IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICTOF DELAWARE

H. LUNDBECK A/S, TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS INTERNATIONAL AG and TAKEDA PHARMACEUTICALS AMERICA, INC.,	:	
Plaintiffs,	:	
v.	:	C.A. No. 18-88-LPS (CONSOLIDATED)
LUPIN LIMITED, et al.,	:	**REDACTED PUBLIC VERSION**
Defendants.	:	

Jack B. Blumenfeld, Megan E. Dellinger, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE

George F. Pappas, Einar Stole, Christopher N. Snipes, Brianna Bharkhda, Priscilla G. Dodson, Han Park, COVINGTON & BURLING LLP, Washington, DC

Megan L. Hare, Jennifer D. Cieluch, COVINGTON & BURLING LLP, New York, NY

Kurt G. Calia, Yiye Fu, COVINGTON & BURLING LLP, Palo Alto, CA

Attorneys for Plaintiffs

John C. Phillips, Jr., David A Bilson, Megan C. Haney, PHILLIPS MCLAUGHLIN & HALL, Wilmington, DE

Marc R. Wezowski, Don J. Mizerk, Matthew M. Kamps, Femi Masha, Philip D. Segrest, Jr., HUSCH BLACKWELL LLP, Chicago, IL

Thomas P. Heneghan, Stephen R. Howe, HUSCH BLACKWELL LLP, Madison, WI

Dustin L. Taylor, HUSCH BLACKWELL LLP, Denver, CO

Attorneys for Defendants Sigmapharm Laboratories, LLC

Kelly E. Farnan, Nicole Pedi, RICHARDS, LAYTON & FINGER P.A., Wilmington, DE

Bradley C. Graveline, SHEPPARD MULLIN RICHTER & HAMPTON LLP, Chicago, IL

Jesse A. Salen, Evan T. Sumner, SHEPPARD MULLIN RICHTER & HAMPTON LLP, San Diego, CA

Attorneys for Defendants Alembic Pharmaceuticals Limited, Alembic Global Holdings S/A and Alembic Pharmaceuticals, Inc.

Dominick T. Gattuso, HEYMAN ENERIO GATTUSO & HIRZEL LLC, Wilmington, DE

Laura A. Lydigsen, Mark H. Remus, Jason Schigelone, CROWELL & MORING, Chicago, IL

Jieun Lee, CROWELL & MORING, Washington, D.C.

Attorneys for Defendants Sandoz Inc. and Lek Pharmaceuticals d.d.

James M. Lennon, DEVLIN LAW FIRM LLC, Wilmington, DE

Deepro R. Mukerjee, Lance Soderstrom, KATTEN MUCHIN ROSENMAN LLP, New York, NY

Jitendra Malik, Ph.D, Joseph M. Janusz, Alissa Pacchioli, KATTEN MUCHIN ROSENMAN LLP, Charlotte, NC

Brian Sodikoff, KATTEN MUCHIN ROSENMAN LLP, Chicago, IL

Attorneys for Defendants Lupin Limited and Lupin Pharmaceuticals, Inc.

Kelly E. Farnan, Renée Mosley Delcollo, RICHARDS, LAYTON & FINGER P.A., Wilmington, DE

B. Jefferson Boggs, MERCHANT & GOULD PC, Alexandria, VA

Christopher J. Sorenson, Karen L. Beckman, MERCHANT & GOULD PC, Minneapolis, MN

Attorneys for Defendants Macleods Pharmaceuticals Ltd. and Macleods Pharma USA, Inc.

John C. Phillips, Jr., David A. Bilson, Megan C. Haney, PHILLIPS MCLAUGHLIN & HALL, Wilmington, DE

Michael J. Gaertner, David B. Abramowitz, Carolyn A. Blessing, Timothy F. Peterson, Jonathan B. Turpin, Christopher J. Cassella, August M. Melcher, LOCKE LORD LLP, Chicago, IL

Attorneys for Defendants Zydus Pharmaceuticals (USA) Inc., and Cadila Healthcare Limited

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OPINION

September 30, 2021
Wilmington, Delaware

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STARK, U.S. District Judge:

Plaintiffs H. Lundbeck A/S ("Lundbeck"), Takeda Pharmaceutical Company Ltd., Takeda Pharmaceuticals International AG, Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc (collectively "Plaintiffs") sued 16 sets of defendants in this consolidated action brought pursuant to the Hatch-Waxman Act, 35 U.S.C. § 271(e). (*See* D.I. 985 Ex. 1 (Joint Statement of Uncontested Facts) ("SF") ¶ 37)) Six sets of defendants proceeded to trial: (1) Alembic Pharmaceuticals Limited, Alembic Global Holding S/A, and Alembic Pharmaceuticals, Inc. (collectively, "Alembic"); (2) Lupin Limited and Lupin Pharmaceuticals, Inc. (collectively, "Lupin"); (3) Macleods Pharmaceuticals Ltd. and Macleods Pharma USA, Inc. (collectively "Macleods"); (4) Sandoz Inc., Sandoz AG, and Lek Pharmaceuticals D.D. (collectively "Sandoz"); (5) Sigmapharm Laboratories, LLC ("Sigmapharm"); and (6) Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd. (collectively "Zydus").[1] Each of the remaining defendants seeks to market its own generic version of Plaintiffs' Trintellix® tablets ("Trintellix") prior to the expiration of certain patents Plaintiffs contend cover Trintellix. (*See* SF ¶ 35)

Lundbeck is the assignee and owner of the eight Patents-in-Suit: U.S. Patent Nos.

[1] The other defendants, all of whom have entered into consent judgments, were: (1) Alkem Labs. Ltd. and S&B Pharma, Inc.; (2) Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals Pvt. Ltd., Amneal Pharmaceuticals Company GmbH, Amneal Pharmaceuticals of New York, LLC, and Raks Pharma Private Limited; (3) Apicore US LLC; (4) Apotex Inc., Apotex Corp., and Apotex Research Private Limited; (5) Cipla Limited and Cipla USA Inc.; (6) Hetero USA INC., Hetero Labs Limited, and Hetero Labs Limited Unit-V; (7) MSN Private Laboratories Limited, MSN Pharmaceuticals, Inc., and MSN Pharmachem Private Limited; (8) Prinston Pharmaceutical Inc., Zhejiang Huahai Pharmaceutical Co., Ltd. and Solco Healthcare US, LLC; (9) Torrent Pharmaceuticals Limited and Torrent Pharma Inc.; and (10) Unichem Laboratories, Limited. (*See* SF ¶¶ 42, 43; D.I. 995)

7,144,884 ("the '884 Patent"), 8,476,279 ("the '279 Patent"), No. 8,722,684 ("the '684 Patent"), 9,861,630 ("the '630 Patent"), 9,101,626 ("the '626 Patent"), 9,090,575 ("the '575 Patent"), 9,278,096 ("the '096 Patent), and 9,125,910 ("the '910 Patent") (collectively, the "Patents in Suit"). (SF ¶ 27) Just as the parties have done, the Court will categorize the Patents-in-Suit as follows:

(a) the '884 and '279 Patents are the "Compound Patents;"

(b) the '684 and '630 Patents are the "Crystalline Form Patents;"

(c) the '626 and '575 Patents are the "Process Patents;"

(d) the '096 Patent is the "Sexual Dysfunction Method of Treatment Patent" or "Sexual Dysfunction Patent;" and

(e) the '910 Patent is the "Cognitive Impairment Method of Treatment Patent" or "Cognitive Impairment Patent."

Not all of the Patents-in-Suit are asserted against all six defendants. Of those claims that are asserted, some defendants contest infringement while others concede infringement. One or more defendants challenge the validity of many asserted of the claims but not of all of them. The status of the parties' remaining disputes with respect to each of the Patents-in-Suit (corresponding to the five categories above) is summarized below:[2]

(1) Alembic:[3] (b) Plaintiffs assert Claims 1, 2, and 3 of the '684 Crystalline

[2] This listing is based on the Court's understanding of the parties' current, post-trial positions. Every issue that is listed here as disputed was the subject of evidence and argument at trial. Some issues that were disputed at certain points during the trial are no longer contested and do not need to be resolved by the Court; they are not listed here nor discussed in this Opinion.

[3] Alembic submitted Paragraph III Certifications for the Compound Patents, indicating that it does not seek approval from the U.S. Food and Drug Administration ("FDA") to market its proposed drug prior to the expiration of those patents. (D.I. 985 Ex. 1A ¶ 30; *see also* 21 U.S.C.

Form Patent and Claims 5, 6, and 7 of the ’630 Crystalline Form Patent against Alembic.

(d) Plaintiffs assert Claims 4, 5, and 7 of the Sexual Dysfunction Patent against Alembic. Like all Defendants, Alembic contends the asserted claims of the Sexual Dysfunction Patent are invalid due to anticipation, obviousness, and lack of adequate written description.

(e) Plaintiffs assert Claim 6 of the Cognitive Impairment Patent against Alembic. Alembic contends this claim of the ’910 Patent is invalid due to anticipation and obviousness.

(2) Lupin: (b) Plaintiffs assert Claims 1, 2, and 3 of the ’684 Crystalline Form Patent and Claims 2, 3, 4, 5, 6, and 7 of the ’630 Crystalline Form Patent against Lupin.

(c) Plaintiffs assert Claim 12 of the ’626 Process Patent against Lupin.

(d) Plaintiffs assert Claims 4, 5, and 7 of the Sexual Dysfunction Patent against Lupin. Like all Defendants, Lupin contends the asserted claims of the Sexual Dysfunction Patent are invalid due to anticipation, obviousness, and lack of adequate written description.

(e) Plaintiffs assert Claim 6 of the Cognitive Impairment Patent against Lupin. Lupin contends this claim of the ’910 Patent is invalid due to anticipation and obviousness.

(3) Macleods:[4] (b) Plaintiffs assert Claim 1 of the ’684 Crystalline Form Patent

§ 505(j)(2)(A)(iii))

[4] Macleods submitted Paragraph III Certifications for the Compound Patents. (D.I. 985 Ex. 1D ¶ 62)

and Claims 2, 3, and 4 of the '630 Crystalline Form Patent against Macleods.

(d) Plaintiffs assert Claim 7 of the Sexual Dysfunction Patent against Macleods. Like all Defendants, Macleods contends the asserted claims of the Sexual Dysfunction Patent are invalid due to anticipation, obviousness, and lack of adequate written description.

(e) Plaintiffs assert Claim 6 of the Cognitive Impairment Patent against Macleods. Macleods contends this claim of the '910 Patent is invalid due to anticipation and obviousness.

(4) Sandoz:[5] (d) Plaintiffs assert Claim 7 of the Sexual Dysfunction Patent against Sandoz. Like all Defendants, Sandoz contends the asserted claims of the Sexual Dysfunction Patent are invalid due to anticipation, obviousness, and lack of adequate written description.

(5) Sigmapharm:[6] (a) Sigmapharm contends the asserted claims of the Compound Patents are invalid due to obviousness.

(b) Plaintiffs assert Claims 1, 2, and 3 of the '684 Crystalline Form Patent and Claims 2, 3, 4, 5, 6, and 7 of the '630 Crystalline Form Patent against Sigmapharm.

(d) Plaintiffs assert Claims 4, 5 and 7 of the Sexual Dysfunction

[5] All claims and counterclaims between Plaintiffs and Sandoz with respect to the Crystalline Form Patents and Cognitive Impairment Patent have been dismissed with prejudice. (D.I. 813, 814, 991) With respect to the Sexual Dysfunction Patent, the parties' disputes relating to Claims 4 and 5 have been dismissed without prejudice. (D.I. 958)

[6] Sigmapharm admits infringement of claims 1-12 and 17 of the '884 Compound Patent and claims 1-5 and 12-15 of the '279 Compound Patent under 35 U.S.C. § 271(a), (b), and/or (c). (D.I. 985 Ex. 1G ¶ 30)

Patent against Sigmapharm. Like all Defendants, Sigmapharm contends the asserted claims of the Sexual Dysfunction Patent are invalid due to anticipation, obviousness, and lack of adequate written description.

(e) Plaintiffs assert Claim 6 of the Cognitive Impairment Patent against Sigmapharm. Sigmapharm contends this claim of the '910 Patent is invalid due to anticipation and obviousness.

(6) Zydus:[7] (a) Zydus contends the asserted claims of the Compound Patents are invalid due to obviousness.

(b) Plaintiffs assert Claim 1 of the '684 Crystalline Form Patent and Claims 8, 9, and 10 of the '630 Crystalline Form Patent against Zydus.

(c) Plaintiffs assert Claim 3 of the '575 Process Patent against Zydus. Zydus contends that this claim is invalid due to obviousness.

(d) Plaintiffs assert Claim 7 of the Sexual Dysfunction Patent against Zydus. Like all Defendants, Zydus contends the asserted claims of the Sexual Dysfunction Patent are invalid due to anticipation, obviousness, and lack of adequate written description.

(e) Plaintiffs assert Claim 6 of the Cognitive Impairment Patent against Zydus. Zydus contends this claim of the '910 Patent is invalid due to anticipation and obviousness.

In January 2021, the Court held a ten-day remote bench trial using videoconferencing

[7] Zydus admits infringement of Claim 17 of the '884 Compound Patent, Claims 5 and 15 of the '279 Compound Patent, and Claim 3 of the '575 Process Patent under 35 U.S.C. § 271(a), (b), (c), and/or (e)(2). (D.I. 985 Ex. 1J ¶¶ 65-66)

technology. (*See* D.I. 1020-39) ("Tr.") Thereafter, the parties submitted post-trial briefing (D.I. 1057, 1047, 1054, 1011, 1059, 1052) and proposed findings of fact (D.I. 1056, 1046, 1053, 1058).

Pursuant to Federal Rule of Civil Procedure 52(a), and having considered the entire record in this case and the applicable law, the Court concludes that:

(1) Defendants Sigmapharm and Zydus have failed to prove that the asserted clams of the Compound Patents are invalid due to obviousness;

(2) Plaintiffs have failed to prove that Alembic's, Lupin's, Macleods', Sigmapharm's, or Zydus' ANDA Products will infringe any asserted claim of the '684 or '630 Crystalline Form Patents;

(3) Plaintiffs have proven that Lupin's ANDA Product will infringe Claim 12 of the '626 Process Patent;

(4) Zydus has failed to prove that Claim 3 of the '575 Process Patent is invalid due to obviousness;

(5) Plaintiffs have failed to prove that any of Defendants' ANDA Products will induce or contribute to infringement of Claims 4, 5, and/or 7 of the '096 Sexual Dysfunction Patent;

(6) Defendants have failed to prove that any of the challenged claims of the '096 Sexual Dysfunction Patent are invalid due to anticipation, obviousness, or lack of adequate written description;

(7) Plaintiffs have failed to prove that Alembic's, Lupin's, Macleods', Sigmapharm's, or Zydus' ANDA Product will contribute to infringement of Claim 6 of the Cognitive Impairment Patent; and

(8) Alembic, Lupin, Macleods, Sigmapharm, and Zydus have failed to prove that Claim 6 of the '910 Cognitive Impairment Patent is invalid due to anticipation or obviousness.

The Court's findings of fact and conclusions of law are set forth in detail below.

FINDINGS OF FACT

This section contains the Court's findings of fact ("FF") on disputes raised by the parties during trial, as well as the facts stipulated to by the parties. (*See* SF) Additional findings of fact are also provided in connection with the Court's conclusions of law later in this Opinion.

I. Introduction

1. Prior to Plaintiffs initiating this action, each of the Defendants notified Plaintiffs that it had filed an Abbreviated New Drug Application ("ANDA") with certifications under Section 505(j)(2)(A)(vii)(IV) of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certifications"), seeking approval from the United States Food and Drug Administration ("FDA") to market generic versions of Trintellix® tablets. (SF ¶ 35)

2. Lundbeck has granted Takeda Japan an exclusive license to the '884, '279, '684, '630, '626, '575, '096, and '910 Patents-in-Suit in connection with the use, importation, distribution, marketing, promotion and sale of Trintellix® in the United States. (SF ¶ 28) Lundbeck has further granted Takeda Japan an exclusive license to U.S. Patent Nos. 8,969,355 ("'355 Patent") and 9,227,946 ("'946 Patent), which were previously asserted against certain Defendants. (*Id.* ¶¶ 25, 28, 36-37, 71-72; *see also* D.I. 988 ("The parties are in agreement and respectfully suggest that the disposition of all claims and counterclaims regarding the '355 and '946 patents can be made by the Court in the Final Judgment Order entered at the conclusion of this case by a simple dismissal with prejudice."))

3. Takeda International has an exclusive sublicense to the ’279, ’684, ’630, ’626, ’575, ’096, and ’910 Patents-in-Suit, and to the ’355 and ’946 Patents, in connection with the commercialization of Trintellix® in the United States. (SF ¶ 29)

4. Takeda USA has an exclusive sublicense to the ’279, ’684,’630, ’626, ’575, ’096, and ’910 Patents-in-Suit, and to the ’355 and ’946 Patents, from Takeda International, which grants it the right to import, distribute, and sell Trintellix® in the United States. (SF ¶ 30)

5. On September 30, 2013, the FDA approved Takeda USA’s New Drug Application (“NDA”) No. 204447 for Trintellix (originally called “Brintellix”) 5 mg, 10 mg, 15 mg, and 20 mg tablets. (SF ¶¶ 31-32) Trintellix’s sole indication is for the treatment of Major Depressive Disorder (“MDD”) in adults. (SF ¶ 68) Trintellix is currently available in the U.S. in 5 mg, 10 mg, and 20 mg strength tablets. (SF ¶ 69)

6. The ’884, ’279, ’684, ’630, ’096, and ’910 Patents-in-Suit – as well as the ’355 and ’946 Patents – are listed in the FDA Publication, “Approved Drug Products with Therapeutic Equivalence Evaluations,” also known as the “Orange Book,” in connection with NDA No. 204447. (SF ¶ 34)

7. No defendant has submitted a Paragraph IV certification regarding the method of treatment (’096 and ’910) patents. (*See* SF ¶ 41)

8. Alembic submitted a Patent Certification and Statement pursuant to 21 C.F.R. § 314.94(a)(12)(viii)(C)(1)(ii) for the ’096 Patent and ’910 Patent. (D.I. 985 Ex. 1A ¶ 30)

9. Lupin submitted ANDA No. 211105 with statements pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) with respect to the ’096 and ’910 Patents. (D.I. 841 at 30 ¶ 28)

10. Macleods submitted a Patent Certification and Statement Pursuant to 21 C.F.R.

§ 314.94(a)(12)(viii)(C)(1)(ii) and 21 U.S.C. § 355(j)(2)(A)(viii) for the '096 Patent and '910 Patent. (D.I. 985 Ex. 1D ¶¶ 63, 79)

11. Sandoz submitted statements pursuant to 21 C.F.R. § 314.94(a)(12)(iii)(A) and 21 U.S.C. § 355(j)(2)(A)(viii) for the '096 Patent. (D.I. 910-1 at 8)

12. Sigmapharm submitted ANDA No. 211084 under 21 U.S.C. § 355(j) for the '096 and '910 Patents. (D.I. 831 at 13 ¶ 58)

13. Zydus submitted ANDA No. 211146 with statements pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) for the '096 and '910 Patents. (D.I. 855 at 13 ¶ 53)

14. Pursuant to 21 U.S.C. § 505(j)(2)(A)(viii), all Defendants have omitted, or "carved out," all of the comparative information related to the method of use claimed in the '096 Patent from their proposed prescribing information, i.e., the subpart of Section 14 of the Trintellix® Prescribing Information that summarizes clinical data related to the '096 Patent and a one-sentence cross-reference to that data in Section 6.1. (*Compare* PTX-4475 at 9, 26-28 *with, e.g.,* PTX-4363 at 10, 28 (Sigmapharm); PTX-4565 at 8, 24 (Lupin); PTX-4566 at 9, 21 (Macleods); PTX-4567 at 12, 29 (Alembic); DTX-1169 at 8, 21 (Sandoz); DTX-1933 at 11, 30 (Zydus))[8]

15. After receiving the Paragraph IV notifications, Plaintiffs filed complaints for patent infringement, alleging that Defendants' submission of ANDAs seeking FDA approval for generic versions of Trintellix® tablets before the expiration of the patents listed in the Orange Book constitutes patent infringement under 35 U.S.C. § 271(e)(2), and further alleging that if

[8] Documents admitted into evidence at trial are cited as "PTX" for Plaintiffs' exhibits and "DTX" for Defendants' exhibits.

