-alanine compounds, and an allyl compound) had moderate to weak anticonvulsant activity, with ED_{50}s of 77, 55, 548, and 33.6 mg/kg, respectively. (Roush Tr. at 741-42; '729 patent at Tbl.1) Thus, the data in the '729 Patent would not have created an expectation in a POSA that nonaromatic, carbon-based groups at R_3 would be promising. (Roush Tr. at 742-43)

126. The two compounds in the '729 patent with the best protective indices (PI) had fluoro-substituted benzyl groups at R. (Heathcock Tr. at 200; Roush Tr. at 593-94, 616-17)[11]

[11] (D,L)-α-Acetamido-N-(3-fluorobenzyl)-2-furan-acetamide (ED_{50} = 13.3 mg/kg; TD_{50} = 135.6 mg/kg; PI = 10.2); and (D,L)-α-Acetamido-N-(4-fluorobenzyl)-2-furan-acetamide (ED_{50} = 12.7 mg/kg; TD_{50}= 144.4 mg/kg; PI = 11.4). ('729 patent at Tbl.1, 18th and 43rd entries)

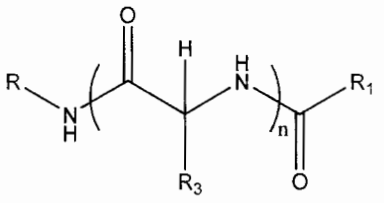
These compounds exhibited "basically no change in activity . . . but a strikingly large improvement in the neurotoxicity data" relative to the compounds with unsubstituted benzyl at R. (Roush Tr. at 617) This suggested that substituted benzyl groups at R might confer desirable properties. (*See* JTX-7 at DEF_566, Tbl.4 (1a vs. 1m))[12]

M. U.S. Patent No. 5,654,301 (the "'301 patent")

127. The '301 patent is a continuation-in-part of the '729 patent and is entitled "Amino Acid Derivative Anticonvulsant." (DTX-2016 ("'301 patent") at DEF_337) The '301 patent was filed on January 12, 1993. The '301 patent is not prior art, but it is the reference patent for Defendants' obviousness-type double patenting claim.

128. UCB listed the '301 patent in the FDA's "Orange Book" in association with NDA Nos. 022-253, 022-254 for Vimpat®. (DTX-2347 at DEF_9936)

129. Claim 39 of the '301 patent is an FAA that covers many millions, if not billions, of compounds of the formula:



(Roush Tr. at 631; '301 patent at 93:3-23)

130. Claim 39 defines the R group as "aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl, or lower cycloalkyl lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group." ('301

[12] D,L-α-acetamido-N-benzyl-2-furan-acetamide (ED_{50} = 10.33 mg/kg; TD_{50} = 40 mg/kg; PI = 3.9). ('729 patent at Tbl.1, 9th entry)

patent at 93:3-23) This broad definition permits R to be any of millions of possible groups. (*See* Heathcock Tr. at 201-02)

131. Claim 39 defines the R_1 group as "hydrogen or lower alkyl . . . unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group." ('301 patent at 93:3-23) The '301 patent defines "lower alkyl" as "containing from 1 to 6 carbon atoms and may be straight chain or branched." (*Id.* at 3:37-39) This definition of "lower alkyl" covers 32 different groups, which can be substituted at various positions with one or more electron donating or electron withdrawing groups. (Roush Tr. at 633-34) The number of possible R_1 groups within claim 39 is thus very large. (*Id.* at 634)

132. Claim 39 requires one of R_2 and R_3 to be "hydrogen and the other is lower alkyl which is substituted with an electron donating group or a[n] electron withdrawing group." ('301 patent at 93:3-23) Thus, the R_3 of claim 39 can be any one of the large number of groups discussed above for R_1 – consisting of thousands, if not millions, of possible groups. (Roush Tr. at 634-35)

133. The '301 patent lists categories of

> [t]he most preferred electron donating and electron withdrawing substituent[s:] . . . halo, nitro, alkanoyl, formyl, arylalkanoyl, aryloyl, carboxyl, carbalkoxy, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, di(loweralkyl)amino, amine lower alkyl mercapto, mercaptoalkyl, alkylthio; and alkyldithio.

('301 patent at 5:14-22) Many of these "substituents" are themselves generic categories, creating a very large group of possible preferred electron-donating and electron-withdrawing groups.

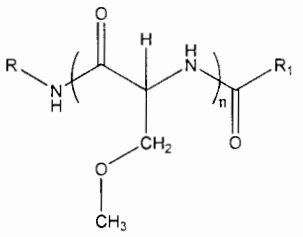
(Roush Tr. at 632-33) These groups apply to any of the R, R_1, or R_3 positions on the FAA molecule. ('301 patent at 93:3-23)

134. Claim 39 permits the repeating unit "n" – for the core C-CNH structure – to be one to four. (*Id.*)

135. Claim 39 does not specify a particular stereochemistry, so it encompasses R enantiomers, S enantiomers, and racemic mixtures of both. (Roush Tr. at 635-36)

136. Lacosamide is one species of the millions of compounds in the genus claimed by claim 39. (Roush Tr. at 636) The '301 patent, however, does not mention lacosamide. (*See* '301 Patent at Tbls.1-4)

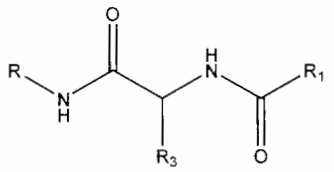
137. Claim 44 depends from claim 39 and defines the R_3 group as methoxymethyl ('301 patent at 94:12-13; Roush Tr. at 636); thus, it covers compounds of the formula:



138. The R and R_1 groups of claim 44 are the same broad genera as those defined for claim 39. ('301 patent at 93:3-23, 94:12-13) Like claim 39, claim 44 permits the value of "n" to be between one and four and the stereochemistry to be R, S, or a mixture thereof. ('301 patent at 94:12-13; Roush Tr. at 635-36) Claim 44 covers a genus of millions of compounds. (Roush Tr. at 637-38; *see also* Heathcock Tr. at 200-02)

139. The PTAB has found that the genus covered by claim 44 of the '301 patent encompasses "thousands of compounds," observing that "a skilled artisan still has to pick from unsubstituted and substituted R (and R_1), and if substituted, which substitution." (JTX-88 at DEF_7503)

140. Claim 45 can depend from "any one of claims 39-44" and limits n to one. ('301 patent at 94:14-15) Thus, claim 45 covers a genus of compounds of the formula:



141. This genus covers "millions and millions if not billions" of compounds. (Roush Tr. at 637) Lacosamide is one species of this genus. (Heathcock Tr. at 201; Roush Tr. at 638)

142. Even when claim 45 is limited to depending from claim 44, which defines the R_3 group as methoxymethyl, genus claim 45 still encompasses millions of possibilities due to the millions of possible choices for R and R_1. (Roush Tr. at 637-38)

143. Claim 46 of the '301 patent should read as follows: "An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claim[s] 39-44 and a pharmaceutical carrier therefor."[13] (SUF ¶89)

144. Claim 47 of the '301 patent claims "[a] method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of any one of claims 39-44." ('301 patent at 94:19-21)

145. Claims 46 and 47 of the '301 patent each cover millions of compounds. Both claims incorporate the large genera of possible R, R_1, and R_3 groups from claim 39. (*See* Heathcock Tr. at 206-07) Even if claims 46 and 47 are limited to the genus of claim 45 as it depends from claim 44, they would still each encompass millions of compounds, due to the millions of possible choices for the R and R_1 groups. (*See* Roush Tr. at 637-38)

[13] The actual text of claim 46 of the '301 patent reads: "An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claim 37-42 and a pharmaceutical carrier therefor."

146. The '301 patent provides tables of pharmacological data for FAA compounds. ('301 patent at Tbls.1-4) None of these tables discloses pharmacological data for lacosamide, 107e, or any compound with a methoxymethyl at R_3. (*See id.*) Table 1 of the '301 patent is the same as Table 1 of the '729 patent. Table 1 demonstrates that not all of the compounds covered by the '301 patent have good anticonvulsant activity. Indeed, some of the compounds listed have no activity at the highest tested dose. (Roush Tr. at 740) Similarly, Tables 3 and 4 of the '301 patent include examples of 22 other compounds. ('301 patent at Tbls.3-4)[14] Fifteen of these compounds had no anticonvulsant activity at the highest tested dose. (*See id.*)

147. The '301 patent does not mention liver toxicity. (*See generally* '301 Patent)

148. The PTO Examiner who examined the application leading to the '551 patent had the '301 patent before her. (*See* Heathcock Tr. at 148) Yet the Examiner never issued a double patenting rejection in her two reviews of the '551 patent. (*See generally* JTX-2, JTX-4)[15]

N. Others' Exploration into FAAs

149. Dr. Kohn was not the only researcher to investigate FAAs. Drs. Paruszewski and Hinko also published on the subject. (JTX-53; JTX-54; JTX-87) While their articles are not prior art, they were published very shortly after the priority date, so they "show[] what other people had been thinking about" as of the priority date. (Heathcock Tr. at 163; *see also* Roush Tr. at 699)

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[14] All of which have unsubstituted benzyl at R and unsubstituted methyl at R_1. ('301 patent at Tbls.3-4)

[15] Defendants assert this is irrelevant because it is "undisputed" that the Examiner "made a chemical error," wrongly believing the '301 patent did not teach or disclose an ether, yet the methoxymethyl at R_3 in claim 44 is an ether. (D.I. 263 (Defendants' Opening Brief ("OB")) at 15) Defendants do not explain how this error was material. Regardless of whether the '301 patent is considered to have been before the Examiner or not, Defendants have failed to meet their burden to show that the asserted claims of the '551 patent are invalid.

150. Dr. Paruszewski was aware of Dr. Kohn's work. (Roush Tr. at 613; JTX-53 at DEF_7495 (citing Kohn)) None of Paruszewski's compounds had a methoxymethyl group at R_3. (Heathcock Tr. at 168-69; Roush Tr. at 613) While Paruszewski used groups at the R and R_1 positions that were not benzyl and methyl, 18 out of 30 of Paruszewski's compounds had unsubstituted benzyl (PDX-88; Roush Tr. at 703-04) and 19 out of 30 had a methyl at R_1. However, only six of his 30 compounds used the benzyl/methyl combination. (Roush Tr. at 617-18; JTX-53 at DEF_7493, Tbl.1; JTX-54 at KOHN_VIM33299, Tbl.1)

151. One change Paruszewski made was to remove the carbonyl (C=O) to which the R_1 group is attached. (Roush Tr. at 620-21; PTX-80 at PLS_VIM20940-41) He included this modification in a prior art patent application published on May 2, 1995. (PTX-80 at PLS_VIM20938) The modification increased anticonvulsant activity (ED_{50} = 31.17 mg/kg) compared to Dr. Kohn's otherwise analogous alanine compound (ED_{50} = 76.54mg/kg). (Roush Tr. at 620-21)

152. Dr. Hinko was also aware of Dr. Kohn's work. (JTX-87 at DEF_7475 (citing Kohn's papers); Roush Tr. at 618) Hinko did not use a methoxymethyl group at the R_3 position; nor did he use a methyl group at R_1. (Roush Tr. at 614; JTX-87 at DEF_7476, Fig. 1(1)) The compounds made by Hinko had a structure based on a piperidine ring, in which "the R_3 is all tied back if you will, connected back into formally the remnants of where the R_1 group has been in Dr. Kohn's structures." (Roush Tr. at 614, 622; JTX-87 at DEF_7476, Fig. 1(1))

153. Hinko also made many modifications to the R group, including "fluorines, tri-fluoro-methyls at different positions, methyls, nitros, [and] chlorines." (Roush Tr. at 618-23; JTX-87 at DEF_7480, Tbl.1) Hinko also "put additional substituents on the carbon connecting the phenyl group to the nitrogen. . . . So these are not phenylmethyl [i.e., benzyl], these . . . are

phenylethyl substituents" at the R position. (Roush Tr. at 619; JTX-87 at DEF_7480, Tbl.1) Only two out of Hinko's 21 compounds used unsubstituted benzyl. (Roush Tr. at 618-19)

O. The '551 Patent-in-Suit

154. The patent-in-suit is United States Patent No. RE 38,551. (SUF ¶ 30) The '551 patent was filed on January 28, 2002 as a reissue of U.S. patent No. 5,773,475. (*Id.*) The '551 patent claims priority to provisional patent application No. 60/013,522, which was filed on March 15, 1996. The '551 patent issued on July 6, 2004 and will expire no later than March 17, 2022.

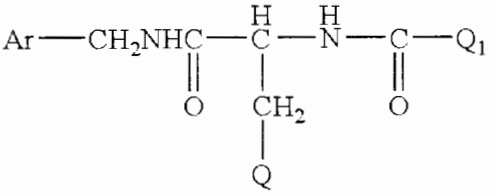
155. RCT is the current owner of the '551 patent. Harris is the exclusive licensee of the '551 patent. UCB BioPharma SPRL is the exclusive sublicensee of the '551 patent for use in humans. (SUF ¶ 31)

156. In the FDA's "Orange Book," the '551 patent is listed in the entries for Vimpat®, as is the '301 patent. (SUF ¶ 32)

157. It is undisputed that the '551 patent was the first public description of lacosamide and that lacosamide was not described in any prior art, including the '301 patent. (Heathcock Tr. at 167, 177; Roush Tr. at 561) The '551 patent provides methods of synthesizing lacosamide. ('551 patent at 11:22–13:14) It also provides physical and spectroscopic data on lacosamide. (*Id.* at 12:17–32, 13:6–14)

158. The '551 patent also contains the first publication of any pharmacological data for lacosamide. (*Id.* at Tbl.1 (listing ED_{50} and TD_{50} data for lacosamide in mice and rats)) The '551 patent compares the physical and pharmacological properties of lacosamide against a number of other compounds to demonstrate lacosamide's superior properties. ('551 patent at Tbls.1,6)

159. Claim 9 of the '551 patent covers one compound, lacosamide. Claim 9, which depends from claims 1 and 8, discloses:

> 1. A compound in the R configuration having the formula:
>
> R
>
> 
>
> wherein Ar is phenyl which is unsubstituted or substituted with at least one halo group; Q is lower alkoxy, and Q1 is methyl.
>
> 8. The compound according to claim 1 which is (R)-N Benzyl 2-Acetamido-3-methoxypropionamide.
>
> 9. The compound according to claim 8 which contains at least 90% (w/w) R stereoisomer.