Defendants were to commercially use, offer for sale, or sell their generic versions of Trintellix®, or induce or contribute to such conduct, it would further infringe the Patents-in-Suit under 35 U.S.C. § 271(a), (b), and/or (c). (*See* SF ¶ 36)

16. On May 29, 2019, the Court granted Plaintiffs' Motion for Leave To File Amended Complaints to add counts for infringement of various additional patents related to Trintellix®, including allegations that certain defendants will contribute to infringement of the method of treatment ('096 and '910) patents, pursuant to 35 U.S.C. § 271(c), and seeking a declaratory judgment consistent with these claims, pursuant to 28 U.S.C. §§ 2201 and 2202. (SF ¶ 39)

17. On June 25, 2020, the Court granted Plaintiffs' Motion for Leave To File Amended Complaints to add allegations that certain defendants will induce infringement of the '096 Patent, pursuant to 35 U.S.C. § 271(b). (SF ¶ 40)

II. Major Depressive Disorder

18. Major depressive disorder ("MDD") is a neuropsychiatric condition, which is associated with significant functional impairment in social, occupational, or other areas of daily life. (SF ¶ 44)

19. The American Psychiatric Association Diagnostic and Statistical Manual ("DSM") diagnostic criteria for MDD require that an individual experiences five or more of nine delineated symptoms during the same two-week period, with at least one of the symptoms being depressed mood or loss of interest or pleasure. (SF ¶ 45)

20. Pharmacologic treatment of MDD began in the 1950s and focused on two different classes of compounds: tricylic antidepressants ("TCAs") and monoamine oxidase inhibitors ("MAOIs"). (SF ¶ 48) More recently, other classes of compounds have been

developed for treatment of MDD, including selective serotonin reuptake inhibitors ("SSRIs"), serotonin norepinephrine reuptake inhibitors ("SNRIs"), and selective norepinephrine reuptake inhibitors ("NRIs" or "sNRIs").

21. ***Tricyclic Antidepressants ("TCAs") and Tetracyclic Antidepressants ("TeCAs").*** TCAs are thought to work, in part, by blocking the reuptake of serotonin and norepinephrine, which in turn, increases synaptic levels of norepinephrine and serotonin. Increased synaptic levels of norepinephrine and serotonin are believed to result in increased stimulation of postsynaptic serotonin and norepinephrine receptors. (SF ¶ 49) TeCAs are thought to work, in part, by increasing the release of serotonin and norepinephrine from nerve cell terminals, thereby resulting in increased norepinephrine and serotonin synaptic levels and increased post-synaptic stimulation of norepinephrine and serotonin receptors. (SF ¶ 59)

22. Examples of TCAs include amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine. (SF ¶ 50) Examples of a TeCAs include mianserin and mirtazapine. (SF ¶ 59; DTX-259)

23. ***Monoamine Oxidase Inhibitors ("MAOIs").*** MAOIs are thought to work, in part, by blocking the monoamine oxidase enzyme, which degrades serotonin, norepinephrine, and dopamine. By inhibiting the monoamine oxidase enzyme, MAOIs are believed to decrease the breakdown of serotonin, norepinephrine, and dopamine, thereby increasing synaptic levels of those neurotransmitters and increasing stimulation of postsynaptic serotonin, norepinephrine, and dopamine receptors. (SF ¶ 51)

24. Examples of MAOIs include phenelzine, tranylcypromine, and isocarboxazid. (SF ¶ 52)

25. ***Selective Serotonin Reuptake Inhibitors ("SSRIs").*** Selective serotonin reuptake inhibitors ("SSRIs") are thought to work, in part, by inhibiting the serotonin reuptake transporter, thereby increasing synaptic levels of serotonin and increasing stimulation of postsynaptic serotonin receptors. (SF ¶ 53)

26. Approved SSRIs include fluoxetine (Prozac®) (approved December 1987), sertraline (Zoloft®) (approved December 1991), paroxetine (Paxil®) (approved December 1992), citalopram (Celexa®) (approved July 1998), and escitalopram (Lexapro®) (approved August 2002). (SF ¶ 54)

27. ***Serotonin Norepinephrine Reuptake Inhibitors ("SNRIs").*** Noradrenaline/serotonin reuptake inhibitors, also known as serotonin norepinephrine reuptake inhibitors ("SNRIs"), are thought to work, in part, by blocking the reuptake of serotonin and norepinephrine (also known as noradrenaline), thereby ultimately increasing postsynaptic stimulation of serotonin and norepinephrine receptors. (SF ¶ 55)

28. SNRIs are also known and referred to as noradrenaline/serotonin reuptake inhibitors. (SF ¶ 56)

29. Approved SNRIs include venlafaxine (Effexor®) (approved December 1993), desvenlafaxine (Pristiq®) (approved February 2008), and duloxetine (Cymbalta®) (approved August 2004). (SF ¶ 57)

30. ***Selective Norepinephrine Reuptake Inhibitors ("NRIs" or "sNRIs").*** Selective noradrenaline reuptake inhibitors, also known as selective norepinephrine reuptake inhibitors ("NRIs" or "sNRIs"), such as reboxetine (Edronax®), are thought to work, in part, by blocking the reuptake of norepinephrine, thereby ultimately increasing postsynaptic stimulation of

norepinephrine receptors. (SF ¶ 58)

31. Other antidepressants not belonging to one of the categories above include bupropion (Wellbutrin®) (approved December 1985) and nefazodone (Serzone®) (approved December 1994). (SF ¶ 60)

32. Bupropion is believed to be a norepinephrine dopamine reuptake inhibitor. (SF ¶ 61)

33. Prior to 2007, SSRIs, SNRIs, and TCAs were associated with high incidents of sexually related adverse events. (Mattingly Tr. 839-40, 846, 861; Clayton Tr. 1086; Rothschild Tr. 1713)[9]

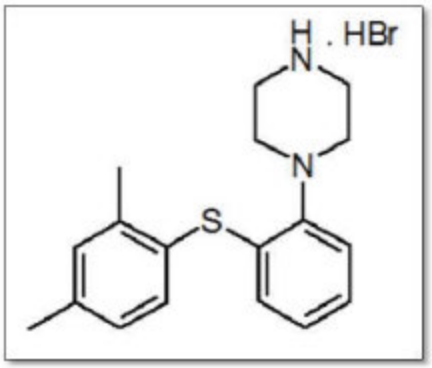
34. Prior to 2006, cognitive function was known to be impaired in some patients with depression. (SF ¶ 62)

III. Plaintiffs' Trintellix® Product

35. Trintellix® is an immediate-release tablet for oral administration that contains the beta (β) polymorph of vortioxetine hydrobromide (HBr). (SF ¶ 63)

36. Vortioxetine HBr is known chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl) phenyl]-piperazine, hydrobromide. The structural formula is:

[9] Citations to trial testimony are in the form: "Tr. [Witness Last Name] [Page]."



(SF ¶ 64)

37. Trintellix® is indicated solely for the treatment of major depressive disorder ("MDD") in adults. Trintellix® has had this single indication since its approval in September 2013. (SF ¶ 68)

38. Trintellix® is currently available in the United States as 5 mg, 10 mg, and 20 mg strength tablets. (SF ¶ 69)

39. Trintellix® is a commercial embodiment of Claims 2 and 3 of the '684 Patent. (SF ¶ 70)

40. The use of Trintellix in accordance with its FDA-approved label is a commercial embodiment of Claims 5, 6, and 7 of the '630 Patent. (SF ¶ 71)

IV. The Patents-In-Suit And Asserted Claims

A. The '884 And '279 Compound Patents[10]

41. Plaintiffs have asserted claims of the '884 and '279 Compound Patents against Sigmapharm and Zydus in this litigation. (SF ¶¶ 78, 92)

[10] Because the '884 and '279 Compound Patents are only asserted against Sigmapharm and Zydus, "Defendants" in relation to the Compound Patents refers to the Sigmapharm and Zydus defendants.

42. Plaintiffs own all rights, title, and interest in and to the Compound Patents. (SF ¶¶ 79, 93)

43. The Compound Patents are directed to, among other things, the compound 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine and methods for using the compound to treat affective disorders, including depression. (SF ¶¶ 72)

44. The '884 Patent is entitled "Phenyl-Piperazine Derivatives as Serotonin Reuptake Inhibitors" and issued on December 5, 2006, to Thomas Ruhland, Garrick Paul Smith, Benny Bang-Andersen, Ask Puschl, Ejner Knud Moltzen, and Kim Andersen. (SF ¶¶ 80, 84, 87)

45. The '884 Patent issued from U.S. Application Serial No. 10/488,280, which was filed as Application No. PCT/DK02/00659 on October 2, 2002. (SF ¶ 83) On its face, the '884 Patent claims priority to Danish Application No. 2001 01466, which was filed on October 4, 2001. (SF ¶ 86) The expiration date of the '884 Patent listed in the Orange Book is June 17, 2026. (SF ¶ 85)

46. The asserted claims '884 Patent recite as follows:

> 5. A compound selected from the group consisting of
>
> 1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl]piperazine,
> 1-[2-(4-Bromophenylsulfanyl)phenyl]piperazine,
> 1-{2-[4-(Methylsulfanyl)phenylsulfanyl]phenyl}piperazine,
> 1-[2-(4-Hydroxyphenylsulfanyl]phenyl]piperazine,
> 1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine,
> 1-[2-(3,5-Dimethylphenylsulfanyl)phenyl]piperazine,
> 1-[2-(2,6-Dimethylphenylsulfanyl)phenyl]piperazine,
> 1-[2-(2,5-Dimethylphenylsulfanyl)phenyl]piperazine,
> 2-(4-Methylphenylsulfanyl)phenyl-1-piperazine,
> 1-[2-(4-Chlorophenylsulfanyl)phenyl]-piperazine,
> 1-[2-(4-Methoxyphenylsulfanyl)-4-chlorophenyl]piperazine,
> 1-[2-(4-Methoxyphenylsulfanyl)-4-methylphenyl]piperazine,
> 1-[2-(4-Methoxyphenylsulfanyl)-5-methylphenyl]piperazine,
> 1-[2-(4-Fluorophenylsulfanyl)-5-methylphenyl]piperazine,

1-[2-(4-Methoxyphenylsulfanyl)-5
trifluoromethylphenyl]piperazine,
1-[2-(4-Chlorophenylsulfanyl)phenyl]-3-methylpiperazine and
1-[2-(4-Chlorophenylsulfanyl)phenyl]-3,5-dimethylpiperazine;
or a pharmaceutically acceptable acid addition salt thereof.

17. The compound according to claim 5, wherein the compound is

1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine, or a
pharmaceutically acceptable acid addition salt thereof.

(SF ¶¶ 90-91)

47. The '279 Patent is entitled "Phenyl-Piperazine Derivatives as Serotonin Reuptake Inhibitors" and issued on July 2, 2013 to Benny Bang-Andersen. (SF ¶¶ 94, 102; *see also* D.I. 1053 ¶ 9)

48. The '279 Patent issued from U.S. Application Serial No. 13/367,065, which was filed on February 6, 2012. (SF ¶ 97) U.S. Application Serial No. 13/367,065 is a division of Application No. 12/700,521, filed on February 4, 2010, now U.S. Patent No. 8,110,567, which is a division of Application No. 11/551,188, filed on October 19, 2006, now U.S. Patent No. 7,683,053, which is a continuation of Application No. 10/488,280, filed as Application No. PCT/DK02/00659 on October 2, 2002, now U.S. Patent No. 7,144,884. (SF ¶ 98) On its face, the '279 Patent claims priority to Danish Application No. 2001 01466, which was filed on October 4, 2001. (SF ¶ 101) The expiration date of the '279 Patent listed in the Orange Book is October 2, 2022. (SF ¶ 100)

49. Certain claims of the '279 Patent are reproduced below:

1. A pharmaceutical composition comprising the compound 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable acid addition salt thereof, and at least one pharmaceutically acceptable carrier or diluent.

> 2. A method for the treatment of an affective disorder in an animal, comprising administering to said animal an amount of the composition of claim 1 comprising a therapeutically effective amount of said compound.
>
> 4. The method of claim 2 wherein said affective disorder is depression.
>
> 5. The method of claim 4 wherein said animal is a human.
>
> 12. A method for the treatment of an affective disorder in an animal, comprising administering a therapeutically effective amount of the compound 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutically acceptable acid addition salt thereof to said animal.
>
> 14. The method of claim 12 wherein said affective disorder is depression.
>
> 15. The method of claim 14 wherein said animal is a human.

(SF ¶¶ 105-11)

50. Sigmapharm admits infringement of Claims 1-12 and 17 of the '884 Compound Patent and Claims 1-5 and 12-15 of the '279 Compound Patent. (D.I. 985 Ex. 1G ¶ 30)

51. Zydus admits infringement of claim 17 of the '884 Compound Patent and Claims 5 and 15 of the '279 Compound Patent. (D.I. 985 Ex. 1J ¶¶ 65-66)

B. The '684 And '630 Crystalline Form Patents

52. Plaintiffs have asserted claims of the '684 and '630 Patents, the "Crystalline Form Patents," against Alembic, Lupin, Macleods, Sigmapharm, and Zydus. (SF ¶ 131)

53. Both of the Crystalline Form Patents are entitled "1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine as a compound with combined serotonin reuptake, 5-HT3 and 5-HT1A activity for the treatment of cognitive impairment" and they share nearly identical specifications. (SF ¶ 137)

54. Plaintiffs own all rights, title, and interest in the Crystalline Form Patents. (SF ¶ 134)

55. The Crystalline Form Patents are directed to, among other things, crystalline forms of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, including the alpha (α), beta (β), and gamma (γ) forms. (SF ¶ 73)

56. The Crystalline Form Patents are also directed to 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, which is vortioxetine, and pharmaceutically acceptable salts thereof. (SF ¶ 132)

57. Certain claims of the '684 Patent recite:

> 1. Compound l-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine or a pharmaceutically acceptable salt thereof in a crystalline form characterized by an XRPD pattern as shown in any of FIGS. 1-17.
>
> 2. Compound 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobomide salt in a crystalline form which is characterized by XRPD reflections at 6.89, 9.73, 13.78 and 14.64 ± 0.10° 2θ.

(SF ¶¶ 163-64)

58. Certain claims of the '630 Patent are recited below:

> 1. A method of alleviating a symptom or complication of depression or major depressive disorder, or delaying progression of depression or major depressive disorder, comprising: administering to a patient in need thereof a pharmaceutical composition comprising a hydrobromide salt of a l-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine selected from the group consisting of l-[2-(2,4-dimethylphenylsulfany1)-phenyl]piperazine hydrobromide salt alpha form, l-[2-(2,4-dimethylphenylsulfany1)-phenyl]piperazine hydrobromide salt beta form, l-[2-(2,4-dimethylphenylsulfany1)-phenyl]piperazine hydrobromide salt gamma form, l-[2-(2,4-dimethylphenylsulfany1)-phenyl]piperazine hydrobromide salt

hemihydrate, l-[2-(2,4-dimethylphenylsulfany1)-phenyl]piperazine hydrobromide salt ethyl acetate solvate, and mixtures thereof, wherein said method alleviates a symptom or complication of depression or major depressive disorder, or delays the progression of depression or major depressive disorder, in said patient.

2. The method of claim 1, wherein said hydrobromide salt of 1-[2(2,4-dimethylphenyl sulfanyl)-phenyl]piperazine hydrobromide is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt alpha form.

3. The method of claim 2, wherein the hydrobromide salt of 1-[2-(2,4-dimethylphenyl sulfanyl)-phenyl]piperazine hydrobromide is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt alpha form characterized by an XRPD pattern as shown in FIG. 2.

4. The method of claim 2, wherein the 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt alpha form is characterized by XRPD peaks at 5.85, 9.30, 17.49, and 18.58+/-0.10° 2θ.

5. The method of claim 1, wherein said hydrobromide salt of 1-[2-(2,4-dimethylphenyl sulfanyl)-phenyl]piperazine is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt beta form.

6. The method of claim 5, wherein the hydrobromide salt of 1-[2-(2,4-dimethylphenyl sulfanyl)-phenyl]piperazine is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt beta form characterized by an XRPD pattern as shown in FIG. 3.

7. The method of claim 5, wherein the 1-[2-(2,4-dimethylphenyl sulfanyl)-phenyl]piperazine hydrobromide salt beta form is characterized by XRPD peaks at 6.89, 9.73, 13.78, and 14.62 +/-0.10° 2θ.

8. The method of claim 1, wherein said hydrobromide salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt gamma form.

9. The method of claim 8, wherein said hydrobromide salt of 1-[2- (2,4-dimethylphenylsulfanyl)-phenyl]piperazine

> hydrobromide is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt gamma form characterized by an XRPD pattern as shown in FIG. 4.
>
> 10. The method of claim 8, wherein the 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt gamma form is characterized by XRPD peaks at 11.82, 16.01, 17.22, and 18.84 +/-0.10° 2θ.

(SF ¶¶ 167-76)

59. The Court construed the term "characterized by an XRPD [pattern] as shown in [any of] FIG[S] . . .," as used in the asserted claims of the Crystalline Patents, to mean "identifiable by reference to an x-ray powder diffraction pattern as shown in [any of] FIG[S]." (SF ¶ 155)

60. The Court construed the term "1-[2[(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt [alpha, form, beta form, gamma form]," as used in the '630 Patent, to mean "vortioxetine hydrobromide salt crystalline form described in the specification as the [alpha / beta / gamma] form and being identifiable by reference to the [alpha / beta / gamma] form in the specification." (SF ¶ 156)

61. The Court construed the term "1-[2[(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt [hemihydrate / ethyl acetate solvate]," as used in the '630 Patent, to mean "a [hemihydrated crystalline form / crystalline ethyl acetate solvate] of vortioxetine hydrobromide, referred to in the patent specification as ['hemihydrate' / 'ethyl acetate solvate'], that can be distinguished from other forms." (SF ¶ 157)

62. The Court construed the term "alleviates / alleviating," as used in the '630 Patent, to mean "mitigates / mitigating." (SF ¶ 158)

63. The Court construed the term "mixtures thereof," as used in the '630 Patent, to

mean "mixtures of only the foregoing listed forms." (SF ¶ 159)

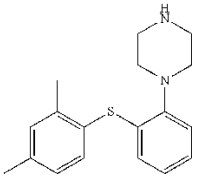
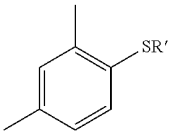
C. The '626 And '575 Process Patents

64. Plaintiffs own all rights, title, and interest in and to the Process Patents. (SF ¶ 112)

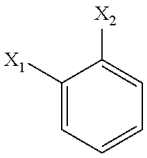
65. The '626 Patent is entitled "Process for Preparing 1-[2-(2,4 dimethylphenylsulfanyl)-phenyl]piperazine or Pharmaceutically Acceptable Salt Thereof." (SF ¶ 113)

66. The '626 Patent is directed to, among other things, processes for synthesizing 1-[2 (2,4-dimethylphenylsulfanyl)phenyl]piperazine or a pharmaceutical acceptable salt thereof. (SF ¶ 74)

67. Certain claims of the '626 Patent recite:

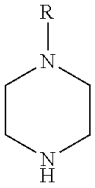
> 1. A process for the preparation of
>
> 
>
> or a pharmaceutically salt thereof, the process comprising reacting compound II
>
> [II]
>
> 
>
> wherein R′ represent hydrogen or a mono-valent metal ion, with a compound of formula III

[III]



wherein X1 and X2 independently represent halogen, and a compound

[IV]



wherein R represent hydrogen or a protecting group, in the presence of a solvent, a base and a palladium catalyst consisting of a palladium source and a phosphine ligand at a temperature between 60° C. and 130° C.