160. Claims 10 through 13 disclose:

> 10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1-9 and a pharmaceutical carrier therefor.
>
> 11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1-9.
>
> 12. The method according to claim 11 wherein the animal is a mammal.
>
> 13. The method according to claim 12 wherein the mammal is a human.

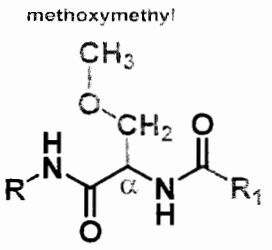
161. After the '551 patent issued, RCT told the PTO that the '301 patent covered lacosamide. In an application to extend the term of the '301 patent, RCT represented that

"claims 39-45" of the patent "claim the active ingredient ... lacosamide." (DTX-2095 at DEF_4996) That document also represented that claim 46 of the '301 patent "cover[s] a therapeutic composition" of lacosamide and that "[c]laim 47[] cover[s] a method of treating central nervous system disorders" with lacosamide. (DTX-2095 at DEF_4997-98)

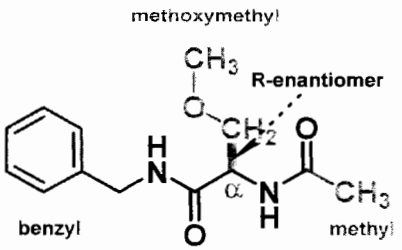
162. The PTO accepted RCT's representations, concluding that "U.S. Patent No. 5,654,301, which claims the human drug product Vimpat® (lacosamide) Tablet and a method of using" it, "is eligible for patent term extension." (DTX-2218 at DEF_5206) The PTO noted, however, that RCT "also ha[d] applied for patent term extension of U.S. Patent No. RE38551" based on Vimpat®'s approval, and that "the certificate of extension is issued to the patent having the earliest date of issuance unless applicant elects a different patent." (*Id.*) RCT elected to extend the '551 patent – the later-expiring patent. (*See id.* at DEF_5209)

P. Differences Between the '301 and '551 Patents

163. The differences between claims 44 and 45 of the '301 patent, on the one hand, and claim 9 of the '551 patent, on the other, are that claim 9 fills in the variables of the claim 44/45 equation, so as to narrow the genus of claims 44 and 45 to the species of a single compound, lacosamide. These differences are depicted below and can understood in three parts.



'301 Claim 45
(depending on claim 44)



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

164. First, claim 9 selects "n is equal to 1 for lacosamide," whereas in claim 44, n can be 1-4. (Roush Tr. at 675; '301 patent at 93:3-23, 94:12-13) Claim 45 of the '301 patent (like

claim 9 of the '551 patent) "specifies that n must be one." (Heathcock Tr. at 143; '301 patent at 94:14-15)

165. Second, claim 9 specifies "the D or R configuration" in at least 90% purity, whereas in claims 44/45 "the stereochemistry is not defined," so it could be the R or S enantiomer (of any degree of purity) or the racemic mixture of R and S. (Heathcock Tr. at 95, 147)

166. Third, claim 9 selects substituents for R (benzyl) and R_1 (methyl) that fall within the scope of claims 44/45. (Roush Tr. at 674-75; Kohn Tr. at 514) In claims 44/45, "the R group ... is variable, but the definition includes benzyl"; and "R_1 is variable" as well, "[b]ut that variable group includes methyl." (Heathcock Tr. at 145-46)

Q. Secondary Considerations of Non-obviousness

i. Skepticism

167. In the mid-1980s, RCT contacted numerous pharmaceutical companies in search of a partner to help develop Dr. Kohn's FAAs. (*See* JTX-131 (1985); JTX-135 (1985); PTX-252 (1985); PTX-254 (1985); PTX-259 (1985); PTX-260 (1985); Vellturo Tr. at 918)

168. Many of these companies were skeptical that FAAs would meet the demand that existed for new AEDs. (*See* Vellturo Tr. at 923) For example, Boehringer Ingelheim declined a license offer because "[b]ased on the present profile of the agents, we feel they would not offer a significant market advantage over current treatments." (PTX-252)

169. In 1986, Eli Lilly took a license to explore Dr. Kohn's FAAs. (Kohn Tr. at 408) Lilly was aware of compounds 107e and 3l but expressed no interest in either. (Kohn Tr. at 425-35; JTX-80; PTX-170; PTX-171) Instead, Lilly chose an FAA with a heteroaromatic furanyl group at R_3. (Kohn Tr. at 435-37)

170. In November 1991, Lilly terminated the license it had to the entire class of FAA compounds because the R-furan compound was found to cause severe liver toxicity, adding to skepticism about the safety of FAAs. (Kohn Tr. at 437-38; PTX-215)

171. After Lilly's termination, RCT again sought a development partner, but was met with a lack of interest. (JTX-125 (1992); JTX-126 (1992); JTX-127 (1992); JTX-128 (1992); JTX-129 (1992); PTX-265 (1992); PTX-267 (1992); PTX-268 (1992); PTX-273 (1992); PTX-274 (1992); Vellturo Tr. at 918-19)

172. Many companies voiced skepticism that FAAs would meet the demand that existed for new AEDs. (*See* Vellturo Tr. at 923-24; Kohn Tr. at 439-40; PTX-236) For example, the Upjohn Company turned down a license from Kohn because "the series of compounds have not yet produced a member which demonstrates a lack of toxicity and although there may be theories on solving the problem, the status of this is too early for us to take an active interest." (PTX-268) Merck Sharp and Dohme Research Laboratories ("MSD") stated that the FAAs "do not appear that potent" (PTX-267) and ultimately declined a license because of the "absence of a clear mechanism of action" and insufficient evidence of activity upon oral administration (PTX-273).

173. Eventually, in the mid-1990s, Harris FRC took a license to the FAA compounds. (Kohn Tr. at 449) In the late 1990s, Harris FRC sought an additional partner to develop lacosamide and bring it to market. (*Id.* at 453)

174. Many of the companies contacted by Harris FRC expressed skepticism that lacosamide would be a successful AED or would be any better than the marketed AEDs. (*See* JTX-105; JTX-106; JTX-119; JTX-120; JTX-139; JTX-142; JTX-143; JTX-145; JTX-150; JTX-

151; JTX-152; JTX-155; JTX-156; JTX-157; JTX-159; JTX-160; JTX-161; Vellturo Tr. at 919-20; Kohn Tr. at 453)

175. For example, Zeneca Pharmaceuticals reviewed the data on lacosamide and had "concerns related to safety, potency, dosing and breadth of efficacy." (JTX-105) Glaxo Wellcome did not see a "strong enough basis for moving forward [with lacosamide]" because the mode of action was not clearly defined and it had "other initiatives or approaches that seem[ed] more attractive." (JTX-157)

176. Eli Lilly was offered the opportunity to develop lacosamide even after it had terminated its license to Dr. Kohn's FAAs, but it again had no interest – this time because of concerns over toxicity. (JTX-152)

177. Bristol-Myers Squibb Company declined the opportunity to pursue a license to lacosamide, in part because "its *in vivo* anti-seizure profile is similar to that of phenytoin" and "there were some concerns . . . regarding possible development of tolerance, and some positive results in test[s] of mutagenicity." (JTX-106) ICAgen Inc. was uninterested in licensing the compound because of "serious concerns" relating to toxicity. (JTX-159)

178. Even UCB, which eventually acquired Schwarz Pharma (the company that took a license to lacosamide from Harris), was initially skeptical that lacosamide would be a successful AED. (Klitgaard Tr. at 879-85; JTX-32; JTX-33) UCB was skeptical because it thought lacosamide would be a "me too" drug that offered no patient benefits, and because the available data suggested that lacosamide was an NMDA receptor (i.e., sodium receptor) antagonist which may produce unacceptable psychiatric effects. (Klitgaard Tr. at 882-84)

179. Plaintiffs' expert Dr. Vellturo opined that "there was considerable economic skepticism that lacosamide or the Kohn compounds more generally represented a cost effective

and efficient potential avenue to solve the AED demand that remained in the marketplace." (Vellturo 920:3-25)

180. On January 5, 1996, RCT and Harris finalized "an Option and License Agreement." (Kirkpatrick Tr. at 325-26; JTX-021) "RCT licensed a … patent estate" to Harris, and "lacosamide would fall within the patent estate." (Kirkpatrick Tr. at 326-27)

ii. Long-Felt Unmet Need

181. Before March 15, 1996, there was a long-felt need for a safe and effective epilepsy treatment for patients who were treatment-refractory, were unable to achieve acceptable seizure control, or experienced adverse effects using traditional AEDs. (*See* Pleasure Tr. at 308-10; Bazil Tr. at 784-85; DTX-2249 at DEF_7606; JTX-111)

182. The historic failures to find and develop sufficiently safe and effective AEDs prompted the National Institutes of Health ("NIH") in 1975 to establish the Anticonvulsant Screening Program ("ASP") to facilitate and encourage the discovery of new anticonvulsant agents. (*See*, *e.g.*, Kohn Tr. at 379; Pleasure Tr. at 308–09; DTX-2249 at DEF_7607)

183. The need that existed in 1996 resulted from the "heterogeneous" nature of epilepsy, i.e., the fact that the disease varies greatly from patient to patient. (Bazil Tr. at 766-69; *see also* Pleasure Tr. at 255) For example, different things can cause epilepsy – a brain injury, a stroke, or bleeding in the brain. (Bazil Tr. at 767-68; *see also* Pleasure Tr. at 255) For most patients, the cause of epilepsy is never known. (Bazil Tr. at 767-68) As a result, epilepsy treatments must be individualized to the specific patient. (*Id.* at 768-69)

184. The need in 1996 for an improved AED was also due to numerous shortcomings of the drugs available at the time. (*Id.* at 776–83 (discussing properties of AEDs that were commonly prescribed in 1996); *see also* Pleasure Tr. at 308-10) In 1996, the most commonly

prescribed AED in the United States was phenytoin. (Bazil Tr. at 776) The medical community recognized several disadvantages to phenytoin. (*Id.* at 776-78; PTX-51) The most significant problem with phenytoin was its complicated pharmacokinetics, called "zero order" kinetics, i.e., small dose increases result in disproportionate changes in blood levels. (Bazil Tr. at 776-77; PTX-51 at PLS_VIM1208) Phenytoin also exhibited high drug-drug interaction. (Bazil Tr. at 776-77; PTX-51 at PLS_VIM1208–09) It was known to cause several short-term toxic effects (dizziness, fatigue, unsteadiness) and long-term toxic effects (peripheral neuropathy, cerebellar atrophy). (Bazil Tr. at 776-77; PTX-51 at PLS_VIM001209) Phenytoin is poorly soluble in water, meaning that, to administer it intravenously in 1996, a solution had to be made using a "rather toxic" solvent. (Bazil Tr. at 776-77)

185. Carbamazepine was another commonly prescribed AED in 1996. (*Id.* at 778) Carbamazepine's product label includes a "black box warning" – indicating a serious health concern – for aplastic anemia, a potentially fatal condition in which the body stops making blood cells. (*Id.* at 779-80) Carbamazepine also exhibited drug-drug interactions and caused short-term toxic effects including dizziness, drowsiness, and double vision. (*Id.* at 778-79)

186. A third AED that was commonly prescribed in 1996 was valproic acid. (*Id.* at 778, 780) In 1996, the medical community recognized several disadvantages of valproic acid. (*Id.* at 780-81) Most alarmingly, valproic acid had been linked to liver (hepatic) failure. (*Id.* at 780-81) Valproic acid's product label includes a black box warning for hepatic failure. (*Id.* at 781) Valproic acid was also known to commonly cause tremors and weight gain and to exhibit drug-drug interactions. (*Id.* at 780)

187. Other AEDs available in 1996 also had significant disadvantages. Lamotrigine is very sensitive to coadministration with other AEDs and carries a black box warning. (Pleasure

Tr. at 1016, 1022-23, DTX-2180 at PLS_VIM2212; PTX-140 at DEF_7954) Topiramate causes adverse cognitive effects and interacts with other AEDs. (Pleasure Tr. at 1016-18, 1029-30; DTX-2180 at PLS_VIM2212; PTX-145) Lamotrigine, topiramate, and gabapentin have no IV formulation, which is needed for treatment of status epilepticus. (Pleasure Tr. at 1026, 1028-31; PTX-140; PTX-141; PTX-145)

188. Given the problems with the commonly-prescribed AEDs as of March 15, 1996, there was a long-felt need for an AED that: (1) was highly effective for epilepsy; (2) was safe, particularly with long-term usage; (3) exhibited minimal day-to-day side effects; (4) had multiple dosage formulations and delivery mechanisms, (5) exhibited minimal drug-drug interactions; and (6) had a favorable pharmacokinetic profile. (Bazil Tr. at 784–85; JTX-111 at PLS_VIM966, Tbl.2) This need was recognized throughout the medical community. (Bazil Tr. at 785; JTX-111 at PLS_VIM966, Tbl.2)

189. Vimpat® fulfills a long-felt but unmet need for a safe and effective treatment for some patients who were treatment-refractory, were unable to achieve acceptable seizure control on other AEDs, or experienced adverse effects using other AEDs. (Bazil Tr. at 786, 788-90) Vimpat® also satisfies the need for an AED with the collection of properties desired by the medical community in 1996. (*Id.* at 786) As of 1996, no available AED had the combination of properties that Vimpat® has. (Bazil Tr. at 811)

190. As Dr. Bazil testified, in 1996 (and even to this day), "most patients with epilepsy can have complete or nearly complete seizure control with optimally managed monotherapy that employ[s] traditional AED[s]," and "about half of the remaining patients can achieve improved seizure control with combination AED therapy." (*Id.* at 845-46) However, between 20% and 30% of all epilepsy patients become refractory patients, that is patients for whom two or more

AEDs have failed to control their seizures. (*See* Pleasure Tr. at 977-79; Bazil Tr. at 761; DTX-2176 at 650 ("Approximately one-third of patients with partial onset seizures develop chronic refractory 'drug resistant' epilepsy, the inability to derive sustained seizure freedom following a trial of two anti-epileptic drugs (AEDs) . . . thus requiring treatment with a combination of agents."))

191. Vimpat®'s unique combination of properties includes its effectiveness as an AED. (Bazil Tr. at 812–13, 817; JTX-63 at PLS_VIM670, 672; *see also* Pleasure Tr. at 1035-36, 1040; JTX-61 at PLS_VIM581; DTX-2178 at DEF_8135) Its efficacy, moreover, appears to be maintained over time without the development of tolerance. (*See* JTX-97 at PLS_VIM20326) Long-term treatment with Vimpat® is generally well-tolerated, as there are "no long-term serious reactions that are known." (Bazil Tr. at 790; Pleasure Tr. at 1037-39; JTX-97 at PLS_VIM20317; JTX-107 at PLS_VIM735) Vimpat® also exhibits minimal, dose-dependent, day-to-day side effects. (*See* Bazil Tr. at 790-92, 812-13; Pleasure Tr. at 1035-36; JTX-63 at PLS_VIM671; JTX-61 at PLS_VIM581) Vimpat® is available in multiple dosage formulations and delivery mechanisms, namely: tablet, syrup, and intravenous solutions. (Bazil Tr. at 813-14; Pleasure Tr. at 1035-36; JTX-63 at PLS_VIM668; JTX-61 at PLS_VIM581)

192. Additionally, Vimpat® exhibits minimal drug-drug interactions because it has low potential for pharmacokinetic interaction, has low protein binding, and does not inhibit the metabolism of other drugs. (*See* Bazil Tr. at 813-14; JTX-63 at PLS_VIM668–69; JTX-85 at PLS_VIM20752; *see also* Pleasure Tr. at 1035-39; JTX-61 at PLS_VIM581, 585; JTX-107 at PLS_VIM735) Vimpat® also has a favorable pharmacokinetic profile – it is rapidly and completely absorbed, has negligible first-pass effect in the liver, has an oral bioavailability of 100%, and has simple, dose-dependent, linear pharmacokinetics. (*See* Bazil Tr. at 813-14; JTX-

63 at PLS_VIM668; JTX-85 at PLS_VIM20752; JTX-97 at PLS_VIM20324; *see also* Pleasure Tr. at 1037-39; JTX-107 at PLS_VIM733)

193. Doctors who prescribe Vimpat® have seen it satisfy the need for an improved AED in certain of their patients. (*See* Bazil Tr. at 787-90, 818-19; Pleasure Tr. at 1033-34) Doctors have found that Vimpat® is particularly important in certain scenarios, including when a patient is on other medications, older in age, allergic to other AEDs, high-functioning and concerned about cognitive effects, or in need of quick intravenous administration or a rapid increase in dose. (*See* Bazil Tr. at 788-90)

194. Despite its merits, lacosamide is not effective or approved for all epilepsy patients. (Bazil Tr. at 830; JTX-167 at UCB-VIM 2488553)

195. There has been no direct comparison study comparing lacosamide to other AEDs in refractory patients. (*See* Pleasure Tr. at 977-80; Bazil Tr. at 836)[16]

196. Dr. Bazil testified that "epileptologist[s] such as [himself] . . . continue to be dissatisfied with the current AEDs, including lacosamide," and that "we wish there were sometimes better ones." (*Id.* at 822) UCB's fact witness, Henrik Klitgaard, published an article in which he indicated that lacosamide is one of the third-generation AEDs that "fail[s] to control seizures in 20-30% of patients" and admitted that there is no data supporting the position that lacosamide is superior to other AEDs. (Klitgaard Tr. at 892-94; DTX-2573 at Abstract, 757-58, 762-63)

[16] Although two meta-analysis studies have been published suggesting that no AED is favored over another, those analyses were severely criticized by the epileptologist community as methodologically-flawed, unreliable, and ultimately inconclusive. (*See* Bazil Tr. at 799-811; Pleasure Tr. at 1041-44; DTX-2175; DTX-2176; PTX-8; PTX-50, PTX-78)

iii. Failure of Others to Develop Safe and Effective AEDs

197. Prior to lacosamide, others working in the field tried and failed to develop safe and effective AEDs with favorable pharmacokinetics. Before and after the invention of lacosamide, it was, and continues to be, acknowledged that development of AEDs is difficult due to the complexities in the etiology of epilepsy and the lack of a fully understood mode of action. (*See* Pleasure Tr. at 1044-46; PTX-4 at 443) Dr. Pleasure has reported that only 2.85% of new neurotherapeutic projects have a probability of success. (Pleasure Tr. at 1046; PTX-4 at 443)

198. Between 1975 and 1996, approximately 16,000 compounds were screened by NIH's ASP, and as of 1996 only one compound initially screened for anticonvulsant activity in the ASP, felbamate, had been approved by the FDA. (*See, e.g.*, Kohn Tr. at 379; Pleasure Tr. at 309-10; DTX-2249 at DEF_7607) To date, the ASP has screened over 30,000 compounds, but only 2 or 3 compounds initially screened by the ASP have been approved by FDA. (*See* Pleasure Tr. at 312-13)

199. Felbamate was approved in 1993. (Bazil Tr. at 781) Approximately one year after its launch, it became apparent that felbamate caused two serious adverse reactions: aplastic anemia and liver failure. (*Id.* at 781-82) Although felbamate remains on the market, FDA requires a "black box" warning, indicating that it should only be administered to patients whose epilepsy is so severe that serious risks of hepatotoxicity and aplastic anemia are acceptable. (*See* Pleasure Tr. at 310-12; Bazil Tr. at 782; PTX-139 at PLS_VIM21186–88)

iv. The Unexpected Results of Lacosamide

200. Before March 15, 1996, a POSA would not have expected that lacosamide would exhibit high potency, a high protective index, and minimal liver toxicity. There was no

pharmacological data in the prior art on lacosamide or even on compound 107e. (*See* Heathcock Tr. at 167; Roush Tr. at 561, 585, 595, 640-41; Kohn Tr. at 446)

201. Indeed, there was no data on any side effect profile of any FAA available in the prior art before March 1996. (*See, e.g.*, Heathcock Tr. at 178; Roush Tr. at 561-62; *see also* JTX-9; JTX-10; JTX-11; JTX-80; JTX-56; JTX-65; JTX-67 (Kohn publications, none of which discuss side effects))

202. A POSA in 1996 understood that an improved AED would ideally have several favorable properties, such as: (1) being additive or synergistic with other AEDs; (2) being sustained; (3) having a novel mode of action; (4) having an increased therapeutic index; (5) lacking serious or chronic adverse effects; (6) acute effects, if present, being mild and transient; (7) lacking of teratogenic potential; (8) having multiple dosage formulations; (9) allowing administration by multiple routes (water soluble); (10) having a simple pharmacokinetic profile; (11) not being protein bound; (12) not being metabolized quickly; (13) not inducing hepatic enzymes; and (14) not interacting significantly with other AEDs or other drugs in other ways. (Bazil Tr. at 784-85; JTX-111 at PLS_VIM966, Tbl.2)

203. Given the issues with state of the art AEDs in 1996, it was unexpected to a POSA that lacosamide would possess nearly all, if not all, of the desirable characteristics of an ideal AED. (Bazil Tr. at 811; Kohn Tr. at 448-49; Klitgaard Tr. at 885-87)

204. Yet lacosamide has many, if not all, of the properties that were desired in 1996. (Bazil Tr. at 786, 812-14; PDX-186–88; JTX-40 at KOHN_VIM33274 (reporting for lacosamide: ED_{50} = 4.5 mg/kg, TD_{50} = 27 mg/kg))

v. Praise of Lacosamide by Others

205. Scientists and medical professionals have praised lacosamide for possessing "most of the properties of an ideal AED." (JTX-63 at PLS_VIM672, PLS_VIM668; Bazil Tr. at 811; JTX-85 at PLS_VIM20752; JTX-97 at PLS_VIM20324; *see also* Pleasure Tr. at 1037-39; JTX-107 at PLS_VIM735)

206. Specifically, lacosamide was praised for having a unique mechanism of action (JTX-63 at PLS_VIM672), producing robust synergistic effects (*id.* at PLS_VIM670), being well-suited for long-term treatment (*id.* at PLS_VIM20317), having only mild or moderate side effects (*id.* at PLS_VIM671), having several methods of delivery (*id.* at PLS_VIM668), exhibiting low protein binding (*id.*), not metabolizing (*id.*), and exhibiting minimal interactions with other drugs (*id.*).

207. Lacosamide was not the only AED to receive praise. Lamotrigine, gabapentin, and topiramate also received praise. (Pleasure Tr. at 1011-12; *see, e.g.*, JTX-83 at 314; DTX-2215 at 372, 375, DTX-2174 at 723, 726-27, 732, 737; DTX-2180 at 825; JTX-99 at 444; DTX-2298 at 486)

vi. Vimpat® Has Been a Commercial Success

208. Vimpat® has generated significant sales, totaling $1.67 billion in the U.S. since its launch in May 2009 through February 2015. (*See* Vellturo Tr. at 902-03; PTX-321; PTX-322; PTX-323) As of the time of trial, U.S. net sales were close to $2 billion. (McDuff Tr. at 1082)

209. U.S. net sales of Vimpat® have increased significantly each year since launch. (*See* PTX-321; PTX-322; PTX-323; Vellturo Tr. at 902-05) U.S. net sales of Vimpat® were

$126 million in 2010, $217 million in 2011, $315 million in 2012, $407 million in 2013, and $443 million in 2014. (PTX-322)

210. At least as of 2012, Vimpat® enjoyed the most financially successful AED launch of the past ten years (JTX-70 at UCB-VIM 1677759) and the second-most successful AED launch as measured by total prescriptions written (JTX-70 at UCB-VIM 1677760).

211. Vimpat® has achieved this success despite being launched into a highly genericized marketplace for the treatment of epilepsy, i.e., a market with widespread availability of low-cost AEDs. (Vellturo Tr. at 902-03, 905-06; McDuff Tr. at 1085) In 2009, generic AEDs made up 70% of the prescription share for epilepsy indications in the U.S. (JTX-74; *see also* Vellturo Tr. at 906-07)

212. Vimpat®'s share of U.S. AED sales and prescriptions has continued to grow substantially since its launch in 2009, in contrast to the general trend for branded AEDs. (*See* Vellturo Tr. at 907-10; PTX-324; PTX-325; PTX-326; PTX-327; JTX-78; JTX-74)

213. Vimpat®'s share of total U.S. AED dollar sales of branded AEDs has steadily increased from 9.3% in 2010 to 15% in 2011, 21.3% in 2012, 27.4% in 2013, and more than 31% in 2014 and early 2015. (*See* PTX-324; Vellturo Tr. at 908-09) Vimpat® has the highest dollar share of branded AEDs prescribed for epilepsy in the U.S. (Vellturo Tr. at 908-09)

214. Vimpat®'s share of total U.S. AED dollar sales of both branded and generic AEDs has steadily increased from 6.8% in 2010 to 11.1% in 2011, 16.3% in 2012, 19.8% in 2013, and over 22% in 2014 and the beginning of 2015. (PTX-324; PTX-325; Vellturo Tr. at 908)

215. Vimpat®'s share of total U.S. AED prescriptions has steadily risen from around 0% in 2009 to more than 30% among branded AEDs and nearly 4% among all AEDs in 2015. (JTX-74; Vellturo Tr. at 909-11)

216. Prescriptions for Vimpat® have increased each year since launch. There were more than 300,000 prescriptions written for Vimpat® in the U.S. in 2010, 500,000 in 2011, 650,000 in 2012, 800,000 in 2013, and 950,000 in 2014, totaling more than 3.5 million through February 2015. (JTX-74; Vellturo Tr. at 909-11)

217. Vimpat® significantly outperformed other branded AEDs launched since 2009. (JTX-74; JTX-78; Vellturo Tr. at 911-12)

218. Even as Vimpat®'s marketing spend-to-sales ratio has trended downward from 23.9% in 2009 to below 2% in 2014, Vimpat®'s sales have continued to climb. (*See* Vellturo Tr. at 955; JTX-755) In comparison to other branded AEDs launched recently, Vimpat®'s marketing spend is relatively low and its success cannot be attributed solely to excessive marketing. (*See* Vellturo Tr. at 913-16, 955–56; JTX-75; JTX-77; JTX-166; JTX-121) The marketing spending of 25% of $1.67 billion in sales "is not a high number in the pharmaceutical industry by any stretch." (Vellturo Tr. at 940)

219. There are millions of compounds covered by the claims of the '301 and '729 patents, and no compound covered by those patents other than lacosamide has achieved any success as an approved pharmaceutical. (*See* Vellturo Tr. at 916-18; Roush Tr. at 631, 637, 749)

220. Prior to the invention of lacosamide, incentives existed in the marketplace to develop new AEDs. (*See* Vellturo Tr. at 922-23; JTX-128 (letter from McNeil Pharmaceutical declining interest in FAAs because "we already have one of our own anticonvulsants in an advanced stage of development")) However, at least some pharmaceutical companies may have

been disincentivized from pursuing an FAA as an AED because of RCT's patent coverage and Lilly's license. (McDuff Tr. at 1063-68; JTX-133 at 2) Still, the rights to the compounds were available through licensing. (Vellturo Tr. at 920; McDuff Tr. at 1090-91) While these facts may reduce the weight that should be accorded to the commercial success of Vimpat®, they do not alter the fundamental fact that Vimpat® has been a commercial success.

R. Non-Litigation Challenges to Patentability

221. On July 10, 2014, several of the Defendants filed a petition for *inter partes* review of the '551 patent. (*See* D.I. 214) On January 9, 2015, the PTAB denied that request, finding that the petitioners had not established a reasonable likelihood of showing the unpatentability of at least one of the challenged claims. (*See* D.I. 214-1)

222. On April 29, 2016, the PTO received a request for *ex parte* reexamination of the '551 patent. (*See* D.I. 300-1 at p.2) On June 16, 2016, the PTO instituted an *ex parte* reexamination of claims 1-13 of the '551 patent. (*See* D.I. 300; *see also* D.I. 300-1 at p.2) The PTAB stated: "There is a substantial likelihood that a reasonable examiner would consider the teachings of the '301 Patent, the '729 Patent, Kohn 1991, and LeGall important in deciding the patentability of claims 1-13 of United States Reissued Patent No. RE38,551 E, which question has not been decided in a previous examination of this patent." (*See* D.I. 300-1 at p.7-9)

223. On May 23, 2016, the PTAB instituted an *inter partes* review of the '551 patent. (*See* D.I. 294-1 at p.2; *see also* D.I. 294) The PTAB was not persuaded that the LeGall Thesis is prior art (*see* D.I. 294-1 at pp.8-12), but it was "persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 10-13 as obvious over Kohn 1991 [JTX-80 here], Silverman [not part of the record in this case], and the '729 patent [DTX-2012]" (D.I. 294-1 at p.22).