11. The process according to claim 1, wherein said phosphine ligand is selected from the group consisting of 2,2′-bis-diphenylphosphanyl-[1,1′]binaphtalenyl(rac-BINAP), 1,1′-bis(diphenylphosphino)ferrocene (DPPF), bis-(2-diphenylphosphinophenyl)ether (DPEphos), tri-t-butyl phosphine (Fu's salt), biphenyl-2-yl-di-t-butyl-phosphine, biphenyl-2-yl-dicyclohexyl-phosphine, (2′-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethyl-amine, [2′-(di-t-butyl-phosphanyl)-biphenyl-2-yl]-dimethyl-amine, and dicyclohexyl-(2′,4′,6′-tri-propyl-biphenyl-2-yl)-phosphane

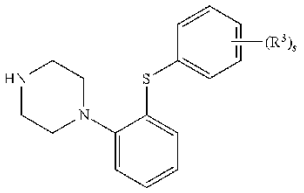
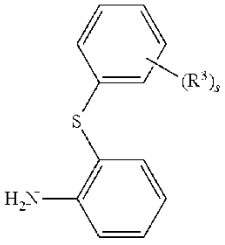
12. The process according to claim 11, wherein said phosphine ligand is rac-BINAP.

68. The ’575 Patent is entitled “Phenyl-Piperazine Derivatives as Serotonin Reuptake Inhibitors.”

69. The ’575 Patent is directed to, among other things, processes for synthesizing a class of compounds that includes 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine or acid addition salts thereof, by reacting a phenylthioaniline compound with an alkylating agent of

either bis(2-chloroethyl)amine or bis(2-bromoethyl)amine to synthesize a piperazine moiety on the phenylthioanaline compound. (SF ¶ 75)

70. Certain claims of the '575 Patent recite:

> 2. A process for the manufacture of a compound represented by formula Ia:
>
> Ia
>
> 
>
> wherein
> s is 2;
> each R^3 is independently selected from a group represented by halogen, cyano, nitro, C_{1-6}-alkyl, or C_{1-6}-alkyloxy;
> or an acid addition salt thereof, the process comprising reacting a compound of formula IVa
>
> IVa
>
> 
>
> with a compound of the formula Cl—CH2—CH2—NH—CH2—CH2—Cl or Br—CH2—CH2—NH—CH2—CH2—Br.
>
> 3. The process of claim 1, wherein the compound of formula Ia is 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine.

D. The Sexual Dysfunction Method Of Treatment Patent ('096 Patent)

71. Plaintiffs own all rights, title, and interest in the Sexual Dysfunction Method of Treatment Patent. (SF ¶ 200)

72. The '096 Patent is entitled "Therapeutic Uses of Compounds Having Combined SERT, 5-HT3 and 5-HT1A Activity." (SF ¶ 201)

73. The ’096 Patent is directed to, among other things, methods for treating a patient diagnosed with depression by administering 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine, where the patient previously received or is still receiving a selective serotonin reuptake inhibitor (“SSRI”), selective noradrenaline reuptake inhibitor (“NRI”), noradrenaline/serotonin reuptake inhibitor (“SNRI”), or a tri-cyclic antidepressant (“TCA”) for the treatment of that disease, and that medication is ceased or reduced or has to be ceased or reduced due to sexually related adverse events. (SF ¶ 86)

74. Takeda submitted a request to the FDA that the ’096 Patent be listed in the Orange Book in connection with Trintellix® on November 13, 2018. (SF ¶ 202)

75. Certain claims of the ’096 Patent are recited below:

> 1. A method for the treatment of a disease selected from the group consisting of depression, anxiety, abuse and chronic pain, comprising the administration of a therapeutically effective amount of l-[2-(2,4-dimethylphenylsulfanyl)phenyl] piperazine (Compound I) or a pharmaceutically acceptable salt thereof to a patient in need thereof:
>
> wherein said patient has previously received medication or is still receiving medication for the treatment of said disease, the medication is ceased or reduced or has to be ceased or reduced due to sexually related adverse events, and the medication is selected from the group consisting of selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors, noradrenaline/serotonin reuptake inhibitors, and tri-cyclics.
>
> 3. The method according to claim 1, wherein said patient is administered the hydrobromic acid salt of Compound I.
>
> 4. The method according to claim 3, wherein said salt is crystalline and characterized by having major x-ray powder diffraction (XRPD) peaks at 6.89, 9.73, 13.78 and 14.62 (°2θ), all ±0.1 (°2θ).
>
> 5. The method according to claim 4, wherein said salt is

characterized by an XRPD pattern as depicted in FIG. 3.

6. The method according to claim 1, wherein Compound I or a pharmaceutically acceptable salt thereof is administered to the patient in unit doses of about 1-50 mg.

7. The method according to claim 6, wherein the patient is administered between about 1 and 20 mg per day of the hydrobromic acid salt of Compound I orally.

(SF ¶¶ 217-22)

76. The term "abuse," as used in Claim 1 of the '096 Patent, means "substance abuse." (SF ¶ 211; *see also* D.I. 396-1)

77. "[T]herapeutically effective amount," as used in Claims 1 and 8 of the '096 Patent, means "an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease and its complications in a therapeutic intervention comprising administration of said compound." (SF ¶ 212; *see also* D.I. 459-1 at 2)

78. The term "has to be ceased or reduced due to sexually related adverse events," as used in Claim 1 of the '096 Patent, means "has to be ceased or reduced due to an adverse event involving dysfunction in one or more areas of sexual functioning, including, desire, arousal, physical response, orgasm, or satisfaction." (SF ¶ 213; *see also* D.I. 683)

79. The parties are in agreement that the asserted claims of the '096 Patent do not require that administration of vortioxetine reduces TESD. (D.I. 1054 at 53; D.I. 1059 at 43; D.I. 1047 at 78; D.I. 1011 at 39; D.I. 1052 at 24)

E. The Cognitive Impairment Method Of Treatment Patent ('910 Patent)

80. Plaintiffs own all rights, title, and interest in the '910 Patent. (SF ¶ 178)

81. The '910 Patent is entitled "1-[2-(2,4 dimethylphenylsulfanyl)-phenyl]piperazine as a compound with combined serotonin reuptake, 5-HT3 and 5-HT1*A* activity for the treatment

of cognitive impairment." (SF ¶ 179)

82. The '910 Patent is directed to, among other things, methods for treating cognitive impairment involving decline in speed of processing, executive function, attention, or verbal learning and memory in a patient diagnosed with depression using 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine. (SF ¶ 76)

83. The '910 Patent specification states that "[c]ognitive deficits or cognitive impairment include a decline in cognitive functions or cognitive domains, e.g. working memory, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving e.g. executive function, speed of processing and/or social cognition." (SF ¶ 193) The specification adds that "[c]ognitive impairment is among the classic features of depression, such as e.g. major depressive disorder." (SF ¶ 194)

84. Plaintiffs assert Claim 6 of the '910 Patent against all Defendants. However, the Court granted Sandoz's motion to dismiss the counts against it that were based on assertion of the '910 Patent. (*See* D.I. 908, 927, 991)

85. Takeda submitted a request that the '910 patent be listed in the Orange Book in connection with Trintellix® on May 24, 2018. (Orange Book Patent Exclusivity for N204447)[11]

86. Certain claims of the '910 Patent are recited below:

> 1. A method of treating cognitive impairment involving decline in speed of processing, executive function, attention, or verbal learning and memory in a patient diagnosed with depression, the method comprising administering a therapeutically effective amount of Compound I or a pharmaceutically acceptable salt thereof to the patient,
> wherein Compound I is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and the method alleviates a symptom or

[11] *See* https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

> complication of the cognitive impairment or delays the progression of the cognitive impairment.
>
> 3. The method of claim 1, wherein the depression is major depressive disorder.
>
> 6. The method of claim 3, wherein the method comprises administering a hydrobromide salt of Compound I to the patient.

(SF ¶ 196-98)

87. "Cognitive impairment," as used in Claim 6 of the '910 Patent, means "a decline or deficit in one or more cognitive functions or cognitive domains." (SF ¶ 189)

88. "Alleviates," as used in Claim 6 of the '910 Patent, means "mitigates." (SF ¶ 190)

89. The term "therapeutically effective amount," as used in Claim 6 of the '910 Patent, means "an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease and its complications in a therapeutic intervention comprising administration of said compound." (SF ¶ 191)

90. The term "a method of treating cognitive impairment . . . in a patient diagnosed with depression," as used in Claim 6 of the '910 Patent, means "a method for the management and care of a patient diagnosed with depression for the purpose of combating cognitive impairment." (SF ¶ 192)

V. Defendants

A. Alembic

91. Defendants Alembic Pharmaceuticals Limited and Alembic Pharmaceuticals, Inc. (collectively, "Alembic") submitted Abbreviated New Drug Application No. 211066 ("Alembic's ANDA") to the FDA pursuant to 21 U.S.C. § 355(j). (D.I. 985 Ex. 1A ¶ 1)

92. In Alembic's ANDA, Alembic seeks FDA approval for vortioxetine tablets in dosage strengths 5 mg, 10 mg, 15 mg, and 20 mg ("Alembic's ANDA Product"). (D.I. 985 Ex. 1A ¶ 2)

93. In a letter dated December 8, 2017 ("First Notice Letter"), Alembic notified Plaintiffs that Alembic had submitted Paragraph IV Certifications for the '684 Patent, '355 Patent, and '946 Patent. (D.I. 985 Ex. 1A ¶ 3)

94. In a letter dated February 9, 2018 ("Second Notice Letter"), Alembic notified Plaintiffs that Alembic had also submitted a Paragraph IV Certification for the '630 Patent. (D.I. 985 Ex. 1A ¶ 4)

95. The sole indication set forth in the proposed labeling for Alembic's ANDA Product is "the treatment of major depressive disorder (MDD) in adults." (D.I. 985 Ex. 1A ¶ 26)

96. Plaintiffs assert the following claims against Alembic:

1. Claims 1, 2, and 3 of the '684 Crystalline Form Patent;
2. Claims 5, 6, and 7 of the '630 Crystalline Form Patent;
3. Claims 4, 5, and 7 of the Sexual Dysfunction Method of Treatment ('096) Patent; and
4. Claim 6 of the Cognitive Impairment ('910) Patent.

(D.I. 985 Ex. 1A ¶ 38)

B. Lupin

97. Lupin filed ANDA No. 211105 ("Lupin's ANDA") seeking FDA approval to market vortioxetine tablets ("Lupin's ANDA Product"). (D.I. 985 Ex. 1C ¶¶ 36-37)

98. Lupin seeks FDA approval for Lupin's ANDA Product for "the treatment of major depressive disorder ("MDD") in adults." (D.I. 985 Ex. 1C ¶ 38)

99. Lupin seeks to manufacture its ANDA Product in four different dosage strengths: 5 mg, 10 mg, 15 mg, and 20 mg. (D.I. 985 Ex. 1C ¶ 39)

100. Lupin notified Plaintiffs in a letter dated November 30, 2017 that it had submitted Lupin's ANDA to the FDA with Paragraph IV Certifications for the '684 Patent (as well as for the '355 and '946 Patents). (D.I. 985 Ex. 1C ¶ 40)

101. In a letter dated April 6, 2018, Lupin notified Plaintiffs that it had also submitted to the FDA a Paragraph IV Certification for the '630 Patent. (D.I. 985 Ex. 1C ¶ 41)

102. Plaintiffs are asserting the following claims against Lupin:

1. Claims 1, 2, and 3 of the '684 Crystalline Form Patent;
2. Claims 2-7 of the '630 Crystalline Form Patent;
3. Claim 12 of the '626 Process Patent;
4. Claims 4, 5, and 7 of the Sexual Dysfunction ('096) Patent; and
5. Claim 6 of the Cognitive Impairment ('910) Patent.

(D.I. 1057 at 1)

C. Macleods

103. Macleods filed ANDA No. 211165 ("Macleods' ANDA") with the FDA seeking approval to commercially manufacture, use, and/or sell vortioxetine tablets in 5 mg, 10 mg, and 20 mg dosages ("Macleods' ANDA Product"). (D.I. 985 Ex. 1D ¶ 1)

104. In a letter dated November 30, 2017, Macleods notified Plaintiffs that it had submitted Macleods' ANDA to the FDA with Paragraph IV Certifications for the '684 Patent (and for the '355 Patent). (D.I. 985 Ex. 1D ¶ 2)

105. In a letter dated February 6, 2018, Macleods notified Plaintiffs that it had submitted to the FDA a Paragraph IV Certification also for the '630 Patent. (D.I. 985 Ex. 1D

¶ 3)

106. The indication set forth in the proposed labeling for Macleods' ANDA Product is "the treatment of major depressive disorder (MDD) in adults." (D.I. 985 Ex. 1D ¶ 13)

107. Plaintiffs are asserting the following claims against Macleods:

1. Claims 1 of the '684 Crystalline Form Patent.
2. Claims 2, 3, and 4 of the '630 Crystalline Form Patent.
3. Claim 7 of the Sexual Dysfunction ('096) Patent.
4. Claim 6 of the Cognitive Impairment ('910) Patent.

(D.I. 985 Ex. 1D ¶ 73; D.I. 1057 at 1)

D. Sandoz

108. Sandoz submitted ANDA No. 210993 seeking FDA marketing approval for vortioxetine tablets in dosage strengths 5 mg, 10 mg, 15 mg, and 20 mg ("Sandoz's ANDA Product"). (D.I. 985 Ex. 1F ¶¶ 1-2)

109. The sole indication set forth in the proposed labeling for Sandoz's ANDA Product in ANDA No. 210993 is "the treatment of major depressive disorder (MDD) in adults." (D.I. 985 Ex. 1F ¶ 14)

110. Plaintiffs assert Claim 7 of the Sexual Dysfunction ('096) Patent against Sandoz. (D.I. 985 Ex. 1F ¶ 30; D.I. 1057 at 1)

E. Sigmapharm

111. Sigmapharm submitted ANDA No. 211084 seeking FDA marketing approval for Vortioxetine Tablets, 10 mg and 20 mg ("Sigmapharm's ANDA Product"). (D.I. 985 Ex. 1G ¶¶ 1-2) Sigmapharm notified Plaintiffs in a letter dated March 20, 2018 that it had submitted Sigmapharm's ANDA to the FDA with Paragraph IV Certifications for the '884, '279, '684, and

’630 Patents (as well as the ’355 and ’946 Patents). (D.I. 985 Ex. 1G ¶ 21)

112. Plaintiffs assert the following claims against Sigmapharm:

1. Claims 5 and 15 of the ’279 Compound Patent.
2. Claim 17 of the ’884 Patent.
3. Claims 1-3 of the ’684 Crystalline Form Patent.
4. Claims 2-7 of the ’630 Crystalline Form Patent.
5. Claims 4, 5, and 7 of the Sexual Dysfunction (’096 Patent).
6. Claim 6 of the Cognitive Impairment (’910) Patent.

(D.I. 985 Ex. 1G ¶¶ 26, 30; D.I. 1057 at 1)

F. Zydus

113. Defendant Zydus Pharmaceuticals (USA) Inc., a wholly owned subsidiary of Cadila Healthcare Limited (“Cadila”) (collectively “Zydus”), filed ANDA No. 211146 (“Zydus’ ANDA”) seeking FDA approval for Vortioxetine Tablets, 5 mg, 10 mg, and 20 mg (“Zydus’ Proposed ANDA Products”). (D.I. 985 Ex. 1J ¶ 8)

114. Zydus seeks FDA approval for its ANDA Product for “the treatment of major depressive disorder (“MDD”) in adults.” (D.I. 985 Ex. 1J ¶ 10)

115. Zydus notified Plaintiffs in a letter dated December 14, 2017 that it had submitted Zydus’ ANDA to the FDA with Paragraph IV Certifications for the ’884 Patent, ’279 Patent, and ’684 Patent (as well as the ’355 and ’946 Patents). In a letter dated March 12, 2018, Zydus notified Plaintiffs that it had also submitted a Paragraph IV Certification for the ’630 Patent. (D.I. 985 Ex. 1J ¶¶ 11-12)

116. Plaintiffs are asserting the following claims against Zydus:

1. Claims 5 and 15 of the ’279 Compound Patent.

2. Claim 17 of the ’884 Compound Patent.

3. Claim 1 of the ’684 Crystalline Form Patent.

4. Claims 8-10 of the ’630 Crystalline Form Patent.

5. Claim 3 of the ’575 Process Patent.

6. Claims 7 of the Sexual Dysfunction (’096) Patent.

7. Claim 6 of the Cognitive Impairment (’910) Patent.

(D.I. 985 Ex. 1J ¶¶ 1, 65-66; D.I. 1057 at 1)

VI. The Witnesses

A. Plaintiffs’ Witnesses

1. Fact Witnesses

117. Dr. Marianne Dragheim is a physician who has worked at Lundbeck for nearly 20 years in connection with clinical pharmacology and pharmacovigilance. (Dragheim Tr. 109-10) She served as the clinical program lead for the vortioxetine compound and is the sole named inventor of the Sexual Dysfunction (’096) Patent. (PTX-17) Prior to joining Lundbeck, Dr. Dragheim was a practicing physician for nearly 10 years, primarily in obstetrics and gynecology. (Dragheim Tr. 110) Dr. Dragheim oversaw certain Phase I clinical trials, all Phase II clinical trials, all Phase III clinical trials, and certain Phase IV clinical trials for vortioxetine. (Dragheim Tr. 110, 112)

118. Dr. Kim Andersen is a medicinal chemist who worked at Lundbeck for about 20 years. (Andersen Tr. 73-74) He built and managed the department of combinatorial chemistry before becoming the Head of Research in 2008. (*Id.*) During his Lundbeck tenure, Dr. Andersen participated in the fast onset project – the project that resulted in the discovery of 1-[2-(2,4-DMPS)P]P (“vortioxetine”) – throughout the 1990s, where he was involved in the program’s

strategy as well as designing and developing multimodal compounds having a dual mechanism of action (SERT inhibition and selective serotonin receptor activity). (Andersen Tr. at 82) Dr. Andersen is a named inventor on the '884 and '279 Patents. (Andersen Tr. 74-84)

119. Dr. Benny Bang-Andersen is a medicinal chemist who has worked at Lundbeck since 1993. (Bang-Andersen Tr. 90-91) Beginning in early 2001, Dr. Bang-Andersen became involved as medicinal chemistry lead in the same fast onset project as Dr. Andersen, finding compounds that allowed faster onset of antidepressant action compared to then-available SSRIs and SNRIs. (Bang-Andersen Tr. 92-95, 97) Dr. Bang-Andersen is a named inventor on the '884, '279, '684, and '575 Patents. (Bang-Andersen Tr. 93-95, 97-103)

120. Dr. Michael Rock is a Lundbeck employee and inventor of the '626 Patent; he has 25 years of experience in the research and development of chemical syntheses. (Rock Tr. 222-23)

121. Virendra Srivastava is Alembic's Head of Regulatory Affairs and Rule 30(b)(6) witness. (Srivastava Tr. 1012-13)

122. Spiridon Spireas is Sigmapharm's Chairman and Chief Executive Officer and Sigmapharm's Rule 30(b)(6) witness. (Spireas Tr. 1046)

123. Govindarajan Kesevan is Zydus' Vice President of Analytical Development and Rule 30(b)(6) witness. (Kesevan Tr. 1023-24)

124. Kumar Singh is Zydus' Senior Vice President of Research & Development and a Rule 30(b)(6) witness. (Singh Tr. 1042-43)

2. Expert Witnesses

125. Dr. David MacMillan is the James S. MacDonald Distinguished University Professor of Chemistry, as well as the Director of the Merck Center for Catalysis at Princeton

University, and has held these positions for approximately 15 years. (MacMillan Tr. 194-95) Dr. MacMillan is an expert in the field of organic chemistry, including chemical reactions and the development and synthesis of organic molecules, such as through palladium catalysis. (MacMillan Tr. at 200) Dr. MacMillan has more than 20 years of experience in the area of organic synthesis and focuses his research on developing new chemical reactions and has published extensively in the area of palladium catalysis. (MacMillan Tr. at 195, 197)

126. Dr. Mickael Morin is a material scientist at Excelus Structural Solutions where he provides synchrotron radiation-based analytical services and scientific consulting in the field of structural characterization of materials and quantitative phase analysis, including x-ray powder diffraction ("XRPD") analysis of pharmaceutical samples to determine their components and identify crystalline forms. (Morin Tr. 351-52) Dr. Morin is an expert in the "characterization and analysis of pharmaceutical compounds using Synchrotron x-ray powder diffraction." (Morin Tr. at 353)

127. Dr. Alan Myerson is a Professor of the Practice of Chemical Engineering at the Massachusetts Institute of Technology. (Myerson Tr. 486; PTX-4397) He has more than 40 years of experience in the area of crystallization and focuses his research on crystalline solid forms, nucleation, and purity crystal interactions, as well as industrial applications of crystallization, pharmaceutical manufacturing, and novel solid oral dosage forms. (*Id.*) Dr. Alan Myerson is an expert in "chemical engineering, the study and analysis of crystalline forms, solid dosage forms of pharmaceuticals and the pharmaceutical manufacturing and the industrial application of crystallization." (Myerson Tr. 490, 492)

128. Dr. Gregory Mattingly is an Associate Clinical Professor and

Psychopharmacology Instructor at the Washington University School of Medicine in St. Louis, Missouri. (Mattingly Tr. 829, 831; PTX-4592 at 2) Dr. Mattingly is also the president of St. Charles Psychiatric Associates, where he sees approximately 100 patients per week and manages a caseload of approximately 1,500 patients. (Mattingly Tr. 833-34; PTX-4592 at 24) Dr. Mattingly is an expert in psychiatric treatment, psychiatric research, psychopharmacology, and medical education, specifically including depression, cognitive disorders, and other psychiatric conditions. (Mattingly Tr. 834)

129. Dr. Anita Clayton is the David C. Wilson Professor and Chair of the Department of Psychiatry and Neurobehavioral Sciences, with a secondary appointment as professor of Clinical Obstetrics & Gynecology, all at the University of Virginia. (Clayton Tr. 1078-79; PTX-103 at 2) Dr. Clayton currently treats approximately eight patients per week and supervises and/or participates in evaluating and making treatment recommendations in consultation with medical residents for 75 patients per week in her role as outpatient attending physician. (Clayton Tr. 1081) Dr. Clayton is an expert in the field of medicine, including the treatment of and clinical research regarding psychiatric disorders and sexual dysfunction, psychopharmacology, sexual dysfunction with psychiatric illness and treatment, and sexual disorders. (Clayton Tr. 1084-85)

130. Dr. Roger McIntyre is a Professor in the Departments of Psychiatry and Pharmacology at the University of Toronto. He also holds appointments as Clinical Professor at the State University of New York (SUNY) Upstate Medical University, Clinical Professor in the Department of Psychiatry and Neurosciences at the University of California School of Medicine, and others. (McIntyre Tr. 1217) Dr. McIntyre is currently the Head of the Mood Disorders

Psychopharmacology Unit, University Health Network, a unit located in Canada's largest academic teaching hospital, where he provides care for patients with depression. (*Id.* at 1223) Dr. McIntyre has approximately 1,000 patient contacts per year. (*Id.*) Dr. McIntyre is an expert in the fields of psychiatry, psychopharmacology, mood disorders, and cognition. (*Id.* at 1224)

131. Dr. Carl Peck is a physician scientist with five decades of combined experience in internal medicine, clinical pharmacology, clinical trial design and analysis, and the development and regulation of pharmaceutical products. (Peck Tr. 1299-1301) From 1987 to 1993, he served as the Director of the Center for Drug Evaluation and Research (CDER), which is the component of the FDA responsible for evaluating and approving all new and generic drugs for use in humans. As the Director of CDER, Dr. Peck's responsibilities included reviewing and commenting on the sufficiency of studies supporting NDAs, ANDAs, and investigational new drug applications ("IND"), supervising other FDA scientists in their review of such studies, and reviewing, editing, and establishing standards for the format and content of prescription drug labels. (*Id.* at 1299-1300) Dr. Peck is an expert on FDA regulation of drugs, including drug labeling. (*Id.* 1301-02)

132. Dr. Paul Reider is an expert in "medicinal chemistry and drug development." (Reider Tr. 157) Dr. Reider is a Professor in the Department of Chemistry at Princeton University. (Reider Tr. 154; PTX-4677 at 1) He has over 40 years of experience, including 27 years working in the pharmaceutical industry at Merck and Amgen, in organic chemistry research and development, synthetic chemistry, medicinal chemistry, pharmaceutical chemistry, and drug discovery and development, including in the context of antidepressant drugs. (Reider Tr. 153-56, 179; PTX-4677 at 1-2) Dr. Reider has worked on the discovery, identification,

development, and/or registration of 14 approved drugs, and has consulted with pharmaceutical companies on many others. (Reider Tr. 153-56; PTX-4677 at 1-2)

B. Defendants' Witnesses

133. Dr. Bart Kahr is a chemist and a professor of chemistry at New York University. Dr. Kahr was recognized as Alembic's expert in crystallography and the study of molecular crystals. (Kahr Tr. 1417-18)

134. Dr. Jeremy Karl Cockcroft is a Senior Lecturer in the Department of Chemistry, University College London, where his area of expertise is powder diffraction, in which he has approximately 40 years of experience. (Cockcroft Tr. 1548) Dr. Cockcroft was recognized as Lupin's expert in the field of crystallization and x-ray powder diffraction. (*Id.* at 1551)

135. Dr. Glenn Micalizio occupies an Endowed Chair at the Department of Chemistry at Dartmouth College. (Micalizio Tr. 1561-63) Dr. Micalizio was recognized as Lupin's expert in the field of chemistry, including in the development of synthetic processes for creating chemical compounds. (*Id.* at 1565-66)

136. Dr. Raj Suryanarayanan is Macleods' expert in crystallography. (Suryanarayanan Tr. 1797-1836)[12]

[12] Although there is no record of Dr. Suryanarayanan being offered, or formally recognized, as an expert, there is also no record of any dispute on this point. To the contrary, after Macleods disclosed in the pretrial order that it would call Dr. Suryanarayanan to testify "as an expert in the areas of materials science of pharmaceuticals, which includes the physical characterization of polymorphic forms of active ingredients, and inactive excipients" (D.I. 987-1 at p. 616 of 889), Plaintiffs' objections did not include any objection to his qualifications (*see id.* at p. 626 of 889). In fact, in post-trial briefing, Plaintiffs cite to Dr. Suryanarayanan for points on which they are in agreement with his testimony. (*See, e.g.*, D.I. 1056 ¶¶ 125, 162, 166, 169, 173) The Court believes that, perhaps due to the remote nature of the trial, the transition from public access to a private virtual break-out room (in which Dr. Suryanarayanan testified) led the parties to overlook the formality of proffering Dr. Suryanarayanan as an expert. However, given the circumstances, the Court has no doubt that Dr. Suryanarayanan is qualified as an expert and now recognizes him

137. Dr. Mark Hollingsworth is an associate professor of chemistry at Kansas State University. (Hollingsworth Tr. 1398) Dr. Hollingsworth was recognized as Sigmapharm's expert in solid state chemistry, crystal growth and polymorphism, solid state properties of pharmaceutical compounds, and powder x-ray diffraction. (*Id.* at 1402-03)

138. Dr. Mark Sacchetti is the scientific director of the Lenor Zeeh Pharmaceutical Experiment Station in the School of Pharmacy at the University of Wisconsin-Madison. (Sacchetti Tr. 1587) Dr. Sacchetti was recognized as Zydus' expert in solid state chemistry and the analysis of polymorphs. (*Id.* at 1591-92)

139. Dr. Anthony Rothschild is a psychiatrist and professor at the University of Massachusetts Medical School. Dr. Rothschild was recognized as an expert in the field of psychiatry, psychopharmacology, and antidepressant therapy, including the treatment of major depressive disorder. (Rothschild Tr. 1637-41)

140. Dr. Peter Rheinstein is a former director of the division of drug advertising and labeling in the FDA's Bureau of Drugs. Dr. Rheinstein is an expert on FDA regulation of drugs, including drug labelling. (Rheinstein Tr. 2105-07)

141. Dr. Salvatore Lepore is a medicinal chemist and a professor at Florida Atlantic University. Dr. Lepore was recognized without objection as an expert in medicinal chemistry, organic chemistry, and the development of drugs. (Lepore Tr. 1877-78)

142. Dr. Victor Reus is a psychiatrist and professor emeritus at the University of California at San Francisco School of Medicine and at the Weill Institute of Neurosciences. Dr. Reus was recognized without objection as an expert in the field of psychiatry,

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as such.

psychopharmacology, and mood disorders, including diagnosis, causation, pathophysiology, and the treatment of major depressive disorder. (Reus Tr. 1970-74)

VII. Person Of Ordinary Skill In The Art ("POSA")

143. The '884 and '279 patents should be evaluated from the perspective of a POSA as of the filing date of the earliest patent application to which they properly claim priority, which is Oct. 4, 2001. (SF ¶¶ 86, 101) On their face, these patents claim priority to Danish Application No. 2001 01466, which was filed on Oct. 4, 2001. (*Id.*) Defendants have referred to the priority date of the '884 and '279 patents as Oct. 2, 2002. (D.I. 1053 ¶ 20) But Defendants have not offered any evidence or argument that the '884 and '279 patents are not entitled to the priority date of Oct. 4, 2001. (*Id.*) Plaintiffs' expert on the Compound Patents, Dr. Reider, testified that his opinions on the validity of the challenged claims of the Compound Patents are not affected by any differences with Defendants' priority date. (D.I. 1058 at ¶ 15)

144. A POSA, as of the time of invention of the Compound Patents, would be a person having knowledge, education, or training equivalent to either (a) a Ph.D. in organic chemistry, or a related discipline; or (b) a B.S. or M.S. in organic chemistry, or a related discipline, with several years of experience in medicinal chemistry or pharmaceutical development. Such a POSA might collaborate with others, including a medical doctor with experience treating affective disorders, such as depression. (Reider Tr. 2026; *see also* Lepore Tr. 1890)

145. Plaintiffs' and Defendants' experts agreed that their opinions would be the same regardless of whether the Court adopts Plaintiffs' or Defendants' definition of a POSA for the Compound Patents. (Reider Tr. 2026; Lepore Tr. 1890)

146. A POSA with respect to the Crystalline Form Patents would include a person holding a "bachelor's degree in chemistry, chemical engineering, pharmaceutical science, or a

related discipline, with some knowledge of crystalline solid forms and characterization, and several years of experience in the pharmaceutical industry, which would include experience with analytical techniques used in the industry; or an advanced degree in the above-listed disciplines or a related discipline, with some knowledge of solid state or analytical chemistry, and less experience" who "may work in consultation with or as part of a team with others, such as a physician with knowledge and experience relevant to the methods of treatment to which the patents are directed." (Myerson Tr. 494; Suryanarayanan Tr. 179)

147. Plaintiffs' and Defendants' experts agreed that their opinions would be the same regardless of whether the Court adopts Plaintiffs' or Defendants' definition of a POSA for the Crystalline Form Patents. (Myerson Tr. 494; Suryanarayanan Tr. 179; Kahr Tr. 1420; Cockcroft Tr. 1551; Hollingsworth Tr. 1403-04)

148. The priority date for Claim 3 of the '575 Patent is Oct. 4, 2001. (DTX-242 at 1)

149. A POSA with respect to the Process Patents would include a person who possesses an advanced degree (Ph.D. or Master's) in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field and at least some experience in the research, design, and development of small molecule drugs or drug candidates, either in academia or industry. The POSA would have substantial knowledge and experience in the design of drugs to meet specific clinical utility, including the understanding of structure activity relationships, biochemical targets, and the role of physical-chemical properties. The POSA would have consulted and/or collaborated with professionals in related areas of pharmaceutical R&D, including analytical, formulation, preclinical, and clinical research and development and would have a good understanding in these related fields. Additional practical experience could also

substitute for the advanced degree. (Lepore Tr. 1890; *see also* MacMillan Tr. 201; Reider Tr. 2026)

150. For the ’096 and ’910 Method of Treatment Patents, Defendants propose that a POSA as of June 16, 2006 would have been a physician who would have possessed a medical degree and would have studied the scientific and medical literature relating to depression, and either (1) possessed Board Certification in Psychiatry; or (2) would have had at least 5 years of experience in the treatment of depression. Further, a POSA would have had access to and would have consulted with a collaborative team of ordinarily skilled artisans including a scientist with expertise in pharmacokinetics, an organic and solid-state chemist, a pharmaceutical formulator, or individuals working in comparable fields with an advanced degree (such as a Ph.D. or M.D.). (Rothschild Tr. 1670-71; Reus Tr. 1974-75; SF ¶ 185)

151. Plaintiffs’ experts each propose the same POSA definition as one another for the ’096 and ’910 Patents, which principally differs from Drs. Rothschild and Reus’s definition based on the fact that Plaintiffs’ experts’ opine that a nurse practitioner or physician’s assistant may qualify as a POSA. (Mattingly Tr. 856-57; Clayton Tr. 1150; McIntyre Tr. 1256-58)

152. A POSA with respect to the Method of Treatment Patents would have an MD or DO with 2-3 years’ experience in diagnosing, evaluating, and treating mood disorders and mental health conditions like depression; or be an NP or a PA with several years of experience diagnosing, evaluating, and treating mood disorders and mental health conditions like depression. If needed, a POSA would have been in consultation with a person of knowledge and relevant experience in chemistry or pharmacy with experience in solid-state forms of pharmaceuticals. (Clayton Tr. 1150) NPs and PAs are clinicians familiar with the medical

literature and prior art, are frequent prescribers of antidepressants, and are often involved in activities that advance the field of antidepressant treatment. (McIntyre Tr. 1258)

153. All parties' experts' agree that their opinions would not change regardless of whether Plaintiffs' experts' definition of the POSA or Defendants' is applied. (Mattingly Tr. 857-58; Clayton Tr. 1151; McIntyre Tr. 1258; Rothschild Tr. 1671-72) The Court agrees that its opinions as to infringement and validity of the Method of Treatment Patents would not differ if it applied Defendants' characterization of a POSA.

VIII. Further Facts Related To Disputes Concerning The '884 and '279 Compound Patents

A. Infringement

154. No dispute as to infringement of any Claims of the Compound Patents was presented at trial.

155. Sigmapharm and Zydus have admitted infringement of claims of the '884 and '279 Patents. (D.I. 985 Ex. 1G ¶ 30 (Sigmapharm); *id.* Ex. 1J ¶¶ 65-66 (Zydus))

B. Invalidity

156. Sigmapharm and Zydus contend that the asserted claims of the Compound Patents are invalid due to obviousness.

1. The Perceived Desirability Of Selectivity

157. At the pertinent dates, a POSA working to discover and develop a new antidepressant or improve upon available antidepressants would have understood the need to search for multimodal molecules capable of balancing numerous pharmacological properties, such as: (1) potency and efficacy against a desired target; (2) the ability of the molecule to arrive at the desired target, which requires accessible pharmacokinetics and bioavailability; (3) the ability to

permeate the blood-brain barrier; and (4) safety and tolerability. (Reider Tr. 2027; PTX-1171; PTX-1172) A POSA would also have known that small changes to a compound's structure could dramatically impact its biological properties, potentially negatively affecting the compound's safety and tolerability. (*See* Reider Tr. 2027)

158. Beginning in the 1980s, and through the early 2000s, the pharmaceutical antidepressant industry focused on developing highly selective molecules targeting specific serotonin receptors. (Reider Tr. 161-62, 179, 2027-28; PTX-1169; PTX-1170) The industry understood that greater selectivity translated into greater safety and tolerability, in part by avoiding off-target activities. (Reider Tr. 161, 2027-28; PTX-1169; PTX-1170)

159. As of October 2001, a POSA would have equated increased selectivity towards specific serotonin receptors with increased safety and tolerability, and would have expected improvements to antidepressants would require selectivity. (Reider Tr. 161, 2027-28; PTX-1169; PTX-1170)

160. The antidepressant landscape in 2001 was dominated by SSRIs and SNRIs, which had replaced TCAs and TeCAs as the standard of care for the treatment of depression. (Reider Tr. 161-62, 187, 2028; PTX-10; PTX-445; PTX-447; PTX-1169; PTX-1170) SSRIs became the first choice therapeutics in the treatment of depression because they are effective, well-tolerated, and have a favorable safety profile compared to the classic TCAs. (Reider Tr. 187, 2070-71; PTX-10) SSRIs and SNRIs significantly improved over TCAs and MAOIs by having vastly improved side effect profiles (though not necessarily improved efficacy). (Reider Tr. 161-62, 187, 2028, 2070-71; Mattingly Tr. 839-41; PTX-10; PTX-445; PTX-447; PTX-1169; PTX-1170)

161. In attempting to prove that the Asserted Claims of the Compound Patents are

obvious, Sigmapharm and Zydus rely on six references. (DTX-256; DTX-257; DTX-259; DTX-349; DTX-367; DTX-371) These references, alone and in combination, fail to disclose all elements of any of the asserted claims. (DTX-256; DTX- 257; DTX-259; DTX-349; DTX-367; DTX-371)

2. "Spanish Works" (ES '127, Planas, and Pinder)

162. ES '127, published in 1991, is a process patent describing a method for synthesizing a broad genus of aromatic compounds, having the structure of formula (I') with R'1, R'2, and R'3 broadly defined to include a large number of substituents. (Reider Tr. 2043-44; DTX-256) All compounds disclosed by ES '127 are phenyl-methyl-phenyl piperazines, with a methylene group bridging the two phenyl groups. (DTX-256) 1-[2-(2,4-DMPS)P]P is not a phenyl-methyl-phenyl piperazine.

163. ES '127 describes the synthesis of 17 exemplary compounds that fall within the genus of formula I'. (Lepore Tr. 1952-53; Reider Tr. 2043-44; DTX-256) ES '127 does not disclose any biological activity for any of these 17 disclosed compounds, including the compounds of Examples 6 and 7 highlighted by Dr. Lepore. (Reider Tr. 2044) Nor does ES '127 suggest any need to modify or improve upon the disclosed compounds. (*See id.*)

164. U.S. Patent No. 4,859,675, related to ES '127, was before the examiner during prosecution of the '279 Compound Patent. (PTX-11)

165. J.M. Planas, et al., *Pharmacological Profile of the Potential New Antidepressant, Sifaprazine*, 3(1) BEHAV. PHARMACOLOGY 48 (1992) ("Planas"), describes sifaprazine as structurally related to mianserin, and pharmacologically similar to TCAs – while also having the advantage of being less anticholinergic and less sedative. (Reider Tr. 2044-45; DTX-371) Planas does not suggest any need to modify or improve upon the sifaprazine molecule. (*Id.*)

166. Planas was identified on the face of the ’279 Compound Patent and the ’575 Process Patent. (PTX-11; DTX-242 at 2)

167. R.M. Pinder, et al., *The Potential Therapeutic Role of the Enantiomers and Metabolites of Mianserin*, 15 BR. J. CLIN. PHARMAC. 269S (1983) (“Pinder”), published in 1983, discusses the pharmacology of mianserin and five enantiomers and metabolites of mianserin: R(-)-Mianserin, S(+)-Mianserin, Desmethylmianserin, 8-Hydroxymianserin, and Mianserin-N-oxide. (Reider Tr. 2045-46; DTX-259) Pinder teaches that mianserin has been known since the 1970s. (DTX-259) Mianserin, a TeCA, does not “inhibit serotonin or dopamine uptake in brain tissue, but blocks noradrenaline uptake to an extent similar to that of some of the tricyclic antidepressants.” (*Id.*) Comparing the pharmacology of mianserin and its enantiomers and metabolites, Pinder concludes that mianserin has the superior activity profile. (Reider Tr. 2045-46; DTX-259) Pinder does not suggest any need to modify or improve upon the mianserin molecule. (Reider Tr. 2045-46)

168. None of the “Spanish Works” discloses 1-[2-(2,4-DMPS)P]P or Dr. Lepore’s biarylether piperazine motif. (Lepore Tr. 1916-17, 1922-23; Reider Tr. 2044-46; DTX-256; DTX-259; DTX-371) Nor do any of the “Spanish Works” disclose any desirable antidepressant activity. (Reider Tr. 2044-46; DTX-256; DTX-259; DTX-371)

3. “Czech Works” (Kopicová and Jílek)

169. Z. Kopicová, et al., *Neurotropic and Psychotropic Compounds. L. Derivatives of 1-(2-phenylthiobenzyl)piperazine and 1-(2-benzylbenzyl)piperazine*, 37 COLL. CZECH. CHEM. COMMS. 1371 (1972) (“Kopicová”), published in 1972, was identified on the face of the ’279 Compound Patent and the ’575 Process Patent. (PTX-11; DTX-242 at 1)

170. Kopicová describes the preparation of 28 compounds which are either

phenylthiobenzyl-piperazines or benzylbenzyl-piperazines (compounds III-XXX). (Reider Tr. 2047, 2050; DTX-349) None of the disclosed compounds is a biarylether piperazine. (Reider Tr. 2047, 2050) Kopicová teaches that these compounds, including compound V relied on by Dr. Lepore, generally exhibit hypotensive activity (i.e., low blood pressure). (*Id.*) Kopicová does not suggest any need to modify or improve upon any of its disclosed compounds. (*Id*.)