S. Additional Facts Relating to Indefiniteness

224. In connection with claim construction, the Court rejected Defendants' argument that the Court's construction of "therapeutic composition" renders claim 10 indefinite. (D.I. 240 at 11)

225. The '551 patent teaches that epilepsy treatment involves "long-term and consistent administration of anticonvulsant drugs." ('551 patent at 1:27–38) A POSA would understand that the '551 patent is directed towards the treatment of epilepsy, which can require life-long treatment. (Bazil Tr. at 772; Heathcock Tr. at 114, 177 (explaining that liver toxicity is an important consideration "if you are going to take something for a long time which is what . . . chronic means"))

T. Additional Facts Relating to Reissue

226. U.S. Patent App. No. 08/818,688 (the "'688 Application"), which resulted in U.S. Patent No. 5,733,475 (the "'475 Patent"), was filed on Monday, March 17, 1997. (JTX-3)

227. The '688 Application claims priority to U.S. Provisional App. No. 60/013,522 (the "'522 Provisional"), which was filed on March 15, 1996. The day that the '522 Provisional had been pending for a year, March 15, 1997, was a Saturday. The prosecuting attorney believed the Monday filing date for the '688 Application would allow for a claim of priority to the '522 Provisional. (Cohen Tr. at 338-39)

228. At the time, the law prohibited a non-provisional application from claiming priority to a provisional application filed more than twelve months earlier, even if the twelve-month period expired on a weekend or holiday. *See* 37 C.F.R. § 1.78(a)(3) (1996).

229. At the Examiner's request, the attorney authorized withdrawing the priority claim after the Examiner informed the attorney that the '688 Application could not lawfully claim

priority to the '522 Provisional. (Cohen Tr. at 339-40) The '688 Application issued as the '475 Patent in 1998. (JTX-3)

230. In 1999, Congress enacted the American Inventors Protection Act of 1999 ("AIPA"), which amended the pertinent filing-date rule as follows: "If the day that is 12 months after the filing date of a provisional application falls on a Saturday, Sunday, or Federal holiday . . . , the period of pendency of the provisional application shall be extended to the next succeeding secular or business day." AIPA § 4801(d) (codified at 35 U.S.C. § 119(e)(3)).

231. Congress applied this new law retroactively to encompass provisional applications filed on or after June 8, 1995, in contemplation that applicants who had previously erred would be allowed to correct their mistake. *See* AIPA § 4801(d).

232. On January 28, 2002, Dr. Kohn filed an application for reissue of the '475 Patent in order to claim priority to the '522 Provisional. (DTX-2024; Cohen Tr. at 341-42) The '551 Patent issued on July 6, 2004. (JTX-1 at (45))

233. The reissue application for the '551 patent was filed solely to add back the removed claim of priority. (Cohen 340-41; DTX-2024 at 1)

U. Defendants' ANDA Filings

234. Each of the Defendants submitted an Abbreviated New Drug Application ("ANDA") to the FDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of a generic copy of UCB's Vimpat® products. Specifically:

i. Accord submitted to the FDA ANDA No. 205011;

ii. Alembic submitted to the FDA ANDA No. 204974;

iii. Amneal submitted to the FDA ANDA Nos. 204857 and 204839;

iv. Aurobindo submitted to the FDA ANDA No. 204994;

v. Breckenridge and Vennoot submitted to the FDA ANDA No. 204921;

vi. Sun submitted to the FDA ANDA No. 205031;

vii. Actavis submitted to the FDA ANDA No. 204855;

viii. Apotex submitted to the FDA ANDA Nos. 204986 and 206355;

ix. Mylan submitted to the FDA ANDA No. 205026; and

x. Zydus submitted to the FDA ANDA No. 204947.

(SUF ¶¶ 33-81)

235. Each ANDA included a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that, in the applicant's opinion, the '551 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, offer for sale, and/or importation of the proposed ANDA products. (*Id.*)

V. Infringement

236. The filing of each of the ANDAs meets all of the elements of asserted claims 9, 10, and 13 of the '551 patent under 35 U.S.C. § 271(e)(2). (*See* D.I. 208)

237. Each of the Defendants' ANDA products or the administration of any of Defendants' ANDA products according to their indicated use will meet all of the elements of the asserted claims 9, 10, and 13 of the '551 patent. (*See* D.I. 208)

238. Upon final approval of Defendants' ANDAs, the commercial manufacture, use, sale, or offer for sale within the United States, or importation into the United States, of Defendants' ANDA products, and their administration according to their indicated use, will meet all of the elements of the asserted claims 9, 10, and 13 of the '551 patent. (*See* D.I. 208)

II. LEGAL STANDARDS

A. Presumption of Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1289-90 (Fed. Cir. 2012) (obviousness-type double patenting); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (obviousness); *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1351 (Fed. Cir. 2013) (anticipation); *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1347 (Fed. Cir. 2007) (indefiniteness); *In re: Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 523-26 (Fed. Cir. 2012) (improper reissue). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first modification in original). A defendant's burden to prove invalidity is "especially difficult when the prior art [on which it relies] was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

B. Obviousness-Type Double Patenting

Under the doctrine of obviousness-type double patenting, a party is prohibited "from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001) ("*Eli Lilly I*"). "[T]he fundamental reason for [this] rule is to prevent unjustified timewise extension of the right to exclude granted by a patent

no matter how the extension is brought about." *Id.* at 968.[17] The doctrine thus "ensures that the public gets the benefit of the invention after the original period of monopoly expires," *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. Rheumatology Trust*, 764 F.3d 1366, 1373 (Fed. Cir. 2014), and also "prevent[s] multiple infringement suits by different assignees asserting essentially the same patented invention," *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013).

The double patenting inquiry consists of two steps. "First, the court construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct." *Abbvie*, 764 F.3d at 1374 (internal quotation marks omitted); *see also Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1377 (Fed. Cir. 2012) ("*Eli Lilly IV*") (applying two-step analysis). At step two, to be "patentably distinct" and valid a claim must not be obvious over or anticipated by an earlier claim by the same inventor. *Abbvie*, 764 F.3d at 1374.[18]

> In the context of claimed chemical compounds, an analysis of nonstatutory obviousness-type double

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[17] "An obviousness-type double patenting rejection is analogous to a rejection for obviousness under § 103, except that the patent principally underlying the rejection is not considered prior art." Robert L. Harmon, *Patents and the Federal Circuit* 1215 (9th ed. 2009). As the Federal Circuit has explained:

> The judge made law of obviousness-type double patenting was developed to cover the situation where patents are not citable as a reference against each other and therefore can not be examined for compliance with the rule that only one patent is available per invention. Double patenting thus is applied when neither patent is prior art against the other, usually because they have a common priority date.

Eli Lilly, 251 F.3d at 973.

[18] The legal standards applicable to obviousness and anticipation are set out below.

> patenting – like an analysis under § 103 [statutory obviousness] – entails determining, *inter alia*, whether one of ordinary skill in the art would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success.

Otsuka, 678 F.3d at 1298.

Unlike with statutory obviousness, when considering obviousness-type double patenting in the context of chemical compounds, courts do not apply a lead compound analysis. Instead of comparing the patent-in-suit to a promising compound in the prior art, courts consider the differences between the patent-in-suit and the reference patent. *See id.* at 1297 ("[W]hen analyzing obviousness-type double patenting in cases involving claimed chemical compounds, the issue is not whether a skilled artisan would have selected the earlier compound as a lead compound. That is so because the analysis must necessarily focus on the earlier claimed compound over which double patenting has been alleged, lead compound or not."). In other words, courts treat compounds described in the reference patent effectively as a lead compound, regardless of whether those compounds would actually have been selected as a starting point for innovation. *See id.*

Whether or not a patent is invalid due to double patenting is a question of law. *See In re Hubbell*, 709 F.3d at 1145.

C. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on

underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007).

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning"). To protect against the improper use of hindsight when assessing obviousness, the Court is required to consider objective (or "secondary") considerations (or "indicia") of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Secondary considerations "may often be the most probative and cogent evidence in the record" relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

To determine whether a chemical compound is obvious, courts employ a "lead compound analysis." *See Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 F. App'x 961, 969-70 (Fed. Cir. 2014). This analysis involves two steps. First, the Court identifies a lead compound. A lead compound is a compound that a person of ordinary skill in the art would recognize as a starting point for innovation – "a compound in the prior art that would be most promising to modify in order to obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). When selecting a lead compound, the Court considers the compound's pertinent properties, including activity, potency, toxicity, and structure. *See Otsuka*, 678 F.3d at 1291-93.

After identifying a lead compound, the Court considers whether a person of ordinary skill would have been motivated to modify the lead compound so as to obtain the claimed compound. *See Eisai Co. v. Dr. Reddy's Labs, Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008); *see also Otsuka*, 678 F.3d at 1292 (explaining that courts consider "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success"). If such a motivation exists, then the claimed compound is prima facie obvious. *See id.*

"Obviousness is ultimately a conclusion of law premised on underlying findings of fact[.]" *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1333 (Fed. Cir. 2015) (internal citations and quotation marks omitted).

D. Anticipation

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *see also In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985) (stating patent

is invalid for anticipation where "each limitation of a claim [can] be found in a single reference, practice, or device"). "Anticipation requires clear and convincing proof that a single prior art reference not only discloses all of the elements of the claim within the four corners of the document, but also discloses those elements arranged as in the claim." *Cheese Sys., Inc.*, 725 F.3d at 1351 (internal quotation marks and alterations omitted). "The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim limitation was disclosed in that single reference." *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003).

Whether a claim is anticipated is a question of fact. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006) ("*Eli Lilly III*"); *see also* 35 U.S.C. § 102(a).

E. Indefiniteness

A patent is invalid for indefiniteness "if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). Indefiniteness is a question of law. *See Atmel Corp. v. Info. Storage Devices, Inc.*, 198 F.3d 1374, 1378 (Fed. Cir. 1999).

F. Improper Reissue

Patents may be reissued to correct or perfect a claim to priority. *See Fontijn v. Okamoto*, 518 F.2d 610, 621 (C.C.P.A. 1975). However, when a patentee "made a deliberate choice to forgo the earlier filing date," reissue "is not an available remedy" to reclaim that earlier date. *In re Serenkin*, 479 F.3d 1359, 1362 (Fed. Cir. 2007); *see also* 35 U.S.C. §§ 251, 282(b)(3)(B).

III. DISCUSSION

A. Obviousness-Type Double Patenting

Defendants assert that claims 9, 10, and 13 of the '551 patent are invalid for obviousness-type double patenting because these claims are not patentably distinct from independent claim 44 and dependent claims 45, 46, and 47 of the '301 patent (the "reference patent"). (OB at 3) In Defendants' view, "Plaintiffs improperly extended the term of their patent monopoly by obtaining the '301 patent with genus claims and then filing a later application, with later-expiring claims, that claimed a known and obvious species of the '301 patent's genus – lacosamide." (*Id.* at 3) Before explaining why the Court rejects Defendants' conclusion, the Court makes a few preliminary observations.

First, it is appropriate to subject the claims of the '551 patent to an obviousness-type double patenting analysis because Dr. Kohn was the inventor of both the '551 patent and the '301 patent, yet the '301 patent is not prior art to the '551 patent. *See Eli Lilly*, 251 F.3d at 973.

Second, although Defendants contend that all three asserted claims of the '551 patent are invalid due to double patenting in light of multiple claims of the reference '301 patent, the parties have focused their double patenting presentations on whether claim 9 of the '551 patent is invalid over claims 44 and 45 of the '301 patent. The Court will follow the parties' lead. While the bulk of the discussion below expressly addresses just claims 9 and 45, the analyses for each of the other combinations are not materially different, as is further discussed below.

Third, although the patent-in-suit claims a chemical compound, Plaintiffs acknowledge that no lead compound analysis is needed for the double patenting analysis. (*See* D.I. 271 (Plaintiffs' Answering Brief ("AB")) at 14) This is because the double patenting analysis begins with the reference compound – here the compound claimed by claim 45 of the '301 patent –

whether or not a POSA would actually have selected that compound as the lead compound. (*See id.*)

Fourth, as noted above, an analysis of obviousness-type double patenting takes place in two steps. "First, the court construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct." *Abbvie*, 764 F.3d at 1374 (internal quotation marks omitted). The parties disagree as to how this two-step analysis is to be applied here. Defendants argue that because of the genus-species relationship between claim 45 of the '301 patent and claim 9 of the '551 patent, the Court should assume a POSA would hold constant anything in common between claim 45 and claim 9. As applied here, that would mean that a POSA would not consider changing, for example, the methoxymethyl at R_3 of claim 45. Therefore, in Defendants' view, the Court may only consider the differences between claim 45 and claim 9.

Plaintiffs do not agree that the double patenting analysis required in this case is so narrowly circumscribed. (*See* AB at 14-16) Instead, Plaintiffs emphasize that in an obviousness-type double patenting analysis, like any other obviousness analysis, the Court must consider the claims as a whole. *See Eli Lilly IV*, 689 F.3d at 1376-78; *see also Otsuka*, 678 F.3d at 1297 (explaining that other than starting point for analysis, "a double patenting of the obviousness type rejection is analogous to [a failure to meet] the nonobviousness requirement of [Section 103]"). To Plaintiffs, consideration of the claims as a whole necessarily requires considering not just what is different between the reference patent claims and the asserted patent claims, but also the commonalities between those claims – and, most especially, whether a POSA may have been motivated to alter any of those commonalities.