171. J. Jílek, et al., *Potential Antidepressants: 2-(Phenylthio)aralkylamines*, 54 COLL. CZECH. CHEM. COMMS. 1995 (1989) ("Jílek"), published in 1989, discusses the preparation of several series of compounds, including 2-(phenylthio)benzylamines, 2-(2-(phenylthio)phenyl)ethylamines, and 1-(2-(phenylthio)phenyl)-2-propylamines. (DTX-257) Jílek reviews the Kopicová compounds and data. (*Id.*) Jílek investigated, among other things, antireserpine activity in mice. (Reider Tr. 2046-47, 2050; DTX-257)

172. Based on antireserpine tests, only three of the 29 compounds disclosed in Jílek (VI, XI, and XXV) were linked to potential antidepressant activity. (Reider Tr. 2046-47, 2050; DTX-257) A POSA would have known from Planas that reserpine testing predicts TCA-like pharmacology. (Reider Tr. 2046-47, 2050; DTX-257; DTX-371)

173. None of the "Czech Works" discloses 1-[2-(2,4-DMPS)P]P or Dr. Lepore's biarylether piperazine motif. (Lepore Tr. 1916-17, 1922-23; Reider Tr. 2046-47, 2050; DTX-257; DTX-349)

4. WO '678

174. PCT Patent Application Publication No. WO 01/49678 ("WO '678") is listed on the face of the '884 and '279 Compound Patents and the '575 Process Patent. (PTX-10; PTX-11; DTX-242 at 2)

175. WO '678 describes the preparation of a genus of aromatic compounds having the

structure of formula I, broadly defining various R groups, X, Y, Z, n, and m to encompass billions of compounds. (Lepore Tr. 1944; Reider Tr. 2048-49; DTX-367) WO '678 describes several broad genera of preferred embodiments, including 69 specific compounds all named as the "most preferred embodiment." (DTX-367 at 7-9) All 69 named embodiments are indolyl-alkyl phenoxy-phenyl-containing compounds, wherein X is oxygen. (*Id.*)

176. WO '678 teaches methods for synthesizing the formula I compounds involving 13 intermediate compounds (formulas III-XV). (Lepore Tr. 1948; Reider Tr. 2048-49; DTX-367) WO '678 does not provide any teachings regarding these intermediates (including the formula III intermediate selected by Dr. Lepore) beyond their use in the synthesis of compounds represented by formula I. (*Id.*) Nor does WO '678 teach that the 13 intermediate compounds possess any biological activity or would have, or could be modified to have, any use in treating depression. (*Id.*)

177. WO '678 does not disclose 1-[2-(2,4-DMPS)P]P or Dr. Lepore's biarylether piperazine motif. (Lepore Tr. 1916-17, 1922-23, 1949; Reider Tr. 2048-49; DTX-367) Nor does WO '678 disclose compounds, including compounds of formula III, with any desirable antidepressant activity. (Reider Tr. 1948, 2048-49; DTX-367)

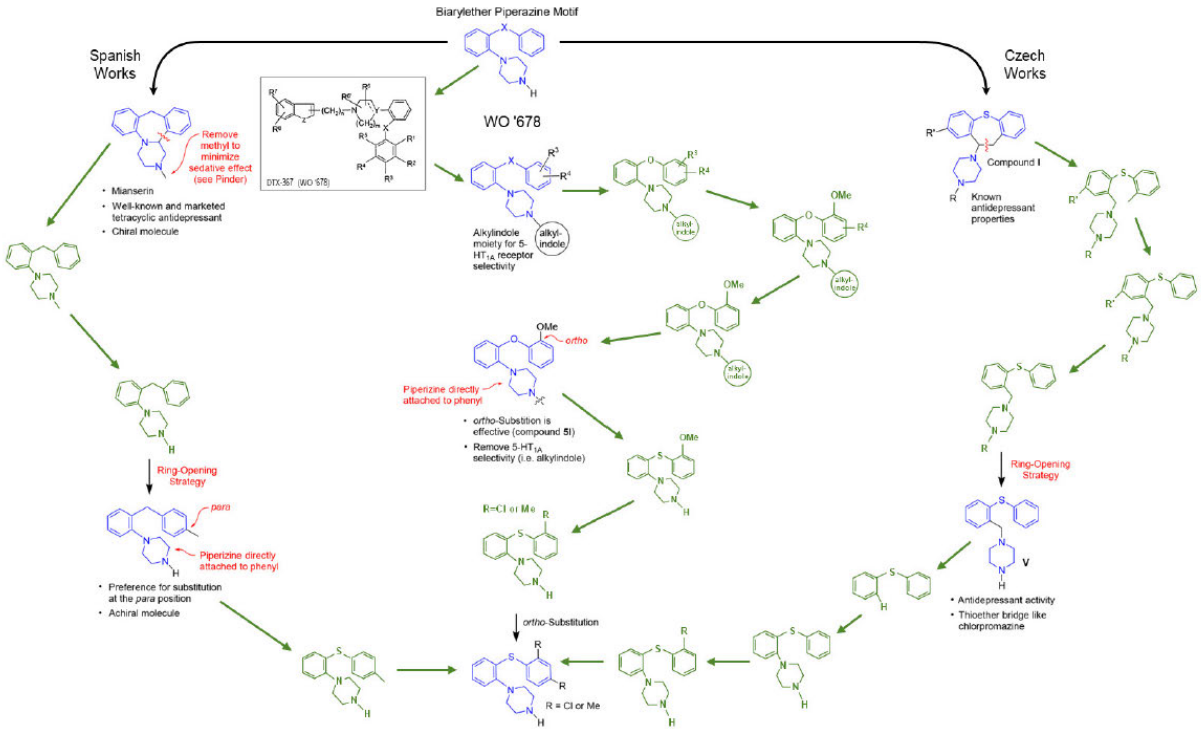
C. Dr. Lepore's Analysis

178. Defendants' expert, Dr. Lepore, does not identify a lead compound known in the prior art as a starting point for developing the claims of the Compound Patents. (Lepore Tr. 1922-23; Reider Tr. 2029-30, 2053-54) Instead, Dr. Lepore divined a pattern or scaffold, which he contends is common to the six prior art references described above, that he labeled a biarylether piperazine motif. (Lepore Tr. 1879-80, 1922-23; Reider Tr. 2029, 2053-54) Dr. Lepore's "motif" is an amalgam of structural elements from multiple references and is not expressly

disclosed in any prior art reference. (*See* Lepore Tr. 1922-23, 1928, 1930-31, 1933; Reider Tr. 2029-30, 2037, 2053-54)

179. Even assuming a POSA would begin her efforts to develop an antidepressant by starting with Dr. Lepore's lead motif, Dr. Lepore acknowledges that multiple modifications would have been necessary to move from the lead motif and arrive at any of the embodiments of any of the asserted claims he contends are invalid as obvious. (*See* Lepore Tr. 1905, 1911)

180. At least the following modifications would have been necessary to move from Dr. Lepore's lead motif to vortioxetine:



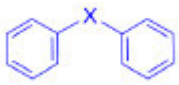
(Reider Tr. 2050-52; PDX15-33)

181. A POSA would not have had any motivation to modify the motif identified by Dr. Lepore or modify specific compounds from ES '127, Planas, Jílek, Kopicová, Pinder, and WO '678 in the many ways necessary to arrive at 1-[2-(2,4-DMPS)P]P. (Reider Tr. 2050-54)

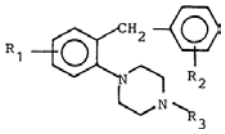
182. A POSA would not make modifications to "optimize" a molecule for metabolic stability without first identifying the metabolites. (DTX-261 at 5; *see also* Reider Tr. 2041-42)

183. Silverman states: "Drug metabolism studies are essential for the determination of the safety of potential drugs. Consequently, prior to approval of a drug for human use the metabolites produced from the drug must be isolated and shown to be nontoxic. These studies also can be a useful lead modification approach. Once the metabolic products are known, it is possible to design a compound that is inactive when administered, but which utilizes the metabolic enzymes to convert it to the active form." (DTX-261 at 5)

184. A POSA would understand from Pinder that there is no metabolic activity at the benzylic methylene and, hence, would not have been motivated to make any substitution at this location. (Reider Tr. 2045-46; DTX-259)

185. Introducing a sulfur bridge into diaryl structures – that is, introducing a sulfur at the X position in structures like  – would introduce metabolic instability and potentially result in adverse effects, which is not desirable in drug development. (Reider Tr. 2041-46)

186. The compounds of ES '127, 1-(2-(phenylmethyl)phenyl)piperazines, are depicted by general formula (I). (DTX-256 at 2)



187. The compounds of ES '127 may be substituted at any position of each of the two phenyl rings. (*Id.*) R1 is hydrogen, alkyl containing 1-4 carbon atoms or halogen. (*Id.*) R2 is

hydrogen, alkyl containing 1-4 carbon atoms, halogen or alkoxy containing 14 carbon atoms, and R3 is hydrogen or methyl. (*Id.*) ES '127 does not disclose any compound of formula I that is substituted at the ortho and para positions of the phenyl ring where R2 is methyl. (Lepore Tr. 1958; DTX-256) Nor does ES '127 teach a preference for any particular ring location or for a modification where R2 is methyl and not alkyl containing 2-4 carbon atoms, halogen or alkoxy containing 14 carbon atoms. (*Id.*)

188. A POSA would not have been motivated to make multiple methyl substitutions as proposed by Dr. Lepore. (*See, e.g.,* DTX-256; DTX-259)

D. Objective Indicia of Non-Obviousness

189. Most of the antidepressants available before Trintellix had mechanisms of action similar to one another. (Reider Tr. 163-64)

190. 1-[2-(2,4-DMPS)P]P acts on multiple 5-HT receptors: it is a serotonin transporter inhibitor, 5-HT1D, 5-HT3, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist. (Reider Tr. 158-59; PTX-4678) 1-[2-(2,4-DMPS)P]P is classified as a "multimodal" antidepressant – not as a SSRI, SNRI, TCA, or TeCA. (Reider Tr. 158-59, 166-67, 172; Mattingly Tr. 841)

191. Prior to Trintellix, there were a number of pharmacotherapy options available for MDD, but many patients using them did not experience an adequate response and/or did experience burdensome side effects. (Reider Tr. 163-64, 185-87; Mattingly Tr. 839-41, 859-61; Clayton Tr. 1093-94, 1154-55)

192. By 2001, there was a long-felt but unmet need for an antidepressant that effectively treated the symptoms of MDD and also produced fewer negative side effects. (Reider Tr. 163-64; Mattingly Tr. 858) In particular, there was a need for an antidepressant that

improved cognitive impairment and had a lower incidence of sexually related adverse effects ("SRAEs"), weight gain, and sleep disturbance. (Mattingly Tr. 858; PTX-324 at 1; PTX-132 at 1) Patients experiencing such adverse side effects may not adhere to their treatment regimens and may, consequently, experience negative outcomes. (Clayton Tr. 1093-96; McIntyre Tr. 1229-30; PTX-125 at 17, 22; PTX-124 at 8; PTX-126 at 9; PTX-324 at 2-4, 6-7)

193. 1-[2-(2,4-DMPS)P]P, the active pharmaceutical ingredient ("API") in Trintellix, has been shown to be effective in clinical studies, including maintenance studies. (Dragheim Tr. 114-15, 119-20; Mattingly Tr. 845, 853-54; PTX-2957 at 37; PTX-4475 at 21-26) FDA requires only two positive efficacy studies for approval; 1-[2-(2,4-DMPS)P]P had six positive efficacy studies. (Dragheim Tr. 119-20; Mattingly Tr. 853-54; PTX-4475 at 21-26) It has also been shown to have improved tolerability over other antidepressants, including venlafaxine, duloxetine, escitalopram, and paroxetine, in head-to-head comparisons. (Dragheim Tr. 116-22; PTX-149 at 15; PTX-2957 at 41-42) Cipriani concluded from the largest meta-analysis of antidepressant studies in the world that 1-[2-(2,4-DMPS)P]P is among the antidepressants with the best efficacy and tolerability. (Mattingly Tr. 842-44, 861-62; PTX-4594 at 1, 6, 9)

194. Trintellix has been shown to have no significant effect on body weight in short and long-term treatment. (Mattingly Tr. 845; PTX-4475 at 10-11) In a meta-analysis of 16 1-[2-(2,4-DMPS)P]P studies, Trintellix was found to have a "low incidence of sleep disruption." (PTX-144 at 6, 9; *see also* Mattingly Tr. 845) In lower dosage strengths, 1-[2-(2,4-DMPS)P]P can also be abruptly discontinued without risk of discontinuation syndrome. (Mattingly Tr. 845; PTX-4475 at 3)

195. The clinical effects of 1-[2-(2,4-DMPS)P]P are thought to result from the combination of a direct effect on receptor activity and SERT inhibition. (Reider Tr. 172)

196. No other commercial drug compound with an activity profile similar to 1-[2-(2,4-DMPS)P]P existed at the time of invention. A POSA would not have expected Trintellix to be an effective, well-tolerated, and non-toxic treatment for MDD. (Reider Tr. 158-59, 166-67)

197. 1-[2-(2,4-DMPS)P]P's combination of efficacy and tolerability was unexpected, and would have been surprising to a POSA making comparisons to other antidepressants, such as SSRIs and TCAs. (Reider Tr. 172; Mattingly Tr. 859-62, 878-80)

198. A POSA augmenting SSRI activity would expect any resulting antidepressant to have efficacy and tolerability similar to known SSRIs, but this is not what was found with 1-[2-(2,4-DMPS)P]P. (Reider Tr. 167)

IX. Facts Related To Disputes Concerning The Crystalline Form Patents

A. Infringement

1. General Findings

a. X-Ray Powder Diffraction

199. X-ray powder diffraction ("XRPD") is the gold standard method for characterizing and identifying polymorphic forms of a substance. (Kahr Tr. 1421)

200. XRPD analysis generates a diffractogram, which is a unique pattern of peaks. An XRPD pattern, is in effect, a fingerprint (or barcode) for a particular crystalline form. (Kahr Tr. 1421)

201. It is possible for polymorphs of the same API to share overlapping peaks. (Myerson Tr. 766; Kahr Tr. 1422)

202. Excipients in a pharmaceutical product can also share peaks with the API. (Myerson Tr. 767)

203. Specimen preparation can impact XRPD analysis and can result in experimental

error. (Myerson Tr. 746-47)

204. Plaintiffs' expert, Dr. Morin, analyzed the samples he received from Plaintiffs using synchrotron XRPD ("S-XRPD" or "synchrotron") instrumentation. (Morin Tr. 357) S-XRPD uses high intensity magnetic fields to change direction paths of high-energy elections to produce X-rays with an ultrahigh beam intensity. (Morin Tr. 355-57) The high-beam intensity of the synchrotron contributes to its increased sensitivity over conventional XRPD analysis. (Morin Tr. 355-57; Myerson Tr. 970) The limit of detection is usually significantly better for S-XRPD than it is for conventional laboratory XRPD. (Myerson Tr. 971)

b. Asserted Claims

205. The Crystalline Form Claims are directed to crystalline forms of vortioxetine hydrobromide with specific XRPD peaks and/or XRPD patterns, including the alpha (α) form, the beta (β) form, and the gamma (γ) form of vortioxetine hydrobromide. (PTX-12; PTX-15; PTX-17)

206. The Crystalline Form Patents describe the alpha form of vortioxetine HBr as characterized by Figure 2 of the '684 Patent and four characteristic peaks at 5.85, 9.30, 17.49, and 18.58 ± 0.1° 2θ. (PTX-12; PTX-15; Myerson Tr. 503) The Asserted Claims that cover the alpha form include Claim 1 of the '684 Crystalline Form Patent and Claims 2-4 of the '630 Crystalline Form Patent. These claims are asserted against Lupin, Macleods, and Sigmapharm, whose ANDA Products allegedly containing the alpha form.

207. The Crystalline Form Patents and the '096 Sexual Dysfunction Patent describe the beta form of vortioxetine HBr as characterized by Figure 3 of the '684 Patent and four characteristic peaks at 6.89, 9.73, 13.78, and 14.62 ± 0.1° 2θ. (PTX-12; PTX-15; PTX-17; Myerson Tr. 503) The Asserted Claims that cover the beta form include Claims 1-3 of the '684

Crystalline Form Patent, Claims 5-7 of the '630 Crystalline Form Patent, and Claims 4 and 5 of the '096 Sexual Dysfunction Patent. (PTX-12; PTX-15; PTX-17) These claims are asserted against Alembic, Lupin, and Sigmapharm, whose ANDA Products allegedly contain the beta form.

208. The Crystalline Form Patents describe the gamma form of vortioxetine HBr as characterized by Figure 4 of the '684 Patent and four characteristic peaks at 11.82, 16.01, 17.22, and 18.84 ± 0.1° 2θ. (PTX-12; PTX-15; Myerson Tr. 503) The Asserted Claims that cover the gamma form include Claim 1 of the '684 Crystalline Form Patent and Claims 8-10 of the '630 Crystalline Form Patent. These claims are asserted against Zydus as infringing the gamma form.

c. A Single Characteristic Peak Is Weak Evidence Of The Presence Of A Crystalline Form Characterized By Four Or More Peaks

209. In general, a single peak cannot be used to definitively identify a polymorph, regardless of whether it has already been discovered or whether it remains an unknown polymorph. (*See* Kahr Tr. 1422-26, 1496-97)

210. Dr. Myerson failed to cite to any literature to support his opinion that use of a single peak is a scientifically valid method of identifying a particular crystalline form, particularly when other characteristic peaks are missing. (Myerson Tr. 766)

211. In a properly prepared sample, the absence of a conspicuous peak is strong evidence that the polymorph or form that must have that peak is not present. (Kahr Tr. 1425, 1495, 1506)

d. Defendants' Pre-Suit Internal Testing Is Weak Evidence Of Infringement

212. Defendants' internal documents may not compare their ANDA Products with any

of the Asserted Claims. (*See* Myerson Tr. 769; Kahr Tr. 1527-28)

213. Dr. Myerson has not determined the educational level of Defendants' scientists who performed internal XRPD analysis; nor did he do anything to determine whether they were POSAs under his definition. (*See* Myerson Tr. 744-45)

214. Dr. Myerson admits that he does not know how Defendants prepared their samples for XRPD testing. (*See* Myerson Tr. 754-55)

215. Defendants' diffractograms of their ANDA Products may have many peaks that the alpha, beta, or gamma forms of vortioxetine hydrobromide do not, and vice versa. (*See* Kahr Tr. 1492-95, 1498; *see also* Myerson Tr. 758-63; PTX-872 at 1; PTX-12 at FIG. 3) Defendants' diffractograms prepared using slow-scan XRPD analysis is weak evidence of infringement because a POSA would understand that FIGS. 1-17 of the Crystalline Form Patents and '096 Patent were prepared using regular ("normal") scan XRPD. (*See* Kahr Tr. 1508-09) As Dr. Myerson acknowledged, the Crystalline Form Patents and '096 Patent do not even mention slow-scan XRPD analysis. (Myerson Tr. 765)

216. Both sides' experts agree that there are likely other forms of vortioxetine hydrobromide that have not yet been discovered. (Myerson Tr. 767; Kahr Tr. 1426) It is possible that a peak attributable to a possibly infringing form in a subset of slow-scan XRPD diffractograms is due to the presence of an as-yet-undiscovered polymorph of vortioxetine hydrobromide.

217. Dr. Myerson admits that there were no aging studies performed on some Defendants' placebo. (Myerson Tr. 767-68) A POSA would understand that placebo aging studies are necessary in order to properly control for what may be happening to the excipients, as

the excipients themselves can undergo dynamic processes and produce new crystalline substances. (Kahr Tr. 1518)

218. It is possible that what appears to be a peak attributable to a possibly infringing form in Defendants' diffractograms is mislabeled baseline noise. (Sacchetti Tr. 1621-22; DTX-541 at 4) A scientist, looking for repetition and reproducibility, would not attribute noise in a single diffractogram that did not recur in Defendants' testing to be crystalline material. (Sacchetti Tr. 1618-22; *see also* Myerson Tr. 751; Kahr Tr. 1500-01; DTX541; PTX703; PTX4395; PTX-872)

e. Plaintiffs' Evidence Of Amorphous API Converting To Crystalline Forms Under Unrealistic Conditions Is Weak Evidence Of Infringement

219. For Alembic, Plaintiffs' evidence of an infringing peak in a sample batch that had been stored for 6-months under accelerated conditions, i.e., at an elevated temperature of 40 ºC and 75% relative humidity – conditions above those recommended for normal storage of Alembic's ANDA Product. (Kahr Tr. 1492)

220. For Lupin, Dr. Cockcroft testified that 40° C and 75% relative humidity are "extreme" conditions. (Cockcroft Tr. 1777) Lupin controls environmental conditions during manufacturing of its ANDA Product to not more than 25° C and not more than 45% relative humidity. (DTX-924 at 27) Lupin's proposed prescribing information requires storage at 25° C, with a permitted range of 15° to 30° C – but not including 40° C. (PTX-4531 at 24)

221. For Macleods, Dr. Myerson agreed that the results of stress testing "would allow someone to understand that it is important to keep the Macleods premix both dry and cool." (Myerson Tr. 914) He also testified that placing the Macleods premix "in a humidity container inside a laboratory incubator will cause crystalline form peaks to show up." (*Id.*)

222. For Sigmapharm, Dr. Morin's stress test treatments included, as one example, a combination of 40 ºC and 60% RH, a heat index of more than 135 ºF, which would not reflect normal "market conditions" for sale or storage of Sigmapharm's ANDA Products. (Myerson Tr. 958-60)

223. For Zydus, Dr. Morin exposed the expired tablets in open Eppendorf tubes to temperature and humidity conditions outside of Zydus's required storage and handling conditions. (Sacchetti Tr. 1614-16; DTX534; DTX544.03)

f. Plaintiffs' Testing Of Non-Representative Development Batches Of Defendants' Products Is Very Weak Evidence Of Infringement

224. The only internal Lupin data Dr. Myerson relied on was Lupin testing on a development batch. A development batch is not an exhibit batch. (Myerson Tr. 972) It is not representative of Lupin's ANDA Product that it seeks FDA permission to sell.

225. Dr. Myerson relied on Lupin's testing of this development batch – although, as Dr. Meyerson admitted, it is different from the final formulation of Lupin's ANDA Product. (Myerson Tr. 972-73) Dr. Myerson also admitted that the manufacturing process for the development batch differs from the process used to make Lupin's ANDA Product. (Myerson Tr. 973-74)

226. For Zydus, the research and development samples relied on by Dr. Myerson are composed of different ingredients than Zydus' proposed ANDA products, including having different excipients and an amorphous solid dispersion of vortioxetine hydrobromide in a different polymer than in Zydus' proposed ANDA product. (Myerson Tr. 790-96; PTX-183 at 39-40; PTX-429 at 87; PTX-1615 at 19) They are not representative of what the FDA would approve and what Zydus would sell. (Sacchetti Tr. 1598-99)

g. Plaintiffs' Handling Of Defendants' Product Samples Further Undermines The Probative Weight To Be Accorded to Plaintiffs' Testing Evidence

i) Lupin

227. All of the samples produced by Lupin during discovery, and on which Dr. Morin conducted his tests, were from batches manufactured in either February or March of 2017. (Cockcroft Tr. 1778-79; DTX-930; DTX-931; DTX-932; DTX-933; DTX-934; DTX-935; DTX-936; DTX-937) All of the samples produced by Lupin carried 24 month expiration dates, expiring by March 2019 at the latest. (DTX-930; DTX-931; DTX-932; DTX-933; DTX-934; DTX-935; DTX-936; DTX-937)

228. Lupin's samples were produced to Dr. Martyn Davies (at the direction of Plaintiffs) in the United Kingdom in October 2018, prior to their expiration. Lupin's samples were thereafter returned to Plaintiffs' counsel's office in Washington, DC after being repackaged in new containers. (PTX-1474)

229. Plaintiffs' counsel repackaged the samples once more and began shipping them to Dr. Morin in Switzerland in April 2019, and continued to make shipments until October 2019. (Cockcroft Tr. 1778; PTX-1474)

230. Plaintiffs' counsel did not ship Lupin's ANDA Product samples with any desiccant packs or any other device to control the relative humidity to which the samples would be exposed. (Morin Tr. 460-61; PTX-804)

231. Dr. Morin's testing of Lupin's ANDA Product samples occurred between May and December 2019, after expiration. (Cockcroft Tr. 1778) Dr. Morin did not test any Lupin samples within 24 months of their manufacture. (Cockcroft Tr. 1779)

ii) Macleods

232. Lot no. BVU702 was made in February of 2017. (Suryanarayanan Tr. 1813-14) This lot of experimental tablets expired in January of 2019. (*Id.*)

233. Tablets from lot no. BVU702 were delivered to the Washington, DC office of counsel for Plaintiffs on September 12, 2018. (Dr. Myerson Tr. 810) Selected samples from this lot did not arrive at Dr. Morin's lab until October 10, 2019. (Morin Tr. 433) When the samples arrived (by international air shipment) the tablets were not contained in an ANDA-specified High Density Polyethylene ("HDPE") bottle. (*Id.* at 429-30; Myerson Tr. 811-12)

234. The container containing the samples was also not sealed, and it did not include a silica gel sachet, as required by the Macleods ANDA specifications. (Morin Tr. 429-30) The tablet samples then sat in Dr. Morin's storage locker in ambient conditions, for 32 days before being prepared for analysis. (*Id.* at 434) Once prepared for analysis by Dr. Morin, the sample material was placed in a deep freezer, and stored at -20° C for another 20 days before being analyzed. (*Id.* at 435)

iii) Sigmapharm

235. Plaintiffs' counsel shipped Sigmapharm's 20 mg tablets to Dr. Morin on July 29, 2019 and September 27, 2019, in pill containers different from Sigmapharm's original container (i.e., a HDPE bottle with a heat induction seal). (Myerson Tr. 953-54; Hollingsworth Tr. 1457-58; PTX-1790)

236. Dr. Morin was not provided with samples for testing until after their two-year expiration. (Myerson Tr. 689; Hollingsworth Tr. 1455-57, 1467-68; PTX-421; PTX-422 at 33-35, 38, 52-57)

237. Plaintiffs admit there is no evidence explaining why they delayed testing until

after Sigmapharm's samples had expired. (Closing Argument Tr. 2124-25) The record is devoid of explanation on this point for any of Defendants' samples.

238. Plaintiffs and Dr. Morin handled all samples of Sigmapharm's 20 mg tablets in a manner far from ideal, including by (i) tampering with the storage container specifications in Sigmapharm's ANDA, not only opening the container and removing the foil moisture barrier but also removing Sigmapharm's 20 mg tablets from their container entirely; (ii) storing Sigmapharm's 20 mg tablets (presumably in the pillbox depicted in Dr. Morin's photographs, because there is no evidence to the contrary) under undisclosed conditions in a lawyer's custody with no approved closure or foil seal or desiccant or any other protection for the tablets; (iii) allowing them to expire, exceeding their proposed shelf life; (iv) shipping them to Dr. Morin under unspecified conditions; and (v) subjecting them to Dr. Morin's preparation process that included freezing ground-up tablets for days at -20 ºC (-4 ºF) before he tested them. (Morin Tr. 358-60, 452-53; Hollingsworth Tr. 1455-61; DTX-1491; DTX-1518 at 69; DTX-1537-39; DTX-1523-28; DTX-1499; PTX-1486; PTX-593; PTX-597)

239. Before subjecting the samples to his treatments, Dr. Morin placed them in a locker at his facility at "ambient relative humidity," sometimes for many days. (Morin Tr. 358-59, 433-34, 453)

240. Dr. Morin carried out his stress tests not only outside the ANDA container closure system but outside any container whatsoever, in open Eppendorf tubes that were placed in hot and humid chambers. (Morin Tr. 414-15, 453)

iv) Zydus

241. All samples tested by Dr. Morin were expired and subjected to shipping and handling conditions that would violate the FDA-approved storage and handling conditions set

forth in Zydus' ANDA, including removal from the proposed container closure system and exposure to extreme temperatures and humidity before receipt by Dr. Morin. (Morin Tr. 403-11; Myerson Tr. 801-02; Sacchetti Tr. 1628; DTX535; PTX-821 at 1, 8, 10, 14, 16, 20-21, 25-26)

242. The samples that Dr. Morin tested were both expired and mishandled. (Morin Tr. 403-11; Myerson Tr. 799, 801-02; Sacchetti Tr. 1599-1600, 1628-29; DTX-535; DTX-538; PTX-821 at 1, 8, 10, 14, 16, 20-21, 25-26) Plaintiffs waited at least five months after the tablets expired before they arranged to ship the tablets to Dr. Morin, who tested the tablets about a month later. (Sacchetti Tr. 1599-1600; PTX-817 at 2-3; PTX-1493 at 1-2)

243. Zydus' proposed ANDA product and API samples were tested at least six months past expiry or retest date. (Sacchetti Tr. 1599-1600; DTX-535 at 5; DTX-538 at 25, 33; PTX-817 at 2-3) It is undisputed that Plaintiffs received Zydus' samples over a year before testing was undertaken, prior to proposed ANDA product sample expiry. (Sacchetti Tr. 1599-1601; DTX-535 at 5; DTX-538 at 25, 33; DTX-542; PTX-817 at 2-3; PTX-1493 at 1-2, 4) There is insufficient evidence to find that the samples tested were representative of Zydus' proposed ANDA Product. (Myerson Tr. 800-03; Sacchetti Tr. 1602-03; DTX-554; DTX-564)

244. Dr. Morin did nothing to determine whether Plaintiffs' shipping and handling or his sample preparation methods induced crystallization. (Morin Tr. 402-03; Myerson Tr. 802)

2. Defendant-Specific Findings

a. Alembic

245. Alembic's ANDA Product contains vortioxetine hydrobromide benzyl alcohol hemi solvate ("Form C") as its API. (D.I. 985 Ex. 1A ¶¶ 5-8; Kahr Tr. 1484; DTX-705; PTX-1497 at 1-2)

246. Form C is described in DMF No. 031281, and claimed in U.S. Patent No.

10,071,092, assigned to Alembic. (D.I. 985 Ex. 1A ¶¶ 5-8; PTX-1111)

247. "Benzyl alcohol hemi solvate" has two molecules of vortioxetine hydrobromide for every molecule of benzyl alcohol (2:1 ratio). (Kahr Tr. 1484) Thus, Form C contains benzyl alcohol as part of its crystal structure. (Kahr Tr. 1484; DTX-705)

248. Form C is not a polymorph of vortioxetine hydrobromide because it has a different chemical composition than the alpha, beta, and gamma forms of vortioxetine hydrobromide. (Kahr Tr. 1484-85)

249. Alembic's XRPD testing confirms that Form C is not characterized or identifiable by reference to FIG. 3; nor does it have peaks characteristic of the beta form, i.e., XRPD peaks at 6.89, 9.73, 13.78, and 14.64 ± 0.10 ° 2θ. (DTX-703 at 19; Kahr Tr. 1488-89)

250. Alembic's Form C drug substance is thermodynamically less stable than the beta form of vortioxetine HBr. (Myerson Tr. 569) Plaintiffs allege that over time the Form C vortioxetine in Alembic's ANDA Product converts into beta form. (Myerson Tr. 575-76, 581)

251. Alembic's manufacturing process introduces mechanical forces during the compaction, milling, and compression steps. (Myerson Tr. 570-71; PTX-859; PTX-860) Alembic's manufacturing process introduces heat and water during the film coating process. (Myerson Tr. 571; PTX-853; PTX-859; PTX-860; PTX-3350)

252. Alembic's drug product specifications allow up to 6% water to be absorbed during the shelf life of Alembic's ANDA Product. (Myerson Tr. 571-72; PTX-856)

253. Alembic performed XRPD testing on its API, Form C, that was reported to the FDA as part of its ANDA. (DTX-705 at 19; *see also* Kahr Tr. 1484, 1487-88)

254. Alembic conducted stability studies to confirm that Form C is retained in its

ANDA Product over time, including during its proposed shelf-life of 24 months. (Myerson Tr. 757; PTX-870; PTX-4557; PTX-4559; PTX-4560)

255. Form C is retained in samples of Alembic's ANDA Product that have been stored for at least thirty-six (36) months, which is one year beyond the proposed shelf-life of the product. (Kahr Tr. 1498, 1507; PTX-4557; PTX-4559; PTX-4560)

256. Dr. Myerson admits that at least some of Form C remains in Alembic's ANDA Product. (Myerson Tr. 772)

257. Plaintiffs performed no experiments to determine whether Form C converts to the beta form upon manufacturing, although Dr. Myerson acknowledges they could have done so. (Myerson Tr. 745-46)

258. A POSA would understand that to convert to the beta form, Form C would have to undergo a chemical reaction whereby it loses its solvent molecules. (Kahr. Tr. 1484-85)

259. A POSA would understand that if Form C was undergoing conversion to the beta form, the beta form should accumulate in Alembic's ANDA Product as a function of time. (Myerson Tr. 748-49; Kahr Tr. 1506-07)

260. Dr. Myerson agreed that if Alembic's ANDA Product was undergoing conversion to the beta form, he would expect to see the peaks at 6.89° 2θ, 9.73° 2θ, 13.78° 2θ, and 14.62° 2θ to become more intense or grow in size over time. (Myerson Tr. 748-49) However, when comparing XRPD diffractograms of Alembic's ANDA Product over time (e.g., a period of 3 years), there is no evidence that any of the peaks of the beta form grow in intensity over time. (Kahr Tr. 1506-07; PTX-864 at 11; PTX-870 at 7; PTX-4557 at 17)

261. Prior to suit, Alembic selected a single XRPD peak at approximately 6.8° 2θ to

determine the possible presence of the beta form of vortioxetine HBr in Alembic's ANDA Product. Alembic also determined a limit of detection ("LOD") for the beta form in its ANDA Product (0.3% of the total weight of the tablet, which is 18% of the total drug load in Alembic's 5 mg tablet). (Myerson Tr. 574-77, 581; Srivastava Tr. 1013-15, 1021-22; Kahr Tr. 1516-17, 1520-21; PTX-843 at 1; PTX-1498 at 4; PTX-848 at 7-8)

262. Prior to suit, Alembic conducted XRPD testing on exhibit batches of its ANDA Product (5 mg, 10 mg, 15 mg, and 20 mg) for "polymorphic screening of beta form," recording both regular XRPD scans from 0° to 40° 2θ and slow XRPD scans from approximately 6.65° to 7.18° 2θ. (Kahr Tr. 1520-21; PTX-843; PTX-850; PTX-863; PTX-864; PTX-872; PTX-874; PTX-870; PTX-4557; PTX-4559)

263. Alembic found the 6.8° 2θ XRPD peak to be the "most characteristic, prominent, and non-interference 2θ peak" of the beta form of vortioxetine hydrobromide that had been disclosed by Plaintiffs in the Crystalline Form Patents. (Myerson Tr. 576; *see also* Kahr Tr. 1520-21; PTX-843; PTX-850; PTX-863; PTX-864; PTX-872; PTX-874; PTX-870; PTX-4557; PTX-4559)

264. Alembic's Rule 30(b)(6) witness, Virendra Srivastava, testified that Alembic selected the 6.8° 2θ XRPD peak for the "identification and determination of form beta" in Alembic's ANDA Product. (Srivastava Tr. 1013-15, 1022)

265. Alembic's expert, Dr. Bart Kahr, agrees that the beta form of vortioxetine HBr has an XRPD peak at 6.89° 2θ. (Kahr Tr. 1516)

266. The 6.8° 2θ peak characteristic of the beta form is not present in Alembic's Form C drug substance, placebo, or excipients, or any of the other forms of vortioxetine HBr disclosed

in the Crystalline Form. (Myerson Tr. 575-76, 581; Kahr Tr. 1488-89; PTX-871; PTX-875; DTX-705 at 19)

267. Alembic's expert, Dr. Bart Kahr, admits that the 6.8° 2θ peak cannot be explained by other known peaks in Alembic's ANDA Product. (Kahr Tr. 1516-18)

268. Alembic identified the 6.8° 2θ peak in select exhibit batch of Alembic's ANDA Product. (Myerson Tr. 577-82, 584-86, 982-84, 987; Srivastava Tr. 1016-17; PTX-850 at 1; *see also* PTX-863; PTX-872; PTX-845; PTX-846)

269. In particular, Alembic identified a single peak detected at 6.8° 2θ in exhibit batches of Alembic's ANDA Product: (a) following exposure to accelerated stability conditions (40° C / 75% RH) for three (3) and six (6) months (Myerson Tr. 577-79, 582-85, 768; PTX-845; PTX-846; PTX-850; PTX-863; PTX-872); (b) following exposure to long-term stability conditions (25° C / 60% RH) for 12, 18, and 24 months (all within the proposed shelf life of Alembic's ANDA Product) (Myerson Tr. 579-80, 585-86, 982-83, 984-86, 987; PTX-864; PTX-870); (c) following retesting under long-term stability conditions (25° C / 60% RH) for 36 months, which exceeded the proposed shelf life of Alembic's ANDA Product; and (d) following storage under long-term stability conditions (25° C / 60% RH) for 36 months. (Myerson Tr. 585-86, 986-87; PTX-4557; PTX-4559)

270. Alembic's expert, Dr. Kahr, admits that Alembic detected the 6.8° 2θ peak in exhibit batches of Alembic's ANDA Product stored under accelerated and long-term stability conditions. (Kahr Tr. 1514-16, 1521-25)

271. Alembic's internal documents do not compare Alembic's ANDA Product with any of the asserted claims. (Myerson Tr. 769; Kahr Tr. 1527-28)

272. Dr. Myerson further admits that he did nothing to determine the educational level of the Alembic scientists who performed the XRPD analysis; he did not determine whether they were POSAs under his definition. (Myerson Tr. 744-45)

273. Dr. Myerson admits that he does not know how Alembic prepared its samples for XRPD testing. (Myerson Tr. 754-55)

274. Alembic's expert, Dr. Kahr, compared diffractograms of exhibit batches of Alembic's ANDA Product to FIG. 3 and concluded that Alembic's ANDA Product has many peaks that FIG. 3 does not, and vice versa. (Kahr Tr. 1492-93, 1498) Indeed, at least the first five peaks of FIG. 3, including characteristic peaks at 9.73º 2θ and 13.78º 2θ, are not present in Alembic's ANDA Product. (Kahr Tr. 1494-95; PTX-872 at 1; PTX-12 at FIG. 3)

275. There is not a single diffractogram of Alembic's ANDA Product that shows all four claimed XRPD peaks of the beta form. (Kahr Tr. 1509; PTX-863; PTX-864; PTX-870; PTX-872; PTX-4557; PTX-4559; PTX-4560) That is, Alembic never identified XRPD peaks at all of 6.89, 9.73, 13.78, and 14.62 ± 0.10º 2θ in any sample of its ANDA Product. (Kahr Tr. 1415-16; Myerson Tr. 771-72)

276. At most, Alembic determined the presence of a single peak at approximately 6.8º 2θ on slow-scan XRPD analysis in a subset of its samples. (Srivastava Tr. 1017-18, 1020; *see also* Myerson Tr. 768; Kahr Tr. 1528)

277. Plaintiffs identify only one regular scan XRPD diffractogram where the computer software identifies a peak at 6.84º 2θ. (PTX-872) The diffractogram was taken of a sample (Batch No. 1705001524, hereafter, "Batch No. 1524") that had been stored for 6-months under accelerated conditions, i.e., at an elevated temperature of 40 ºC and 75% relative humidity. (*Id.*)

Such conditions are above those recommended for normal storage of Alembic's ANDA Product. (Kahr Tr. 1492) Dr. Myerson admits that POSAs could reasonably quibble as to whether there even is a peak present at 6.84º 2θ based on visual inspection of the diffractogram. (Myerson Tr. 751) POSAs do in fact disagree that there is a peak present in the diffractogram at 6.84º 2θ that is distinguishable from the stochastic noise. (Kahr Tr. 1500-01)

278. Plaintiffs also point to a subset of diffractograms that were prepared by Alembic using slow-scan XRPD analysis as evidence of a peak at 6.8º 2θ. (PTX-864; PTX-870; PTX-874; PTX-4559)

279. A POSA would understand that the FIGS. 1-17 of the Crystalline Form Patents and '096 Patent were prepared using regular ("normal") scan XRPD. (Kahr Tr. 1508-09) As Dr. Myerson acknowledged, the Crystalline Form Patents and '096 Patent do not even mention slow-scan XRPD analysis. (Myerson Tr. 765)

280. The peak seen at approximately 6.8º 2θ in a subset of slow-scan XRPD diffractograms does not grow in intensity over time. (Kahr Tr. 1506-07; PTX-864 at 11; PTX-870 at 7; PTX-4557 at 17)

281. A peak at 6.89º 2θ is not seen in any regular scan XRPD diffractograms of Alembic's ANDA Product at 12, 18, 24, or 36 months. (PTX-864; PTX-870; PTX-4557; PTX-4559; PTX-4560)

282. As Dr. Myerson admitted, all eight of the XRPD diffractograms of exhibit batches at 36 months are missing at least two claimed characteristic peaks of the beta form. (Myerson Tr. 758-63)

283. Dr. Myerson also admits that there were no aging studies performed on Alembic's

placebo. (Myerson Tr. 767-68) A POSA would understand that placebo aging studies are necessary in order to properly control for what may be happening to the excipients, as the excipients themselves can undergo dynamic processes and produce new crystalline substances. (Kahr Tr. 1518)

284. Both Dr. Myerson and Dr. Kahr agree that there are likely other forms of vortioxetine hydrobromide that have not yet been discovered. (Myerson Tr. 767; Kahr Tr. 146) It is possible that the peak seen at approximately 6.8º 2θ in a subset of slow-scan XRPD diffractograms is due to a not-yet-discovered polymorph of vortioxetine hydrobromide.