Plaintiffs find strong support for their view in *Eli Lilly IV*, 689 F.3d at 1377, in which the Federal Circuit stated:

> [Defendant] contends that the correct [double patenting] analysis involves only the ***differences*** between the claims at issue, so that any features held in common between the claims [of the reference and the asserted patents] . . . would be excluded from consideration. . . . But those differences cannot be considered in isolation – the claims must be considered as a whole. . . . Thus, the district court did not err by examining whether one of ordinary skill in the art would have been motivated to modify the [reference] Compound to create [the compound of the asserted claim], considering the compounds as a whole.

(internal citations omitted) Defendants counter that *Eli Lilly IV*, as applied here, actually supports their position, writing:

> A skilled artisan looking at claim 44 as a whole in 1996, as *Lilly* requires, would see that it specifically calls for a methoxymethyl group at R_3 and, unlike the claimed compound in *Lilly*, invites the skilled artisan to complete the claimed structure by selecting what groups to put at the generic R and R_1 positions – the most obvious of which result in lacosamide.

(D.I. 274 (Defendants' Reply Brief ("RB")) at 3) Defendants also point out that "Plaintiffs do not cite a single double-patenting case in which ***any*** court, let alone the Federal Circuit, has credited an argument that a specific substituent in the earlier claim should be modified." (RB at 4)

The Court does not find it necessary to choose between the parties' competing interpretations of double patenting law in order to resolve the case before it. This is because the Court finds that the asserted claims of the '551 patent are not invalid for double patenting under either side's approach. Because Defendants' position results in a situation in which it is

substantially easier to invalidate the asserted claims than does Plaintiffs' position, the Court will assume, arguendo, that Defendants' position is correct. Therefore, the Court will focus its double patenting analysis on the ***differences*** between claim 45 of the '301 patent and claim 9 of the '551 patent. Additionally, as the Court will point out, the conclusion that the claims of the '551 patent are not invalid for double patenting is even stronger if Plaintiffs are correct that the analysis allows consideration of whether a POSA would retain the commonalities between the claims – especially the methoxymethyl at R_3.

The Court now turns to the double patenting analysis.

i. Differences Between Claim 45 of the '301 Patent and the Asserted Claims of the '551 Patent

The Court has already construed the disputed terms of the asserted claims of the '551 patent. (*See* D.I. 240)[19] The Court is applying these constructions, to the extent relevant, in the analysis here. The parties have not identified any claim construction disputes with respect to claim 45 of the '301 patent.

While claim 45 of the '301 patent and claim 9 of the '551 patent both disclose FAAs, the claims differ substantially in their scope. Whereas claim 45 of the reference patent discloses a genus of compounds encompassing millions of possible FAAs, claim 9 discloses a single compound: lacosamide. (*See* FF 129-133, 159) More particularly, the differences between the claims are: (i) while claim 45 of the '301 patent does not require any particular stereochemistry – and, thus, includes within its scope the R enantiomer, the S enantiomer, and a racemic mixture of both enantiomers – claim 9 of the '551 patent requires a specific stereochemistry, namely the R

[19] The Court's construction of "therapeutic composition" as meaning that the claimed compounds must be "suitable for use as a treatment regimen over an extended period of time (chronic administration)" presupposes that the compound will not result in liver toxicity. A medicine is not suitable for chronic administration if it will be toxic to the liver. (D.I. 241)

enantiomer in at least 90% purity (FF 165); (ii) while claim 45 of the '301 patent allows for any substituted or unsubstituted "aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl, or lower cycloalkyl lower alkyl," so long as there is at least one electron withdrawing group or one electron donating group at R (*see* '301 patent at 93:5-15) – the asserted claims of the '551 patent require an unsubstituted benzyl at R (*see* '551 patent at 38:37-40); and (iii) whereas claim 45 of the '301 patent allows for R_1 to be a substituted or unsubstituted hydrogen or (one of 32) lower alkyls with at least one electron withdrawing group or one electron donating group ('301 patent at 93:16-18), the asserted claims of the '551 patent require the placement of an unsubstituted methyl at the R_1 position (*see* '551 patent at 38:37-40).[20] (*See* FF 163-166)

While there are several differences between claims 9 and 45, there are also several similarities. Both claim FAAs of the same general structure that are effective for treating seizures. Both also require the placement of a methoxymethyl at the R_3 position. And the unsubstituted benzyl of R in lacosamide and the unsubstituted methyl at R_1 of lacosamide are among the structures that are within the broad genus of structures encompassed by claim 45. Notwithstanding these similarities, the double patenting analysis requires the Court to focus on the differences, a task to which the Court now turns.

ii. The Differences Render the Asserted Claims Patentably Distinct from the Claims of the Reference Patent

It is settled law that a claim to a genus of chemical compounds does not necessarily render a patent to a species within that genus obvious or anticipated. *See Abbvie*, 764 F.3d at 1379; *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003)

[20] While the record does not disclose precisely how many structures could be placed at the R_1 position, Dr. Roush testified that there were "many" possibilities. (Roush Tr. at 634)

("*Eli Lilly II*"); *see also Brigham & Women's Hosp. Inc. v. Teva Pharm. USA, Inc.*, 761 F. Supp. 2d. 210, 224 (D. Del. 2011) ("[A]n earlier patent claiming a large genus of pharmaceutical compounds does not preclude a later patent claiming a species within that genus, so long as the species is novel, useful, and nonobvious.").[21]

Some of the differences between the claims would have been obvious to a POSA who started with claim 45 of the '301 patent. For instance, it would have been obvious to modify the compound of claim 45 of the '301 patent to isolate the R enantiomer at 90% or higher purity. This is because it would have been known to a POSA in March 1996 that the R enantiomer had far greater effectiveness as an AED than the S enantiomer, giving a POSA both a motivation to purify the R enantiomer and a reasonable expectation that doing so would yield a successful AED. (*See* FF 90-91) For example, in a 1988 article, Dr. Kohn compared the R and S enantiomers in two FAAs – AAB, containing methyl at R_3, benzyl at R, and methyl at R_1, and APB, containing phenyl at R_3, benzyl at R, and methyl at R_1. (*Id.*) Dr. Kohn reported that the R enantiomers of these compounds were ***ten times*** more potent than the S enantiomers. (*See id.*) Consistent with these observations, Dr. Kohn testified that he "never published any results before 1996 showing that . . . the S or L enantiomer was more active than the D or R." (Kohn Tr. at 509) Dr. Kohn's statements are supported and confirmed by the preferences articulated in the '729 patent, which indicate that the R enantiomer is preferred. (*See* '729 patent at 10:27-28; Roush Tr. at 694-95) These facts are sufficient to show that a POSA would have found it

[21] It is also the law that "species are unpatentable when prior art disclosures describe the genus containing those species such that a person of ordinary skill in the art would be able to envision every member of the class." *Abbvie*, 764 F.3d at 1379. Here, given the millions of compounds that are within the genus of claims 44 and 45 of the '301 patent, the Court concludes that a POSA could not envision every member of the class.

obvious to isolate the R-enantiomer of any FAA that was selected for further development. Plaintiffs did not offer any evidence or data that would support a contrary conclusion.

Crucially, however, other differences between the claims would not have been obvious. First, to a POSA beginning with claim 45 of the '301 patent, it would not have been obvious to place an unsubstituted benzyl at R. Most of the pre-1996 experimentation relating to FAAs was performed at the R_3 position. (*See* FF 73-74) As a result, at the critical date, March 1996, there was relatively little data on which a POSA could draw to form reasonable expectations about the impact of placing an unsubstituted benzyl at R.

The Federal Circuit has emphasized that "predictability is a vital consideration in the obviousness analysis," including obviousness-type double patenting. *Otsuka*, 678 F.3d at 1298 (citing *KSR*, 550 U.S. at 421). In the context of drug development, data is a necessary prerequisite to predicting the impact of modifying a chemical compound. (*See* FF 66) This is especially so because of the unpredictability of drug development. (*See* FF 66-67) Therefore, the absence of data is a strong indication of the non-obviousness of the claimed invention.

Although there were many tests conducted on FAAs with benzyl at R and methyl at R_1 (*see* Heathcock Tr. at 113 (explaining that 75% of Dr. Kohn's compounds contained benzyl at R and methyl at R_1, and most of these were unsubstituted)), these tests, and the resulting data, do not provide much insight into the effectiveness of benzyl and methyl relative to other structures that could be placed at R and R_1. Most of these tests kept the structures at R and R_1 constant in order to assess changes made at the R_3 position. (*See* Kohn Tr. at 410, 508-09) Consequently, any changes (whether increases or decreases) observed in anticonvulsant behavior and/or neurotoxicity would be attributed to the structure at R_3 rather than to the benzyl at R or the methyl at R_1. (*See* Roush Tr. at 681-82) As Dr. Roush explained, "[y]ou can't . . . say he [i.e.,

Dr. Kohn] used only benzyl at R and used only methyl at R_1 and, therefore, say that he's selected them and that they're the best. There is no data to say whether benzyl is best or something else would be the best." (*Id.*) In fact, according to the data that was available at the critical date, the FAAs containing an unsubstituted benzyl demonstrate a range of effectiveness. (*See, e.g.*, '729 patent at Tbl.1)

Again, given how unpredictable drug development is (*see* FF 66), and the high likelihood that any formulation will prove unsuccessful (*see* FF 197), the lack of data strongly contributes to the Court's finding that the placement of an unsubstituted benzyl at R and of an unsubstituted methyl at R_1 render the asserted claims patentably distinct. It is only with improper use of hindsight that one could conclude that it would have been obvious to a POSA to use those structures to fill in the variables.

While the Court's conclusion is motivated largely by the lack of data, it is also the case that the limited data that ***did*** exist at the time would not have led a POSA to place an unsubstituted benzyl at R. In 1987, Dr. Kohn published a paper demonstrating that a compound with a fluoro-substituted benzyl at R had similar anticonvulsant activity to an analogous compound with an unsubstituted benzyl, but with a substantial improvement in neurotoxicity levels. (*See* Roush Tr. at 616; JTX-7 at DEF_566 Tbl.6) These results were confirmed in Kohn's 1990 paper, which showed that in certain FAAs, structures with various fluoro-substituted benzyls yielded a "far superior" protective index while maintaining a comparable anticonvulsant effect (relative to the same compound with an unsubstituted benzyl). (*See* Kohn Tr. at 396, 489 (explaining that replacing unsubstituted benzyl with fluoro-substituted benzyl yielded "an improvement in the overall protective index resulting from a decrease in neurotoxicity of the compound"); JTX-11 at Tbl.2, DEF_272) The data from some of these

experiments were also included in the '729 patent. (*See* '729 patent at Tbl.1 (rows 9, 18, and 43); *see* also JTX-11 at Tbl.2; Roush Tr. at 616-17) Given the data (and lack of data), a POSA starting with claim 45 of the '301 patent would have had no reasonable expectation of achieving a successful AED FAA by placing an unsubstituted benzyl at R.

Further supporting the Court's conclusion is the fact that other scientists who were studying FAAs at approximately the same time as the priority date of the '551 patent did not select an unsubstituted benzyl at R.[22] Drs. Paruszewski and Hinko experimented with each variable in Dr. Kohn's FAA structure, and they did not constantly or even often use an unsubstituted benzyl at R. Dr. Hinko focused extensively on modifications to the R position, such that only two of his 21 compounds contained an unsubstituted benzyl. (*See* FF 153; Roush Tr. at 618-19)

In sum, the placement of unsubstituted benzyl at the R position in claim 9 of the '551 patent is patentably distinct from the millions of possible groups that could be placed at the R position in claim 45 of the '301 patent.

Likewise, it would also not have been obvious for a POSA starting with claim 45 of the '301 patent to place an unsubstituted methyl at R_1. As with the situation that confronted a POSA considering what to place at R, and as noted above, a POSA deciding what to place at R_1 had little data upon which to draw as to the impact of placing an unsubstituted methyl at R_1. (*See* Roush Tr. at 646) Hence, again, the unpredictability of drug development means that the lack of

[22] The work of Drs. Paruszewski and Hinko does not qualify as prior art. Nevertheless, their exploration is relevant because it shows what a POSA would have thought at around the priority date. Specifically, it is probative of the fact that the benefits of lacosamide (including the placement of a benzyl at R and a methyl at R_1) were not apparent until well after the priority date of the '551 patent.

data concerning R_1 is a strong reason why the selection of an unsubstituted methyl would not have been obvious to a POSA in March 1996.

The Court's conclusion with respect to R_1 is also supported by research conducted by others working on FAAs at the same time as Dr. Kohn. Dr. Hinko modified the FAA structure to change the way the structure at R_1 connected with the rest of the molecule.[23] (*See* Roush Tr. at 614; JTX-87 at Tbl.1) Dr. Paruszewski explored a similar change by removing the carbonyl group (C==O) to which the R_1 group is attached.[24] (FF 151)

Defendants point out that Dr. Kohn's limited experimentation with the R_1 position was substantially less promising than his experimentation with the R position, meaning – in Defendants' view – that a POSA would have been less motivated to alter the unsubstituted methyl Dr. Kohn often used at R_1. At the R position, there were many structures that performed comparably to – and, in some ways, better than – unsubstituted benzyl. (FF 89, 93) In contrast, Dr. Kohn found that none of the modifications he made at the R_1 position showed as good

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[23] The Court accords less weight to the evidence of what Drs. Hinko and Paruszewski did at R_1 than it does with respect to what these same scientists did at R, due to the Court's assumption that for double patenting a POSA would effectively "lock in" all that is common between claim 45 of the '301 patent and claim 9 of the '551 patent. From this assumption it would seem to follow that, for purposes of the double patenting analysis, the general structure of the FAA of claim 45 of the '301 patent would be preserved, meaning that the Court should not consider the alterations made by Drs. Hinko and Paruszewski. When this assumption is removed – because it is an incorrect assumption for double patenting, and/or at the general obviousness analysis – the weight given to this evidence increases substantially.