285. Even in those samples where a peak at 6.8º 2θ was determined on slow-scan XRPD analysis, the computer software did not identify the other characteristic peaks of the beta form. (PTX-863; PTX-864; PTX-870; PTX-872; PTX-4557; PTX-4559)

286. There is not a single diffractogram of Alembic's ANDA Product where the computer software identifies a peak at 9.73 ± 0.10º 2θ. (PTX-863; PTX-864; PTX-870; PTX-872; PTX-4557; PTX-4559)

287. Plaintiffs point to only one diffractogram (Batch No. 1524 at 6 months) to establish the presence of a peak at 9.73º 2θ in Alembic's ANDA Product. (PTX-872)

288. Dr. Myerson admits that POSAs could reasonably disagree whether there is a peak at 9.73º 2θ present in the diffractogram. (Myerson Tr. 752) POSAs do in fact disagree that there is a peak present at 9.73º 2θ in the diffractogram. (Kahr Tr. 1501-25)

289. At twenty-four (24) months, or at the end of its proposed shelf-life, Dr. Myerson admits that he is unable to see a peak at the 9.73º 2θ position in Alembic's ANDA Product, even based on visual inspection. (Myerson Tr. 758; PTX-870 at 4)

290. Alembic provided exhibit samples of its API and Drug Product to Plaintiffs. (Myerson Tr. 742-43; DTX-1848; DTX-1850)

291. A POSA would understand that the best way to determine infringement is to personally analyze the samples to fully understand the conditions of sample preparation and storage. (Kahr Tr. 1498)

292. Dr. Myerson did not personally perform any XRPD testing on Alembic's ANDA Product and did not instruct others to do so. (Myerson Tr. 742)

293. Dr. Morin did not report all of the results from his synchrotron analysis, and he only provided testing results on samples that Plaintiffs' counsel instructed him to. (Morin Tr. 472-74)

294. Alembic was the sole Defendant challenging infringement not to receive a report from Dr. Morin.

295. Dr. Myerson relied solely on XRPD analysis that Alembic performed in forming his opinions on whether Alembic's ANDA Product infringes the asserted claims. (Myerson Tr. 744)

b. Lupin

296. Lupin (like Macleods, Sigmapharm, and Zydus) describes the vortioxetine HBr in its ANDA Product as amorphous. (Myerson Tr. 601, 648-49, 687, 713-14; PTX-429; PTX-2062 at 17; PTX-420; PTX-421; PTX-214; PTX-215) Plaintiffs contend that Lupin's amorphous API converts to the alpha and beta crystalline forms. (Myerson Tr. 713)

297. Lupin's manufacturing process introduces mechanical forces including compression, atmospheric humidity up to 45%, and temperatures as high as 40 to 50°C. (Myerson Tr. 717-18; PTX-217 at 17-27; PTX-905; PTX-1507)

298. Lupin's release specification for its ANDA Product is not more than 5.5% water and Lupin's regulatory specification for its ANDA Product is not more than 6.5% water. (Myerson Tr. 716-17; PTX-906; PTX-3814; PTX-3815; PTX-3816) This shows that the drug product is allowed to absorb moisture during its shelf-life. (Myerson Tr. 716-17)

299. Lupin's manufacturing process begins by preparing a drug and binder solution. To create this, Lupin takes crystalline vortioxetine hydrobromide and fully dissolves it in a mixture of copovidone and methyl alcohol. (Cockcroft Tr. 1765; DTX-924 at 17) The active ingredient then becomes amorphous and is no longer in crystalline form. (Cockcroft Tr. 1765) Dr. Myerson agreed that the dissolution step should remove any crystalline vortioxetine hydrobromide. (Myerson Tr. 977)

300. Lupin's drug binder solution is then top sprayed over microcrystalline cellulose to form granules containing amorphous vortioxetine hydrobromide, which are subsequently dried and milled. (Cockcroft Tr. 1765; DTX-924 at 17-18) The granules are later blended, milled, and blended with extragranular sodium starch glycolate and magnesium stearate to form a lubricated blend. (DTX-924 at 18) Tablet compression and coating follows. (Cockcroft Tr. 1765; DTX-924 at 19-20)

301. Dr. Cockcroft testified that once the vortioxetine hydrobromide is dissolved during the manufacturing process, it remains in the amorphous form throughout the remainder of the process. (Cockcroft Tr. 1765)

302. The FDA requested that Lupin perform testing to establish that its vortioxetine hydrobromide is converted to the amorphous form during manufacture and maintains its amorphous form thereafter. (Cockcroft Tr. 1765-66; DTX-925 at 11)

303. Lupin prepared a Polymorphic Evaluation Report to respond to the FDA's request. (Cockcroft Tr. 1766; DTX-925 at 11; DTX-926; DTX-927) In it, Lupin performed X-ray powder diffractions on samples at various stages of its ANDA Product Manufacturing Process. (DTX-926; DTX-927) These stages included the Drug Substance Stage, the Dried Granules Stage, the Lubricated Blend Stage, the Core Tablets Stage, and the Coated Tablets Stage. (Cockcroft Tr. 1766; DTX-926; DTX-927)

304. Lupin's Polymorphic Evaluation Report established that the vortioxetine hydrobromide, after being converted to amorphous form at the start of Lupin's manufacturing process, remains in the amorphous form at each subsequent stage of the process. (Cockcroft Tr. 1766-67; DTX-925 at 11 ("Based on the study, it was observed that the Vortioxetine Hydrobromide (Crystalline form) is completely converted to the amorphous form in drug product, and the same is retained throughout the drug product manufacturing process."); DTX-927 at 6 ("The provided X-ray diffraction data of final drug product at different storage conditions i.e. Initial Stage, 6 Months Accelerated condition (40°C/75%RH) and 12 Month Long Term condition (25 ºC/60% RH) indicates that, the drug substance Vortioxetine Hydrobromide (Crystalline form) is completely converted to the amorphous form in the final drug product and is retained throughout the shelf life of the drug product."); DTX-926)

305. The diffraction pattern for the drug substance alone showed sharp peaks characteristic of a highly crystalline material, while the diffraction patterns for the Dried Granules Stage, Lubricated Blend Stage, Core Tablets Stage and Coated Tablets Stage showed "broad lumps" that are "characteristic of an amorphous material." (Cockcroft Tr. 1766-67; DTX-926)

306. Dr. Myerson admitted that other than the diffractogram of the API itself, there were no other diffractograms in Lupin's Polymorphic Evaluation Report that showed peaks establishing the presence of any crystalline form of vortioxetine hydrobromide. (Myerson Tr. 978-79)

307. Lupin also conducted 18-month long term stability studies on each strength of its ANDA Product. (Cockcroft Tr. 1767; DTX-929) Lupin's 18-month long term stability studies established that Lupin's ANDA Product contains a stable amorphous form of vortioxetine hydrobromide for at least 18 months after manufacture. (Cockcroft Tr. 1767-68) Dr. Cockcroft testified that none of the diffractograms in Lupin's 18-month long term stability data showed any evidence of crystalline forms of vortioxetine hydrobromide. (Cockcroft Tr. 1768; DTX-929)

308. During development, Lupin performed XRPD testing on a development batch of its ANDA Product and a corresponding placebo. (Myerson Tr. 719-21; PTX-983; PTX-12) After one month at 40° C / 75% RH, Lupin detected crystalline peaks that were not present in the corresponding placebo and align with Figure 2 of the '684 Patent, which corresponds to the possible presence of the alpha form of vortioxetine HBr. (Myerson Tr. 719-21; PTX-983; PTX-12)

309. The only internal Lupin data Dr. Myerson relied on was Lupin testing on this development batch. The development batch is not an exhibit batch. (Myerson Tr. 972) It is not representative of Lupin's ANDA Product that Lupin seeks FDA permission to sell.

310. Dr. Myerson relied on Lupin's testing of this development batch – although, as Dr. Meyerson admitted, it is different from the final formulation of Lupin's ANDA Product. (Myerson Tr. 972-73) Dr. Myerson also admitted that the manufacturing process for the

development batch differs from the process used to make Lupin's ANDA Product. (Myerson Tr. 973-74)

311. Dr. Myerson admitted that peaks at 17.49 or 18.58 ° 2θ, which the '630 Patent discloses as being characteristic of the alpha form, were missing in Lupin's development batch. (Myerson Tr. 974-75)

312. The asserted patents describe the beta form of vortioxetine hydrobromide as characterized by Figure 3, having four major x-ray diffraction peaks at 6.89, 9.73, 13.78, and 14.62 ± 0.1° 2θ, having a melting point ~231° C, absorbing 0.6% of water when exposed to high relative humidity, and having a solubility of 1.2 mg/ml in water. (PTX-12; PTX-15; PTX-17)

313. Plaintiffs' expert, Dr. Morin, tested four "reference" samples of Lupin's ANDA Product that were untreated (i.e., not subjected to any elevated temperature or relative humidity conditions). The four untreated reference samples are labelled MMCB25-H1, MMCB87-H1, MMCB139-H1, and MMCB206-H1. (Cockcroft Tr. 1770-72)

314. For each of the four untreated reference samples of Lupin's ANDA Product tested by Dr. Morin, Dr. Cockcroft compared the data generated by Dr. Morin with the diffraction patterns and major peaks identified in the patents. (Cockcroft Tr. 1770-72) Specifically, Dr. Cockcroft compared Dr. Morin's data with Figures 2 and 3 of the Crystalline Form Patents, corresponding to the alpha and beta forms, respectively. (*Id.*) Dr. Cockcroft also analyzed Dr. Morin's data in view of the four major peaks listed in the Crystalline Form Patents for the alpha form (5.85, 9.30, 17.49, and 18.58° 2θ) and the four major peaks listed for the beta form (6.89, 9.73, 13.78, and 14.62° 2θ). (*Id.*)

315. Having undertaken this analysis, Dr. Cockcroft opined that none of the four

reference samples tested by Dr. Morin showed any evidence of the alpha or beta forms of vortioxetine hydrobromide. (Cockcroft Tr. 1769-70) Dr. Cockcroft explained for each of the four reference samples there was no evidence of the alpha or beta forms when overlaying Dr. Morin's data with Figures 2 and 3 of the Crystalline Form Patents, or when looking for any of the four major peaks listed in the patents as associated with the alpha or beta forms. (Cockcroft Tr. 1770-72)

316. Dr. Myerson concluded that no alpha or beta form of vortioxetine hydrobromide were observable in the untreated Lupin samples. (Myerson Tr. 980)

317. Dr. Morin tested a total of 20 samples of batch nos. M790265, M790268, and M790271 of Lupin's ANDA Product. (D.I. 985, Ex. 1C ¶¶ 55-59, 88-89; Morin Tr. 546; PTX-214 at 206) In addition to the four untreated samples, the remainder were subjected to the following six treatment conditions: (1) 22° C / 50% RH; (2) 22° C / 75% RH; (3) 30° C / 75% RH; (4) 40° C / 30% RH; (5) 40° C / 60% RH; and (6) 40° C / 75% RH. (PTX-800)

318. Dr. Morin observed conversion of Lupin's drug product to the alpha and beta forms of vortioxetine HBr after exposure to 40° C / 75% RH. (Morin Tr. 554-57; Cockcroft Tr. 1791; PTX-802 at 23-25) After treatment, the alpha and beta peaks Dr. Morin detected grew in number and intensity over time. (Morin Tr. 555-57)

319. Dr. Cockcroft testified that 40° C and 75% relative humidity are "extreme" conditions. (Cockcroft Tr. 1777) Lupin controls environmental conditions during manufacturing of its ANDA Product to not more than 25° C and not more than 45% relative humidity. (DTX-924 at 27) Lupin's proposed prescribing information requires storage at 25° C, with a permitted range of 15° to 30° C – but not including 40° C. (PTX-4531 at 24)

320. Using the more precise synchrotron radiation source, Dr. Morin's data showed a peak characteristic of the alpha form at 17.42° 2θ when testing the reference alpha sample. (Cockcroft Tr. 1773) As explained by Dr. Cockcroft, the feature at 17.54° 2θ in Lupin's samples is "literally miles away." (Cockcroft Tr. 1773)

321. Lupin's Standard Test Procedure identifies a peak attributable to sodium starch glycolate, an excipient in Lupin's ANDA Product, as displaying a peak at 17.6° 2θ. (Cockcroft Tr. 1775; DTX-947 at 4) Dr. Cockcroft explained that because the peak lists in Lupin's Standard Test Procedure were generated using laboratory scale XRPD instruments, the precision is in the order of ±0.1° 2θ. (Cockcroft Tr. 1775; DTX-947 at 1-2, 4) Therefore, the peak at 17.6° 2θ attributable to the sodium starch glycolate in Lupin's ANDA Product may appear between 17.5 and 17.7° 2θ. (Cockcroft Tr. 1775) The peak at 17.54° 2θ in Dr. Morin's data, therefore, is likely a sodium starch glycolate peak. (Cockcroft Tr. 1776; DTX-947 at 4)

322. All of the samples produced by Lupin during discovery, and on which Dr. Morin conducted his tests, were from batches manufactured in either February or March of 2017. (Cockcroft Tr. 1778-79; DTX-930; DTX-931; DTX-932; DTX-933; DTX-934; DTX-935; DTX-936; DTX-937) All of the samples produced by Lupin carried 24 month expiration dates, expiring by March 2019 at the latest. (DTX-930; DTX-931; DTX-932; DTX-933; DTX-934; DTX-935; DTX-936; DTX-937)

323. Lupin's samples were produced to Dr. Martyn Davies (at the direction of Plaintiffs) in the United Kingdom in October 2018, prior to their expiration. Lupin's samples were thereafter returned to Plaintiffs' counsel's office in Washington, DC after being repackaged in new containers. (PTX-1474)

324. Plaintiffs' counsel repackaged the samples once more and began shipping Lupin's samples to Dr. Morin in Switzerland in April 2019, and continued to make shipments until October 2019. (Cockcroft Tr. 1778; PTX-1474)

325. Plaintiffs' counsel did not ship Lupin's ANDA Product samples with any desiccant packs or any other devices to control the relative humidity to which the samples would be exposed. (Morin Tr. 460-61; PTX-804)

326. Dr. Morin's testing of Lupin's ANDA Product samples occurred between May and December 2019, after expiration. (Cockcroft Tr. 1778) Dr. Morin did not test any Lupin samples within 24 months of their manufacture. (Cockcroft Tr. 1779)

c. Macleods

327. The specifications of the Macleods ANDA application mandate that its active ingredient be in amorphous form. (Myerson Tr. 832-33) (conceding Macleods' API specification requires amorphous form) The active ingredient is mixed with a polymer that stabilizes the vortioxetine hydrobromide in an amorphous matrix, called a premix. (Suryanarayanan Tr. 1801) (explaining premix design) The polymer used is co-povidone, and its ratio to active ingredient substantially reduces the propensity of the active ingredient to nucleate, which is the first step of crystallization. (Suryanarayanan Tr. 1801-02)

328. The Macleods ANDA specifications mandate that the active ingredient maintain its amorphous form in the tableted form. (D.I. 985 Ex. 1D ¶ 24; Suryanarayanan Tr. 1799-1800, 1811-12; *see also* Myerson Tr. 843)

329. The specifications of the Macleods ANDA require that its tablets be sealed within HDPE bottles that meet specific water permeability specifications. (Myerson Tr. 813, 849-51) Two silica gel sachets, designed to absorb water in the bottle, must also be included within each

sealed bottle of the Macleods ANDA Product. (Myerson Tr. 813, 850-51; Suryanarayanan Tr. 1813 (testifying that silica gel sachets absorb water and keep tablets dry)) Macleods tested its finished tablets for compliance with its amorphous specifications. (Suryanarayanan Tr. 1816-17)

330. Macleods' manufacturing process introduces mechanical forces during the compaction and compression steps. (Myerson Tr. 652; PTX-2062 at 50-54; PTX-3857 at 4, 6-7)

331. Macleods' manufacturing process introduces heat and water during the film coating process. (Myerson Tr. 652; PTX-2062 at 54-55; PTX-3857 at 5, 8) The film coating material includes water. (Myerson Tr. 652-53; PTX-2062 at 54-55; PTX-3857 at 5, 8) The inlet, outlet, and bed temperatures during the film coating material are 60 ± 10°C, 40 ± 10°C, and 45 ± 10°C. (Myerson Tr. 652-53; PTX-2062 at 55; PTX-3857 at 5, 8)

332. Macleods' LOD for the alpha form of vortioxetine HBr in its drug product is about 1.2% on a weight basis with respect to the tablet or about 12% on a weight basis with respect to the drug load. (Myerson Tr. 654; PTX-933 at 7-8, 10) The LOD of 12% with respect to the drug load means that Macleods' method would not be able to detect the alpha form of vortioxetine HBr if it is present in less than 12% of the drug load. (Myerson Tr. 655) As Dr. Myerson stated, below a limit of detection, "[y]ou just don't know if it's there or not." (Myerson Tr. 814)

333. Isolated experimental testing by Macleods identified certain tablets stored in blister packs as not in compliance with the Macleods amorphous specifications. (Myerson Tr. 660-61) Some of this data included testing on an experimental 15mg tablet lot. (Myerson Tr. 661; Suryanarayanan Tr. 1823; PTX-935 at 1; PTX-936 at 1)

334. Macleods used the XRPD peaks at 5.85° and 18.58° 2θ to identify the alpha form

of vortioxetine HBr in its drug substance and drug product. (D.I. 985 Ex. 1D ¶ 40; Myerson Tr. 654-55; PTX-933 at 7; PTX-1520 at 7)

335. In May-June 2019, Macleods conducted XRPD tests on its drug product stored under long-term stability conditions for 24 months in 30-tablet bottles, 90-tablet bottles, and blister packages. (PTX-4563 at 104-07, 116-19, 128-31, 140-43, 152-55, 164-67, 176-79, 188-91, 200-03)