[24] Defendants contend that scientists were deterred from using an unsubstituted benzyl at R and an unsubstituted methyl at R_1 due to Plaintiffs' "blocking patent" rights. Viewed in light of all of the evidence, this argument is not persuasive. The record lacks clear and convincing evidence that the patents were the reason Drs. Hinko and Paruszewski did not fill in R and R_1 with the structures required to arrive at lacosamide. Instead, given the evidence before the Court, it appears that these other scientists did not do so because it was not obvious to do so. Furthermore, the Court is not persuaded that Plaintiffs' patents were "blocking patents," as explained in connection with commercial success below (*see infra*).

activity as the unsubstituted methyl. (*See* Kohn Tr. at 468-69) While this fact arguably means that a POSA would have been more likely to have placed an unsubstituted methyl at R_1 than to have placed an unsubstituted benzyl at R, the lack of data, in tandem with the fact that other scientists responded to Dr. Kohn's work by modifying the FAA structure in different ways, supports the Court's conclusions that it would not have been obvious to place an unsubstituted methyl at R_1.

In sum, the placement of an unsubstituted methyl at the R_1 position in claim 9 of the '551 patent is patentably distinct from the large number of structures that could be placed at the R_1 position in claim 45 of the '301 patent.

The Court has considered all of Defendants' arguments for a contrary conclusion and finds them unavailing. A few, however, merit comment.

Defendants emphasize that the '729 patent disclosed that benzyl is "especially preferred" for placement at the R position. (*See* FF 118-119; D.I. 263 at 8) Similarly, the '729 patent expresses a preference for unsubstituted methyl at R_1. (FF 119) While Defendants are correct, the double patenting analysis requires a POSA to start with the '301 patent's claim 45, not with the '729 patent. Moreover, in light of the totality of evidence in the record – which includes the lack of data showing the effect of placing an unsubstituted benzyl at R, the lack of data showing the effect of placing an unsubstituted methyl at R_1, and the data showing positive results from placing something ***other than*** an unsubstituted benzyl at R– it is only with impermissible hindsight that a POSA would have focused on the "especially preferred" language of the '729 patent's disclosure.

Defendants further argue that Plaintiffs knew about lacosamide when they added genus claims 39-47 to the '301 patent. While this appears to be correct (*compare* FF 79-80 (showing

that Dr. Kohn had synthesized and tested lacosamide by late 1994) *with* DTX-2016 (showing that genus claims of '301 patent were added in October 1995)), it does not impact the Court's analysis, which must focus on the hypothetical inquiry of what the POSA would have done – ***not*** what the real inventor actually did do. "The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka*, 678 F.3d at 1296. Here, regardless of whether it was obvious for ***Dr. Kohn*** to move from the reference patent to the patent-in-suit, the evidence does not clearly and convincingly demonstrate that it would have been obvious for a POSA to have done so.

In the end, the Court finds that while it may not have been ***surprising*** for a POSA to have placed an unsubstituted benzyl at R and an unsubstituted methyl at R_1, it also would not have been ***obvious*** for a POSA to have done either of these things.[25] Accordingly, claim 9 of the '551 patent is patentably distinct from claim 45 of the '301 patent. Therefore, the asserted claim is not invalid due to double patenting.

iii. Further Evidence Against a Finding of Double Patenting Invalidity

"In the chemical context, we have held that an analysis of obviousness-type double patenting requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success." *Eli Lilly IV*, 689 F.3d at 1378 (internal quotation marks omitted). As the Court explained in the preceding section, a POSA starting with claim 45 of the '301 patent would not have had reason to modify

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[25] The Court recognizes that Defendants' burden does not require them to prove that placement of an unsubstituted benzyl at R and an unsubstituted methyl at R_1 is the "***most desirable*** combination available." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). The Court's conclusion is that Defendants have failed to show, by clear and convincing evidence, that the claimed invention is even ***an obvious*** combination.

that earlier compound to arrive at lacosamide and would not have had a reasonable expectation of success if she had done so.

The record also contains an overwhelming amount of evidence that a POSA starting with claim 45 of the '301 patent would actually have been motivated to modify at least one aspect of the claim 45 compound: the methoxymethyl at R_3. The placement of methoxymethyl at R_3 is not a "difference" between claim 45 of the '301 patent and the asserted claims of the '551 patent; rather, it is something the claims from both patents share in common. The Court's conclusion that claim 9 of the '551 patent is patentably distinct from claim 45 of the '301 patent is based on the conclusions already discussed above with respect to the unsubstituted benzyl at R and unsubstituted methyl at R_1. Still, considering the totality of the claims, and considering the extensive "real-world" evidence of what a POSA starting with claim 45 of the '301 patent would have known and expected, the Court finds that such a POSA would have been motivated to replace the nonaromatic methoxymethyl at R_3 with an aromatic compound. As explained above, the Court assumes, without deciding, that this finding is not relevant to the legal analysis required for double patenting.[26] If it were legally relevant, this additional evidence – which the Court discusses below – strongly supports the Court's conclusion that claim 9 is not invalid for double patenting.[27]

Claims 44 and 45 of the '301 patent require the placement of methoxymethyl at the R_3 position of the compound. (FF 137) Methoxymethyl is nonaromatic. (FF 72) In 1996, a POSA

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[26] Again, the Court is assuming, arguendo, that all ***commonalities*** between the reference patent claim and the asserted claims of the patent-in-suit are effectively "locked in," so the relevant inquiry is solely whether the ***differences*** between those claims are patentably distinct.

[27] This evidence is relevant to the general obviousness inquiry, and there it does strongly support the Court's conclusion that the asserted claims are not invalid for obviousness. (*See infra.*)

working on an FAA as an AED would have been motivated to replace methoxymethyl with an aromatic compound.

The bulk of the prior art relating to FAAs consisted of experiments at the R_3 position. (*See* Roush Tr. at 618; FF 73-74) In these experiments, aromatics ***consistently*** performed better than nonaromatics. (*See* FF 74, 99-103 (showing that 30% of aromatics had excellent activity, as compared to just 3% of nonaromatics)) Indeed, experiments showed a sharp decrease in anticonvulsant activity when an aromatic structure was replaced with a nonaromatic structure. (*See* FF 101) Because the development of AEDs is data-driven (FF 66), the data produced from these experiments would have provided a strong motivation for a POSA to replace the methoxymethyl at R_3 of claim 45 of the '301 patent with an aromatic structure. (*See* Roush Tr. at 681-82 ("[A] person of skill looks at this and says having a heteroaromatic at R_3, that's important.")) Such a motivation, if pursued, would have taken a POSA directly away from the claimed invention of the asserted claims of the '551 patent.

The only nonaromatic structures that showed anticonvulsant activity comparable to the aromatic structures were nitrogen-based rather than carbon-based. (FF 125) Because methoxymethyl is carbon-based (*see* FF 63, 137 (showing that formula for methoxymethyl contains carbon, but not nitrogen)), this means that even if a POSA elected to keep a nonaromatic structure at R_3, the POSA would still have been motivated to move away from methoxymethyl to a nitrogen-based nonaromatic structure.

Defendants argue that the LeGall Thesis would have motivated a POSA to place an unsubstituted benzyl at R, place an unsubstituted methyl at R_1, and keep methoxymethyl at R_3. (*See* D.I. 263 at 5-6 ("Thus, compound 107e would have led a skilled artisan directly to the unsubstituted benzyl and methyl groups at R and R_1.")) The Court disagrees. While the LeGall

Thesis describes compound 107e, it does not provide any data for the compound. (*See* FF 108-109; *see also* FF 112-113 (finding that any potential in compound 107e was based on its similarity to compound 86b, which itself was not particularly potent)) The lack of data means that a POSA would not have given much weight to LeGall's discussion of compound 107e. (*See* Roush Tr. at 600) Second, taken as a whole, the LeGall Thesis would not have motivated a POSA to use a nonaromatic compound such as the methoxymethyl group at R_3. Instead, the data contained in the LeGall Thesis revealed that heteroaromatic compounds were more active than nonaromatic compounds and that nonaromatic compounds showed little or no potency. (*See* Roush Tr. at 743; FF 106, 111)

Similar to the situation with respect to R_3, if one removes the assumption that all of the commonalities between claim 45 of the '301 patent and claim 9 of the '551 patent are effectively "locked in" for the double patenting analysis, then the work of Drs. Hinko and Paruszewski relating to R_1 takes on greater significance in supporting the Court's conclusion that Defendants have failed to meet their burden. Both of these scientists did work that altered the fundamental structure of Dr. Kohn's FAA, including altering the fundamental structure of the compounds claimed by claim 45. In particular, Dr. Hinko "tied" the R_3 position to the R_1 position (*see* FF 152) and Dr. Paruszewski removed the carbonyl group used to attach the R_1 position to the FAA (*see* FF 151). These experiments by real-world POSAs exploring problems similar to Dr. Kohn around the priority date of the patent-in-suit further support the nonobviousness of the selection of an unsubstituted methyl at R_1.

iv. The Other Double Patenting Challenges Also Fail

While the discussion above focuses on the comparison between claim 45 of the '301 patent and claim 9 of the '551 patent, the conclusion is the same with respect to Defendants'

other double patenting contentions, the analysis for which is not materially different. For at least all of the same reasons that claim 9 of the '551 patent is patentably distinct from claim 45 of the '301 patent, so, too, are claims 10 and 13 of the '551 patent (which claim applications and methods of using the compound claimed in claim 9) patentably distinct from claim 45. (*See* Roush Tr. at 642; Pleasure Tr. at 278-79; OB at 11) Likewise, for at least all of the same reasons that the asserted claims of the '551 patent are patentably distinct from claim 45 of the '301 patent, so, too, are they patentably distinct from claim 44 (which, unlike claim 45, does not require "n" – which is the number of times the middle portion of the FAA compound is repeated – to equal one but allows it to range from one to three, s*ee* FF 134, 140) – and from claims 46 and 47 of the '301 patent (which claim applications and methods of using the compound claimed in claim 45).[28]

Accordingly, Defendants have failed to meet their burden to show that any of the asserted claims of the '551 patent are invalid for obviousness-type double patenting over any of the identified claims of the reference '301 patent.

v. Objective Indicia of Nonobviousness

Generally, when considering whether a patent is invalid for obviousness-type double patenting, the Court is required to consider objective indicators of nonobviousness, if such evidence is presented. *See Eli Lilly IV*, 689 F.3d at 1381. Here, however, given the Court's conclusions above, it is not strictly necessary to consider whether Plaintiffs have proven any objective indicia of nonobviousness. The asserted claims would not be invalid for obviousness-

[28] Claim 45 differs from claim 44 only in that claim 44 allows n to take on any value between one and four (inclusive), while claim 45 requires n to equal 1. (*See* FF 134-140) The parties do not make any obviousness arguments that apply to claims 44, 46, and/or 47 that do not apply to claim 45.

type double patenting even if Plaintiffs have failed to prove any objective indicia. Nonetheless, because the parties devoted a substantial amount of time at trial and discussion in their briefing to these secondary considerations of nonobviousness, the Court will address this evidence. In doing so, the Court concludes that Plaintiffs have proven that these indicia further confirm the Court's conclusion as to nonobviousness. None of this evidence supports a conclusion of obviousness.

Defendants argue that Plaintiffs' evidence of objective indicia is "irrelevant" (RB at 18) because claim 13 broadly covers a "method of treating a central nervous system disorder," while Plaintiffs' secondary considerations evidence relates only to use of lacosamide for treating just of epilepsy. "Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). The claimed invention must be "coextensive" with the subject of the secondary evidence. *See id.*

The claim language on which Defendants' contention is based appears only in claim 13 and not in asserted claims 9 and 10. Even as to claim 13, the Court is not persuaded that the secondary considerations analysis is as narrow as Defendants contend. The Court agrees with Plaintiffs that the record establishes that lacosamide, which is in each of the asserted claims, "was unknown in the prior art, had never been used previously for any purpose, and [that] the objective indicia pertain to its [i.e., lacosamide's] only approved use – as an AED." (D.I. 277 (Plaintiffs' Surreply Brief ("SRB")) at 3) Therefore, Plaintiffs' evidence of secondary considerations is sufficiently commensurate with the scope of the asserted claims.

Plaintiffs presented evidence relating to several objective indicia: skepticism, long-felt but unmet need, failure of others, unexpected results, praise, commercial success, and copying.

(SRB at 1-2) *See generally Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1555 (Fed. Cir. 1995). The Court now turns to that evidence, and concludes that many of them support a finding of nonobviousness, and none of them support a finding of obviousness. [29]

a. Skepticism

The Court finds that there was some skepticism associated with developing lacosamide. (*See* FF 167-180) When Dr. Kohn was searching for a pharmaceutical partner, many companies were skeptical of FAAs. (FF 168) Companies rejected FAAs because the compounds had not yet "demonstrate[d] a lack of toxicity," did "not appear that potent," and did not have a clear mechanism of action. (FF 172) Even after Dr. Kohn entered into an agreement with Harris FRC, he had trouble obtaining an additional partner to develop lacosamide and bring it to market. (FF 174) Many of the companies expressed doubt that lacosamide would be successful and/or that lacosamide would be more effective than the already existing AEDs. (FF 175-179) While some of these rejections were made without knowledge of the '301 patent, they continued even after the '301 patent was published and after that patent issued. (*See id.*)

Accordingly, the Court concludes that evidence of skepticism supports a finding of nonobviousness.

b. Long-Felt but Unmet Need

Prior to March 15, 1996, there was a long-felt need for a safe and effective epilepsy treatment for patients who were treatment-refractory, were unable to achieve acceptable seizure control, or experienced adverse side effects when using traditional AEDs. (*See* FF 181-196) Dr.

[29] The Court's conclusions with respect to secondary considerations of non-obviousness are focused here on double patenting. Most of what is discussed here is equally pertinent to the general obviousness inquiry, a point the Court will discuss further when it addresses general obviousness.

Bazil's testimony that lacosamide controls seizures for some of these patients – i.e., some portion of epilepsy sufferers whose seizures are otherwise uncontrolled – went unrebutted by Defendants. (*See* SRB at 7) While the record clearly shows that Vimpat® did not solve the problem for all people with epilepsy, and, thus, did not fully satisfy the unmet need, it has proven effective at controlling seizures in a segment of the population who had previously gone without relief from other available AEDs. More generally, Vimpat® satisfies the need for an AED with the collection of properties the medical community still found lacking in any of the AEDs available in March 1996. (*See* FF 189)

Accordingly, the Court concludes that evidence of satisfying at least a portion of a long-felt but unmet need supports a finding of nonobviousness.

c. Failure of Others

The Court finds that there was a failure of others to develop safe and effective AEDs before lacosamide and before March 15, 1996. (*See* FF 197-199) Developing a safe and effective AED is difficult because the etiology and mode of action of epilepsy are not fully understood. (*See* FF 197) Out of approximately 16,000 compounds screened for anticonvulsant activity by the NIH between 1975 and 1996, only one – felbamate – was approved by the FDA, but a year after its launch felbamate was linked to serious adverse reactions. (*See* FF 198-199) Even Defendants' expert, Dr. Pleasure, has reported that less than 3% of new neurotherapeutic projects have a probability of success. (*See* FF 197)

Accordingly, the Court concludes that evidence of failure of others supports a finding of nonobviousness.

d. Unexpected Results

The Court finds that lacosamide demonstrated substantial unexpected results. (*See* FF 200-204) Prior to the '551 patent, there was no data relating to compound 107e or to lacosamide. (*See* FF 108, 200) The data that did exist suggested that heteroaromatic compounds were more promising and that nonaromatic compounds with structures similar to lacosamide exhibited liver toxicity. (*See* FF 74, 77) It was unexpected, then, that lacosamide turned out to demonstrate substantial anticonvulsant activity without high toxicity values. (*See* Pleasure Tr. at 305 (explaining that, absent data, "you can't reasonably expect good pharmacokinetic or safety [results]")) The Court agrees with Plaintiffs, who write:

> A POSA would have had no reason to expect that any FAA, let alone lacosamide, would possess the favorable combination of ideal properties that lacosamide enjoys: high potency, low neurotoxicity, high protective index, minimal liver toxicity, desirable dosing and formulations, favorable pharmacokinetic properties, minimal dose-dependent and reversible side effects, little to no drug-drug interaction, and a distinct and novel mechanism of action.

(SRB at 10-11)

Accordingly, the Court concludes that evidence of unexpected results supports a finding of nonobviousness.

e. Praise

The Court finds that lacosamide received a considerable amount of praise. (*See* FF 205-207) Scientists and medical professionals have praised lacosamide for its advantages over other AEDs and for possessing "most of the properties of an ideal AED." (FF 205-206) Even Dr. Pleasure, Defendants' expert, acknowledged: "I'm sure . . . lacosamide is a useful medication." (Pleasure Tr. at 1011) While other AEDs have also received praise (*see* FF 207), this does not

undermine the fact that lacosamide has received a considerable amount of praise – something that would have been considerably less likely to have occurred had lacosamide been obvious.

Accordingly, the Court concludes that evidence of praise supports a finding of nonobviousness.

f. Commercial Success

The Court finds that lacosamide is a commercial success. (*See* FF 208-220) In order to establish commercial success, Plaintiffs must show that Vimpat®, which has lacosamide as its active ingredient, achieved significant sales in a relevant market, which here is the AED market. *See Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010). Plaintiffs have made such a showing.

From its launch in May 2009 through February 2015, Vimpat® has generated revenues of $1.67 billion (FF 208) and has experienced an increase in annual sales each year (FF 209). Ranked by gross revenue, Vimpat® has been the most successful AED in at least a decade. (FF 210) Vimpat® has also been the second-most successful AED as ranked by number of prescriptions written. (*Id.*) Notably, Vimpat® has achieved its success despite being launched into an AED market that is heavily genericized. (FF 211) Even though generic AEDs comprise roughly 90% of all AED prescriptions in the United States, Vimpat®'s share of U.S. prescriptions has continued to grow each year it has been on the market. (FF 212, 215-216 (explaining that annual prescriptions for Vimpat® have increased from 300,000 in 2010 to 950,000 in 2014))

Defendants contend that Vimpat®'s commercial success, if any, is not attributable to its nonobvious nature but, instead, due to the existence of Plaintiffs' blocking patents, which dissuaded others from developing lacosamide. (RB at 24) The record does not support

Defendants' contention. As Plaintiffs observe, "[r]ather than using the patents to block development efforts, RCT and Harris, on behalf of Dr. Kohn, offered licenses to them." (SRB at 4) In 1991, Lilly terminated its license to the entire class of FAA compounds. (FF 170) After the termination, RCT offered to license the FAA compounds to other companies. (*See* FF 171; SRB at 4; Vellturo Tr. at 920) The availability of a license meant that companies had the opportunity to pursue FAAs. At most, the disincentives that other potential developers would have encountered prior to 1996 reduces the weight the Court should give to the strong evidence of Vimpat®'s commercial success. Still, the record as a whole supports a finding of commercial success.

Defendants further argue that the success of Vimpat® is attributable not to the merits of lacosamide but instead to the marketing efforts made on its behalf. (RB at 13-14) The record belies this contention. Vimpat®'s sales have continued to grow despite a sharp reduction in marketing expenditures; the marketing-sales ratio has decreased substantially since the drug launched. (*See* JTX-75; Vellturo Tr. at 955) Further, the total amount of money spent to market Vimpat® has been small relative to what has been expended on other branded AEDs. (*See* JTX-75)

Accordingly, the Court concludes that evidence of commercial success supports a finding of nonobviousness.

g. Copying

Plaintiffs contend that the fact that Defendants want to copy Vimpat® is additional evidence that Vimpat® was nonobvious. (*See* OB at 31-32) In *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013), the Federal Circuit stated that "evidence of copying in the [generic drug] context is not probative of non-obviousness."

Plaintiffs make no attempt to distinguish *Bayer*. Accordingly, the Court concludes that the undisputed evidence of copying is not probative of nonobviousness.

B. Obviousness

Having concluded that the asserted claims of the '551 patent are not invalid due to obviousness-type double patenting, the Court now turns to Defendants' contention that these claims are invalid due to statutory obviousness. Specifically, Defendants contend that claim 9 is invalid for obviousness "based on LeGall's synthesis of compound 107e as a racemic mixture that contains lacosamide – with or without other prior art." (OB at 20) "Examples of prior art references that would render claim 9 obvious include the LeGall thesis alone, the LeGall thesis and the '729 patent; and the LeGall thesis, the '729 patent, and Kohn 1991." (OB at 23)[30] As explained below, the Court disagrees with Defendants.

Essentially all of the discussion above in the context of double patenting applies equally with respect to obviousness. The Court focuses here on the differences in the analyses. They are principally that: (i) while the Court assumed, arguendo, that for double patenting a POSA would retain all of the features that are common to the reference patent claims and the challenged asserted claims, with obviousness even Defendants do not argue for such a restriction, so the Court must consider whether a POSA would have modified any of the common features between the prior art and the asserted claims; and (ii) while for double patenting the Court's analysis must begin with the compound of the reference patent's claim, for obviousness the Court must apply a lead compound analysis. Both of these distinctions favor Plaintiffs. That is, both of these

[30] Defendants acknowledge that the conclusion with respect to the obviousness of claims 10 and 13 should be the same as the conclusion with respect to claim 9. (*See* OB at 23) The Court focuses its analysis on claim 9.

distinctions – because they require Defendants to prove more things – make it more difficult for Defendants to prove the claims of the patent-in-suit are invalid for obviousness.

It follows, and the Court here expressly concludes, that for the same reasons that Defendants have failed to prove, by clear and convincing evidence, that any of the asserted claims of the '551 patent are invalid due to obviousness-type double patenting, so, too, have Defendants failed to prove, by clear and convincing evidence, that any of the asserted claims of the '551 patent are invalid due to obviousness. The Court's discussion of obviousness, below, therefore, is fairly truncated.

i. A POSA Would Not Have Used Methoxymethyl at R_3

As explained above as "Further Evidence Against a Finding of Double Patenting Invalidity," a POSA on March 15, 1996, in possession of all of the prior art relied on by Defendants, would not have been motivated to use methoxymethyl at the R_3 position of an FAA being developed as an AED. Instead, such a POSA would have been motivated to use a heteroaromatic structure at R_3. Methoxymethyl is nonaromatic, not heteroaromatic. Relatedly, a POSA would have had no reasonable expectation of success in developing an effective AED from an FAA by using methoxymethyl at R_3.

Therefore, in addition to the deficiencies with Defendants' showing with respect to an unsubstituted benzyl at R and an unsubstituted methyl at R_1, Defendants' failure of proof with respect to the use of methoxymethyl at R_3 means that Defendants have failed to prove that claim 9 is invalid due to obviousness.

ii. Defendants Have Failed to Satisfy the Lead Compound Analysis

The Court agrees with Plaintiffs that, as concerns obviousness, the Court must apply a "lead compound analysis." This is because the claims at issue disclose a chemical compound.

(*See* AB at 6-7) Defendants counter that a lead compound analysis is inappropriate because the claimed compound, lacosamide, can be derived from a racemic mixture. (*See* AB at 20-21) Defendants cite no binding nor persuasive authority for their contention.[31] Thus, the Court will undertake a lead compound analysis to determine whether the claimed chemical compound would have been obvious in light of a previous chemical compound.

In doing so, the Court must first consider whether a POSA "would have selected the asserted prior art compound as a lead compound, or starting point, for further development."

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[31] Defendants point to *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007), in which the Federal Circuit held:

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

See also Spectrum Pharms., Inc. v. Sandoz Inc., 802 F.3d 1326, 1334 (Fed. Cir. 2015) ("If it is known that the desired activity all lies in one isomer, surely, it is better, and there is generally motivation, to try to obtain the purest compound possible."). *Aventis* is not inconsistent with a lead compound analysis. While the term "lead compound analysis" does not appear in the *Aventis* opinion, the approach it described amounts to the same thing: it requires the party challenging a patent to identify a prior art compound, show that a POSA would have been motivated to select that compound, and show that a POSA would have been motivated to modify the compound in order to obtain the patented compound. *See Aventis*, 499 F.3d at 1301 (explaining that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness"). Applied to the current case, the framework articulated in *Aventis* means that lacosamide would be obvious if, but only if, (1) a POSA would know that compound 107e (the racemic mixture) possessed promising or desirable properties sufficient to warrant the POSA's attention, (2) a POSA would know that compound 107e's properties derive from the R enantiomer, and (3) a POSA would know how to isolate the R enantiomer from the racemic mixture. As explained below, while Defendants have proven elements (2) and (3), they have failed to prove element (1).

Pfizer Inc. v. Teva Pharm. USA, Inc., 555 F. App'x 961, 969 (Fed. Cir. 2014); *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). If so, the Court must next consider whether it would have been obvious to move from the prior art compound to the patented compound. *See Otsuka Pharm. Co.*, 678 F.3d at 1292.

Defendants contend that a lead compound analysis (if required) would begin with a POSA's selection of compound 107e from the LeGall Thesis, as supported by the teachings of the '729 patent. (*See* OB at 20-21) The Court disagrees.

First, the record demonstrates that in March 1996, a POSA would not have selected ***any*** FAA as a lead compound. As of 1996, a POSA seeking to develop an AED would have started by looking at FDA-approved drugs or at compounds with demonstrated clinical efficacy. (FF 64) This approach would have yielded hundreds of potential starting points, none of which would have been FAAs. (*Id.*) As of March 1996, no FAA had been approved by the FDA as an AED and no FAA had been identified as a well-advanced preclinical candidate. (FF 65) In fact, the literature at the time relating to AED development does not even acknowledge FAAs.[32]

If, despite the record, a POSA were to have selected an FAA as a starting point, there is no basis to find that such a person would have selected compound 107e from the LeGall Thesis as the lead FAA compound. The LeGall Thesis contains no data pertaining to compound 107e. To the contrary, the overall thrust of the LeGall Thesis made compound 107e substantially less

[32] For example, in 1994, *Epilepsy Research* published a paper entitled "Strategies in Antiepileptic Drug Development: Is Rational Drug Design Superior to Random Screening and Structural Variation?" (JTX-91; FF 64) The paper contained a broad survey of AEDs and AED development, but did not reference or discuss FAAs. (*See generally* JTX-91) Similarly, a paper entitled "Antiepileptic Drugs: Pharmacological Mechanisms and Clinical Efficacy with Consideration of Promising Developmental Stage Compounds" described different types of AEDs, but did not discuss FAAs. (*See* FF 64)

promising than aromatic alternatives; and the appeal of compound 107e is based on its similarity to another compound (86b), which itself was not particularly promising. The fact that the LeGall Thesis speculated that compound 107e "may have good anticonvulsant activity" does not nearly amount to making 107e something a POSA would likely select as a starting point in developing an AED.

Defendants argue that if a POSA did not select 107e as a lead compound, then the POSA would have instead selected compound 31, from Kohn 1991, as its lead compound.[33] Again the Court disagrees. By 1996, nonaromatic compounds (like 31) were generally disfavored, as the bulk of the literature on FAAs showed that aromatic FAAs demonstrated better anticonvulsant activity. (*See* Roush Tr. at 576-77, 597-98; FF 88)

Even if, contrary to the evidence, a POSA would have selected a nonaromatic FAA as a lead compound, such a person would not have selected compound 31. Compound 31 is a nonaromatic FAA containing $NH(OCH_3)$ at the R_3 position. (JTX-80 at DEF_710) Compound 31 also contains an N-O bond, which is unstable and can easily be altered at physiological pH. (*See* FF 98) Because of this instability, medicinal chemists at the time avoided working with compounds that had an N-O bond. (Roush Tr. at 605)

The Court's conclusion that a POSA would not have been motivated to select compound 31 as a lead compound is corroborated by the fact that compound 31 was not seriously explored or pursued by anyone (including Dr. Kohn), despite the fact that data relating to the compound was

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[33] Defendants make this argument in one sentence of one footnote. Arguments that are presented in limited form in footnotes are entitled to little weight. *See infra* at note 36 (explaining that arguments made in footnotes are disfavored and entitled to little weight). As presented, the argument does not persuade the Court that a POSA would have chosen compound 31 as a lead compound. Nevertheless, out of an abundance of caution, the Court will address the argument in full.

published in 1991 and available to researchers. (*See* Heathcock Tr. at 187 (explaining that he did not know of any researchers who identified 3l as having structural promise)) Notably, Eli Lilly, which was working with Dr. Kohn and which had tested compound 3l, decided to focus its FAA development efforts on compounds with an aromatic group at R_3. (*See* FF 96)

Hence, Defendants' obviousness position fails at the first step of the lead compound analysis. Nonetheless, ***if*** a POSA were to have selected a nonaromatic FAA as a lead compound, and ***if*** a POSA were to have specifically selected compound 3l as her FAA of choice, Defendants have failed to prove that such a person would have been motivated to change the $NHOC_3$ of compound 3l to the CH_2OCH_3 of lacosamide. The record does not establish that a POSA contemplating such a change would have had a reasonable expectation that such a substitution would yield a promising result.

In arguing to the contrary, Defendants rely on the concept of "bioisoterism" (*see* Heathcock Tr. at 131-32), which teaches that some structures – in this case amine (–NH–) and methylene ($–CH_2–$) – "impart similar physical or chemical properties to a molecule" and are "frequently interchangeable in drugs." (*See* JTX-68 at DEF_780) Defendants argue that a POSA would have been motivated to replace the NH structure in compound 3l with a CH_2 structure. This argument is based on the fact that the structures are bioisoteric, and that comparable activity was observed when the same substitution was used to change compound 3a to compound 2a. (OB at 22 n.10)

The Court is not persuaded. A POSA could have made any of a variety of structural changes to compound 3l to affect its potency – including homologation, chain branching, and ring-chain transformations (*see* JTX-69 at DEF_807-15) – and Defendants do not explain why a POSA would have chosen bioisoterism instead of these other methods. Defendants have also not

shown that a POSA would have had a reasonable expectation of success with a bioisoterism approach. Bioisoteric substitutions can change the way a molecule interacts with biological receptors. (*See* Roush Tr. at 607-12) Because these changes are unique to each molecule and could drastically impact drug performance, a POSA would not have been able to predict the effect of a bioisoteric substitution. (*See id.* at 611-12 (explaining that bioisoteric substitutions are "really not predictable" and that any predictions about how substitution would impact drug efficacy would be "very, very tenuous at best")) Thus, a POSA would not have had a reasonable expectation of success from substituting an amine for a methylene in compound 31. Indeed, Dr. Roush identified other instances from Dr. Kohn's work in which substituting an amine with a methylene had a ***negative*** impact on drug performance. (Roush Tr. at 610-11)

Thus, Defendants have failed to meet their burden under either prong of the lead compound analysis.

iii. Objective Indicia of Obviousness Support Plaintiffs

For the reasons already given above, the Court finds that the objective indicia support a finding of nonobviousness. Specifically, Plaintiffs have demonstrated that lacosamide was met with skepticism, satisfied a long-felt but unmet need for a segment of the population suffering from refractory epilepsy, demonstrated unexpected results, received praise, and was a commercial success. Plaintiffs also demonstrated that others failed to develop safe and effective AEDs. Although not necessary in order for Plaintiffs to prevail – given the Court's findings above, that Defendants have failed to meet their burden – these objective indicia contribute to and support the Court's decision that the asserted claims are nonobvious. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986) (explaining that objective

evidence "must be considered ***before*** a conclusion on obviousness is reached and is not merely 'icing on the cake'").

C. Anticipation

Defendants contend that the LeGall Thesis anticipates claim 9 of the '551 patent. (OB at 17-19) Their argument is based on the contention that the description and/or production of a racemic mixture of compound 107e (with methoxymethyl at R_3) necessarily discloses and anticipates the enantiomers of that mixture, including the R enantiomer, which is lacosamide. (*See id.* at 18) The Court disagrees.

In *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008), the Federal Circuit held that "[t]he knowledge that enantiomers may be separated is not 'anticipation' of a specific enantiomer that has not been separated, identified, and characterized." Similarly, in *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978), the Court of Customs and Patent Appeals – a predecessor to the Federal Circuit – held that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate." Defendants' attempts to distinguish these cases are unavailing.[34]

Defendants refer the Court to a line of cases holding that a prior art disclosure of a small genus anticipates each member of that genus. (*See* OB at 18 (citing cases)) These cases do not help Defendants meet their burden to show anticipation here. Compound 107e is not a genus – it

[34] Defendants' arguments that *Sanofi* is somehow limited to its facts, and that the anticipation claim there was rejected on enablement grounds, are unsupported by a plain reading of *Sanofi* and the underlying district court opinion it affirmed. Defendants also argue that *Sanofi* is inapplicable because the prior art in this case expressed a specific preference for the R-enantiomer. But the LeGall Thesis did not express a preference for the R-enantiomer. While other prior art did disclose such a preference, anticipation must be based on a single piece of prior art. To the extent Defendants' argument is actually one of obviousness, the Court has considered and rejected their obviousness defenses.

is a mixture containing two components. Lacosamide is not a "species" or instance of compound 107e.

All that the LeGall Thesis discloses about compound 107e is that it "may have" good anticonvulsant activity, not that it does have good anticonvulsant activity. (*See* DTX-2019 at DEF_245; FF 112) This speculation – which is not supported by any actual data – is based on an analogy to compound 86b. (Roush Tr. at 602) LeGall tested compound 86b, and found that it was six times less active than furan, a heteroaromatic compound that was the most promising of the compounds disclosed by LeGall. (*Id.* at 602-03)

In fact, as Defendants' expert, Dr. Pleasure, confirmed, LeGall disclosed no efficacy data, no toxicity data, and no pharmacological data of any kind for compound 107e. (Pleasure Tr. at 303) Nor, as Dr. Pleasure admitted, does LeGall even suggest that 107e may have good pharmacokinetic properties, good safety, or minimal drug interaction. (Pleasure Tr. at 304) Nor does the LeGall Thesis disclose the R enantiomer – and the characteristics of this enantiomer were unknown in March 1996. (*See generally* DTX-2019; *see also* FF 107)[35]

Accordingly, the Court concludes that claim 9 of the '551 patent is not invalid due to anticipation.

D. Indefiniteness

Defendants contend that the claim term "therapeutic composition" is indefinite and, therefore, claim 10 of the '551 patent is invalid due to indefiniteness. "[A] patent is invalid for

[35] Further undermining Defendants' contentions is the fact that Lily was aware of compound 107e (*see* FF 169) and decided not to pursue it. Instead, consistent with the teaching of the LeGall Thesis, Lilly selected furan – a heteroaromatic, unlike 107e – as a lead compound to test. (*Id.*)

indefiniteness if its claims, read in light of the specification . . . and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc.*, 134 S. Ct. at 2124.

During the claim construction process, the parties disputed the meaning of "therapeutic composition." The Court adopted Plaintiffs' proposed construction, which was: "A composition suitable for use as a treatment regimen over an extended period of time (chronic administration)." (D.I. 240 at 5) In reaching this decision, the Court rejected Defendants' contention that Plaintiffs' construction would render claim 10 invalid for indefiniteness. Defendants' principal argument was that a POSA would not know "exactly how long" a period is required to constitute "chronic administration." (*Id.* at 11) The Court held that "Defendants ha[d] not presented clear and convincing evidence showing that claim 10 is indefinite." (*Id.*)

At trial, Defendants raised this issue again, now relying on the testimony of Dr. Pleasure. (*See* Pleasure Tr. at 289-90) Dr. Pleasure's testimony does not alter the Court's conclusion. The Court's decision at claim construction was based on the intrinsic evidence, and that evidence has not changed. Dr. Pleasure's testimony does not overcome that intrinsic record. Moreover, it is undisputed that epilepsy is a chronic condition that requires long-term treatment. (*See* FF 36, 70)

While Dr. Pleasure testified that a POSA would not "know the objective boundaries" of the "extended period of time" required by the claims (Pleasure Tr. at 289), the record is devoid of any evidence that a POSA would need "clear guidelines" or "explicit guidance" or "the upper and lower limits" in order to distinguish chronic administration from non-chronic administration. (Pleasure Tr. at 289-90) Defendants have failed to present clear and convincing evidence that a POSA would not know the scope of this claim term with "reasonable certainty." To the contrary,

the Court is persuaded that a POSA would have reasonable certainty as to what constitutes "chronic administration" in the context of claim 10 of the '551 patent.

Again, then, the Court concludes that Defendants have failed to prove that claim 10 is invalid for indefiniteness.

E. Improper Reissue

Finally, Defendants argue that the '551 patent is invalid because it was improperly reissued. In particular, Defendants contend that "[b]ecause RCT 'made a deliberate choice to forgo the earlier filing date,' 'reissue [wa]s not an available remedy' to reclaim it, and the '551 patent is thus invalid." (OB at 25) The Court disagrees.

U.S. Patent App. No. 08/818,688 (the "'688 Application"), which resulted in U.S. Patent No. 5,733,475 (the "'475 patent"), was filed on Monday, March 17, 1997. (JTX-3) U.S. Provisional App. No. 60/013,522 (the "'522 Provisional") was filed on March 15, 1996 – more than one year prior to the filing of the '688 Application. The one-year anniversary of the filing of the '522 Provisional, March 15, 1997, was a Saturday. Plaintiffs' prosecuting attorney believed that he could wait until the next business day after the one-year anniversary – that is, until Monday, March 17, 1997 – before filing the '688 Application and still claim priority to the '522 Provisional. (Cohen Tr. at 338-39) At the time, however, the law prohibited a non-provisional application from claiming priority to a provisional application filed more than 12 months earlier, even if the 12-month period expired on a weekend or holiday. *See* 37 C.F.R. § 1.78(a)(3) (1996). This prohibition stood in contrast to the general PTO rule that PTO deadlines falling on a weekend or holiday are extended to the next business day. *See* 37 C.F.R. § 1.7 (1996).

After the PTO Examiner informed the prosecuting attorney that the '688 Application could not lawfully claim priority to the '522 Provisional, the prosecuting attorney authorized withdrawing the prior claim. (Cohen Tr. at 339-40) Thereafter, in 1998, the '688 Application issued as the '475 patent. (JTX-3)

In 1999, Congress enacted the American Inventors Protection Act of 1999 ("AIPA"), which amended the pertinent filing-date requirement to read as follows: "If the day that is 12 months after the filing date of a provisional application falls on a Saturday, Sunday, or Federal holiday . . . , the period of pendency of the provisional application shall be extended to the next succeeding secular or business day." AIPA § 4801(d) (codified at 35 U.S.C. § 119(e)(3)). Congress applied this new law retroactively to encompass provisional applications filed on or after June 8, 1995, in contemplation that applicants who had previously erred would be allowed to correct their mistake. *See* AIPA § 4801(d).

On January 28, 2002, Dr. Kohn took advantage of the AIPA and filed an application for reissue of the '475 patent in order to claim priority to the '522 Provisional. (DTX-2024; Cohen Tr. at 341-42) The '551 patent issued on July 6, 2004. ('551 patent at cover)

Defendants argue that this reissue was improper because RCT, through its prosecuting attorney, agreed to surrender the original priority date. *See In re Serenkin*, 479 F.3d 1359, 1362-63 (Fed. Cir. 2007) (explaining that patent reissue to fix priority date is not allowed if patent attorney consciously surrendered correct priority date). This argument, however, fails to take into account that RCT did not intentionally surrender its priority date but, instead, was acting at the direction of the PTO Examiner, based on contemporaneous law that later changed. The AIPA, with its new, extended period for pendency of a provisional application expressly applies retroactively to provisional applications filed on or after June 8, 1995, which includes Plaintiffs'

'522 Provisional application filed on March 15, 1996. Moreover, unlike the patentee in *Serenkin*, Dr. Kohn did not seek reissue to obtain a benefit. (*See* AB at 34)

Patents may be resissued to correct or perfect a claim in priority. *See Fontjin v. Okamoto*, 518 F.2d 610, 621 (C.C.P.A. 1975). That is what occurred here, consistent with the AIPA. Accordingly, Defendants have failed to prove that the '551 patent is invalid due to improper reissue.

IV. CONCLUSION

The Court agrees with Plaintiffs' general characterization of the record:

> Vimpat® is the result of Dr. Kohn's decade long search for a safe, effective and well-tolerated AED using FAAs – a class of compounds that, when Dr. Kohn began his work, lacked any evidence of the anticonvulsant activity, low neurological toxicity, high margin of safety (PI), and minimal adverse effects, such as low toxicity, needed for an AED.

(AB at 35) Lacosamide, the result of Dr. Kohn's work, is the first – and remains, to date, the sole – FAA that has received FDA approval for treatment of epilepsy. It has helped many refractory sufferers of epilepsy and is a commercial success.

For these and the other reasons detailed throughout this Opinion, Defendants have failed to prove by clear and convincing evidence that the asserted claims of the '551 patent are invalid for obviousness-type double patenting, obviousness, anticipation, indefiniteness, or improper reissue.[36] An appropriate Order will be entered.

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[36] In addition to these defenses, Defendants reference two other invalidity positions, but only in conclusory fashion and only in footnotes. (*See* OB at 24 n.1 (arguing that '551 patent is invalid for lack of adequate written description and for lack of enablement)) Defendants do not explore these arguments in depth and do not reference them outside of the footnote in which they are introduced. Assuming, arguendo, that Defendants have adequately preserved these conclusory arguments, *but see SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1320 (Fed. Cir. 2006) (stating that arguments raised only in footnotes are not preserved); *Robocast, Inc. v. Apple Inc.*, 2014 WL 2622233, at *1 (D. Del. June 11, 2014) (explaining that arguments made in footnotes are disfavored), the Court has not been persuaded by either of them. The record does not reveal clear and convincing evidence that the asserted claims lack adequate written description or enablement. (*See* AB at 34)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB, INC., UCB BIOPHARAMA SPRL, RESEARCH CORPORATION TECHNOLOGIES, INC. and HARRIS FRC CORPORATION,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 13-1206-LPS CONSOLIDATED
ACCORD HEATLHCARE, INC., et al.,	:	
Defendants.	:	

ORDER

At Wilmington this **12th** day of August**, 2016**:

For the reasons set forth in the Memorandum Opinion issued this date,

IT IS HEREBY ORDERED that:

1. The parties shall meet and confer and submit, no later than **August 19, 2016**, a proposed order consistent with the Memorandum Opinion, to enter final judgment **FOR** Plaintiffs and **AGAINST** Defendants.

2. The parties shall, no later than **August 16, 2016**, submit a proposed redacted version of the Memorandum Opinion.

HON. LEONARD P. STARK
UNITED STATES DISTRICT COURT