336. Macleods detected crystalline peaks (that are not present in placebo tablets) in three drug product samples in blister packages stored under long-term stability conditions for 24 months. (Myerson Tr. 656-59; Suryanarayanan Tr. 1823-26; PTX-4563 at 16, 19, 76, 207-09; PTX-933 at 73-75; PTX-4562 at 83-84; PTX-4563 at 85-86)

337. Macleods' May 9, 2019 XRPD testing of a 20 mg drug product sample from batch BVU701 in blister packages stored under long-term stability condition (25° C / 60% RH) for 24 months, detected peaks at 3.5253°, 4.5°, 5.2511°, 5.7418°, 6.9592°, 11.9°, 13.9°, 16.2000°, 17.0°, 18.2°, 18.8°, 20.3°, 21.8429°, 22.8480°, and 23.5412° 2θ. (PTX-4563 at 207) The peaks at 5.7418°, 6.9592°, 13.9°, 16.2000°, 18.2°, 20.3°, 22.8480°, and 23.5412° 2θ are within 0.1° of the peaks found in Macleods' alpha form reference sample but not in its placebo tablet. (*See* PTX-933 at 57-59 (alpha), 73-75 (placebo); PTX-1520 at 56-58 (alpha); PTX-4562 at 70-72 (alpha), 83-84 (placebo); PTX-4563 at 72-74 (alpha), 85-86 (placebo))

338. Macleods' June 8, 2019 XRPD testing of a 10 mg drug product sample from batch BVS702 in blister packaging stored at 30° C / 75% RH for 24 months detected peaks at 3.5163°, 5.2149°, 5.4409°, 5.7°, 6.9°, 13.9°, 16.1978°, 18.2°, 20.2°, 21.8412°, 22.4423°, and 23.4955° 2θ. (PTX-4563 at 209) The peaks at 5.7°, 6.9°, 13.9°, 16.1978°, 18.2°, and 23.4955°

2θ are within 0.1° of the peaks found in Macleods' alpha form reference sample but not in its placebo tablet. (*See* PTX-933 at 57-59 (alpha reference), 73-75 (placebo); PTX-1520 at 56-58 (alpha reference); PTX-4562 at 70-72 (alpha reference), 83-84 (placebo); PTX-4563 at 72-74 (alpha reference), 85-86 (placebo))

339. Macleods' June 12, 2019 XRPD testing of a 20 mg drug product sample from batch BVU702 in blister packaging stored at 30° C / 75% RH for 24 months detected peaks at 3.5374°, 5.2318°, 5.4230°, 5.7°, 7.0°, 13.9°, 16.2377°, 18.2°, 21.8261°, 22.4423°, and 23.4800° 2θ. (PTX-4563 at 208) The peaks at 5.7°, 7.0°, 13.9°, 16.2377°, 18.2°, and 23.4800° 2θ are within 0.1° of the peaks found in Macleods' alpha form reference sample but not in its placebo tablet. (*See* PTX-933 at 57-59 (alpha reference), 73-75 (placebo); PTX-1520 at 56-58 (alpha reference); PTX-4562 at 70-72 (alpha reference), 83-84 (placebo); PTX-4563 at 72-74 (alpha reference), 85-86 (placebo))

340. The crystalline peaks that Macleods detected in drug product samples from batches BVU701, BVS702, and BVU702 that were stored under long-term stability conditions for 24 months in the blister packages included peaks that correspond to the alpha form of vortioxetine HBr and not to Macleods' placebo tablet. (Myerson Tr. 657-59; Suryanarayanan Tr. 1824-25 ("They are alpha peaks . . . at 5.85."); PTX-4563 at 207-09; PTX-933 at 57-59 (alpha reference), 73-75 (placebo); PTX-1520 at 56-58 (alpha reference); PTX-4562 at 70-72 (alpha reference), 83-84 (placebo); PTX 4563 at 72-74 (alpha reference), 85-86 (placebo))

341. On December 21, 2020, Macleods notified the FDA that "on account commercial reasons," it wished to withdraw the blister package from its ANDA. (Suryanarayanan Tr. 1828-29; PTX-4575 at 4) Macleods is not seeking approval to sell its products in a blister pack

configuration. (Myerson Tr. 839-41; *see also* Suryanarayanan Tr. 1819 (testifying Macleods "will be withdrawing the blister pack from the ANDA and it will not be commercialized as part of ANDA"))

342. All testing done by Macleods on its tablets, both initially and during all stability testing, when the tablets were packaged 30 and 90 count bottles, confirmed the tablets to be within specification – amorphous in form. (Suryanarayanan Tr. 1816-17) Accelerated and long-term stability studies conducted by Macleods on tablets stored in its HDPE bottles confirmed, without exception, that no crystallization of its tablet occurred. (*Id.* at 1818)

343. Macleods seeks approval to sell its ANDA product only in 30 and 90 counter HDPE bottles. (Myerson Tr. 813)

344. The FDA also asked that Macleods conduct a stress test of its premix, a study in which the premix was intentionally removed from its ANDA-specified packaging, and exposed to various heat and moisture conditions not permitted by the final ANDA specifications. (Myerson Tr. 665)

345. Macleods detected XRPD peaks at 18.1314° and 20.3288° 2θ in the drug substance sample exposed to 40° C /75% RH for 28 days. (PTX-929 at 30) Macleods detected XRPD peaks at 5.7295°, 17.4650°, 18.1282°, and 20.3120° 2θ in the drug substance sample exposed to 50°C/90% RH for 28 days. (*Id.* at 31) Macleods detected XRPD peaks at 5.7156°, 6.9353°, 9.1635°, 12.7649°, 13.9824°, 14.2478°, 16.1842°, 17.3788°, 18.1093°, 18.4685°, 19.2812°, 20.3402°, 21.0748°, 21.4798°, 22.0687°, 22.9035°, 23.4312°, 23.6732°, 24.0139°, 24.4985°, and 25.7359° 2θ in the drug substance sample exposed to 60° C / 75% RH for 28 days. (*Id.* at 32) Macleods detected XRPD peaks at 14.387°, 21.422°, 22.117°, 22.946°, 23.488°,

23.743°, and 24.588° 2θ in the drug substance sample exposed to 25° C / 80% RH for 24 hours. (*Id.* at 33) These peaks are within 0.1° of the peaks found in Macleods' alpha form reference sample but not in its placebo tablet. (*See* PTX-933 at 57-59 (alpha), 73-75 (placebo); PTX-1520 at 56-58 (alpha); PTX-4562 at 70-72 (alpha), 83-84 (placebo); PTX-4563 at 72-74 (alpha), 85-86 (placebo))

346. The data from the FDA stress test confirmed that (when stored at temperature conditions specified by the ANDA, and not stress testing conditions), the premix maintained its amorphous form for 28 days. (Myerson Tr. 665) Further, it also maintained its amorphous form after exposure for 12 hours to light. (*Id.*)

347. Macleods reported out-of-specification XRPD results for the stability tests dated August 19, 2017 of Vortioxetine Hydrobromide Premix samples from Batch Nos. E/1218/A17002, E/1218/A17003, and E/1218/A17004 stored for 6 months at 25° C / 60% RH. (Myerson Tr. 662-63; PTX-937 at 2) Macleods found that the "[d]iffractogram pattern . . . does not exhibit[] amorphous pattern" for these samples. (Suryanarayanan Tr. 1829-30; PTX-937 at 2)

348. Macleods conducted internal testing related to this out-of-specification alert. (Suryanarayanan Tr. 1808-10) The out-of-specification result was investigated, and samples from the same lots were tested again by two different analysts. (*Id.* at 1809-10) The conclusion was that the first analyst performing the study had improperly handled the sample. (*Id.* at 1810) Macleods concluded that the out-of-specification XRPD results are "attributed due to exposure of sample holder . . . to air and not due to quality of product." (Suryanarayanan Tr. 1830; PTX-937 at 11)

349. Dr. Morin tested 14 samples from Macleods' drug substance batch E/1218/A17002 – 2 untreated samples; 2 samples treated at 22° C / 75% RH for 3 and 5 days, respectively; 5 samples treated at 40° C / 30% RH for 1, 3, 5, 7, and 14 days, respectively; and 5 samples treated at 40° C / 75% RH for 1, 3, 5, 7, and 14 days, respectively. (Morin Tr. 522-23; PTX-807 at 2; PTX-809 at 8-16; PTX-4679)

350. Dr. Morin did not detect any crystalline peak in the 2 untreated Macleods drug substance samples he tested. (Morin Tr. 523; PTX-809 at 8-13; PTX-4679)

351. Dr. Morin detected alpha peaks that are within 0.10° of the 5.85°, 9.3°, 17.49°, and 18.58° 2θ in the Macleods drug substance samples treated at 22° C / 75% RH, 40° C / 30% RH, and 40° C / 75% RH. (D.I. 985 Ex. 1D ¶ 54; Morin Tr. 523-24; Myerson Tr. 666-67; PTX-4679)

352. Dr. Morin detected other XRPD diffraction peaks characteristic of the alpha form of vortioxetine HBr in the Macleods drug substance samples treated at 22° C / 75% RH, 40° C / 30% RH, and 40° C / 75% RH. (D.I. 985 Ex. 1D ¶ 56; Morin Tr. 524, 526; PTX-809 at 8-16)

353. Dr. Morin tested 25 tablet samples from Macleods' 20 mg drug product batch BVU702 – 3 untreated samples; 1 sample treated at 22° C / 50% RH for 14 days; 3 samples treated at 22° C / 60% RH for 5, 7, and 10 days, respectively; 5 samples treated at 22° C / 75% RH for 1, 3, 5, 7, and 10 days, respectively; 3 samples treated at 30° C / 60% RH for 5, 7, and 10 days, respectively; 5 samples treated at 30° C / 75% RH for 1, 3, 5, 7, and 10 days, respectively; 3 samples treated at 40° C / 60% RH for 5, 7, and 10 days, respectively; and 2 samples treated at 40° C / 75% RH for 1 and 3 days, respectively. (Morin Tr. 528-29, Myerson Tr. 671-72; PTX-807 at 2-3; PTX-809 at 17-37; PTX-4679)

354. Dr. Morin's S-XRPD analysis of the untreated sample MMCB223-I1 showed XRPD peaks at 5.85, 9.3, 17.49, and 18.58 ± 0.1° 2θ. (D.I. 985 Ex. 1D ¶ 58; PTX-4679) At least the XRPD peaks at 5.85, 9.3, and 18.58 ± 0.1° 2θ that Dr. Morin detected in the sample MMCB223-I1 correspond to the alpha form of vortioxetine HBr. (Morin Tr. 529-30; Myerson Tr. 667-68; PTX-4679) The alpha peak that is within 0.10° of 17.49° 2θ is not seen in the diffractogram. This may or may not be because it is too small and exists under the LOD. (Myerson Tr. 505-07, 668) (Myerson Tr. 814)

355. Macleods' ANDA Product (MMCB223-I1), a tablet that came from Macleods Lot No. BVU702, exhibited peaks consistent with the alpha (α) form of vortioxetine hydrobromide before exposure to the temperature and/or humidity test conditions. (D.I. 985 Ex. 1D ¶ 57; PTX-807 at 2; PTX-809 at 17-19)

356. Dr. Morin did not detect vortioxetine HBr alpha peaks in two other untreated Macleods tablet samples (MMCB117-I1 and MMCB143-I1). (Morin Tr. 530; Myerson Tr. 670; PTX-4679)

357. Dr. Morin detected the alpha form of vortioxetine HBr in the treated Macleods tablet samples under all of the treatment conditions that he applied (22° C / 50% RH, 22° C / 60% RH, 22° C / 75% RH, 30° C / 60% RH, 30° C / 75% RH, 40° C / 60% RH, and 40° C / 75% RH), which increased in intensity after the treatments. (D.I. 985 Ex. 1D ¶ 59; Morin Tr. 531, Myerson Tr. 666-67; PTX-4679)

358. Lot no. BVU702 was made in February of 2017. (Suryanarayanan Tr. 1813-14) This lot of experimental tablets expired in January of 2019. (*Id.*)

359. Tablets from lot no. BVU702 were delivered to the Washington, DC office of

counsel for Plaintiffs on September 12, 2018. (Myerson Tr. 810) Selected samples from this lot did not arrive at Dr. Morin's lab until October 10, 2019, ten months after they had expired. (Morin Tr. 433) When the samples arrived (by international air shipment), the tablets were not contained in an ANDA-specified HDPE bottle. (*Id.* at 429-30; Myerson Tr. 811-12)

360. The container containing the samples was not made of HDPE, was not sealed, and it did not include a silica gel sachet, as required by the Macleods ANDA specifications. (Morin Tr. 429-30) Dr. Morin did not know long that tablet had been in counsel's office in Washington, D.C. before he received it. (Morin Tr. 430-31) The tablet samples were then in Dr. Morin's storage locker, un-sealed, in a non-ANDA complaint container, without a desiccant, in ambient humidity conditions, for 32 days before being prepared for analysis. (Morin Tr. 434) Once prepared for analysis by Dr. Morin, the sample material was placed in a deep freezer, and stored at -20° C for another 20 days before being analyzed. (Morin Tr. 435)

361. Dr. Myerson agreed that the results of this stress testing "would allow someone to understand that it is important to keep the Macleods' premix both dry and cool." (Myerson Tr. 914) He also testified that placing the Macleods' premix "in a humidity container inside a laboratory incubator will cause crystalline form peaks to show up." (*Id.*)

362. Dr. Morin followed counsel's direction and did not report testing data that counsel instructed him not to report. (Morin Tr. 474)

363. Dr. Morin exposed the treated Macleods samples to heat and humidity conditions outside of the ANDA-specified packaging and storage conditions. (Morin Tr. 422-24)

d. Sigmapharm

364. It was a fundamental objective to develop Sigmapharm's vortioxetine tablets using only an amorphous form of vortioxetine HBr as the drug product intermediate. (Myerson

Tr. 690-91; PTX-422)

365. Sigmapharm experimented and specifically chose a high level of povidone as an excipient in order to attempt to slow crystallization of its ASD below detectable levels. (Myerson Tr. 691, 693-95; Spireas Tr. 1050, 1052)

366. Sigmapharm's amorphous premix is an amorphous solid dispersion ("ASD"). (Myerson Tr. 688, 942-43)

367. Almost all ASDs made using povidone have good physical stability. (Hollingsworth Tr. 1407–08; DTX-1315 at 93)

368. Sigmapharm's manufacturing process takes place in open factory conditions, and permits atmospheric RH up to 65%. (Myerson Tr. 699-700; PTX-559; PTX-566; PTX-1552) Sigmapharm's manufacturing procedure does not protect its drug product intermediate, final drug product, or intermediates thereof from atmospheric moisture. (*See* Myerson Tr. 699–700)

369. Sigmapharm's release specification for its 10 mg and 20 mg tablets permits the product to have not more than 5.0% water content. Sigmapharm's stability specification for its 10 mg and 20 mg tablets permits the product to have not more than 6.0% water content. The water content specifications mean that Sigmapharm's vortioxetine tablets can absorb additional moisture from the atmosphere up to 5.0% upon release or up to 6.0% during storage, and remain compliant with Sigmapharm's shelf-life specification. (Myerson Tr. 700-01; PTX-558, PTX-569; PTX-4231)

370. Although Sigmapharm's ANDA allows for its tablets to contain water up to 5% at release and up to 6% during stability testing, the actual water content of its tablets according to Plaintiffs' testing is 2.76%. (Myerson Tr. 943-46) Sigmapharm's stability testing of its ANDA

product shows that when the moisture content (loss on drying) is as high as 5.25%, "[n]o crystalline form of Vortioxetine HBr is present." (Hollingsworth Tr. 1468-69; DTX-1534 at 50)

371. Sigmapharm's manufacturing process introduces mechanical forces during the milling, compaction, and compression steps, and introduces heat and water at subsequent steps. (Myerson Tr. 698-700; PTX-559; PTX-566; PTX-1552)

372. Sigmapharm employs an elaborate procedure for packaging its ANDA Product, drug product intermediate, and in-process manufacturing products – involving double polyethylene lined containers with a silica gel desiccant placed in between the polyethylene bags of each container and storing the containers for the drug product intermediate under refrigerated conditions (2°C-8°C). (Myerson Tr. 700; PTX-559; PTX-566; PTX-1552)

373. Sigmapharm's proposed label for its ANDA Product does not specify any moisture or humidity limitations. (PTX-165; PTX-1551; PTX-4363; Myerson Tr. 701-02)

374. Sigmapharm's proposed prescribing label states: "Store at 77 °F (25 °C); excursions permitted to 59 °F to 86 °F (15 °C to 30 °C) [*see* USP Controlled Room Temperature]." (PTX-165 at 27; *see also* DTX-1532 at 59) USP 659 states that "articles must be protected from moisture, freezing, and excessive heat (*see* General Definitions) when no specific directions or limitations are provided" and "[w]here no specific directions or limitations are provided in the article's labeling, articles must be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution" (DTX-1459 at 2-3; *see also* Hollingsworth Tr. 1470-71)

375. Sigmapharm's proposed packaging says "Tamper evident: Do not accept if the seal over the bottle opening is broken or missing." Sigmapharm's ANDA Product includes a

tablet coating, a HDPE plastic container, a heat induction foil seal, and instructions for handling and storage. (Myerson Tr. 947-49)

376. Dr. Morin performed S-XRPD measurements on 11 samples of drug product intermediate from Sigmapharm exhibit batch no. API0010018, which Dr. Morin also referred to as Sigmapharm's drug substance. (Morin Tr. 381; Myerson Tr. 690; PTX-593; PTX-594)

377. Dr. Morin tested samples of Sigmapharm's drug product intermediate that were exposed to three different temperature and humidity conditions: (1) room temperature (22° C / 75% RH); (2) 40° C / 30% RH; and (3) 40° C / 75% RH. (Morin Tr. 381; PTX-593)

378. Dr. Morin tested two samples of Sigmapharm's drug product intermediate – MMCB7-J1 and MMCB99-J1 – without exposing the samples to stress conditions, called "reference." (Morin Tr. 381-82; PTX-593)

379. Dr. Morin did not detect any crystalline peaks in the untreated samples of Sigmapharm's drug product intermediate, which "means that the untreated drug substance does not contain any detectable crystalline form." (Morin Tr. 381-82; PTX-595; PTX-596)

380. After treatment of samples of Sigmapharm's drug product intermediate, Dr. Morin observed the appearance of peaks that correspond to the alpha and beta forms of vortioxetine HBr. (Morin Tr. 382-83, 386; PTX-595; PTX-596; PTX-814)

381. Dr. Morin first observed the alpha and beta forms three days after treatment of samples of Sigmapharm's drug product intermediate at 22° C / 75% RH. (Morin Tr. 382-83; PTX-596; PTX-814)

382. Dr. Morin observed all four major XRPD peaks associated with the beta form and many other peaks associate with the beta form in Sigmapharm's drug product intermediate

treated at 22° C / 75% RH. (Morin Tr. 383, 386; PTX-595; PTX-596)

383. Dr. Morin performed S-XRPD measurements on 20 samples of Sigmapharm's 20 mg tablets labelled J, J1, Tablet, and Tablet (J1) from Sigmapharm exhibit batch no. BB0940092; tablets labelled J2 and Tablet (J2) are from Sigmapharm exhibit batch no. SB0940091. (Morin Tr. 387-88, Myerson Tr. 690; PTX-593; PTX-594)

384. Dr. Morin tested samples of Sigmapharm's ANDA Product that were exposed to six conditions: (1) 22° C / 50% RH; (2) 22° C / 75% RH; (3) 30° C / 60% RH; (4) 30° C / 75% RH; (5) 40° C / 60% RH; and (6) 40°C and 75% RH. (Morin Tr. 387; PTX-593)

385. Dr. Morin did not detect any crystalline forms of vortioxetine HBr in untreated samples of Sigmapharm's drug products. (Morin Tr. 364-65, 381-82, 387-88)

386. After treatment of samples of Sigmapharm's ANDA Product, Dr. Morin observed the appearance of peaks that correspond to the alpha and beta forms of vortioxetine HBr. (Morin Tr. 388-91; PTX-595; PTX-596; PTX-814; DTX-1498 at 8)

387. Dr. Morin observed all four major reflections of the beta form five days after treatment of samples of Sigmapharm's ANDA Product at 22° C. (Morin Tr. 388; PTX-596; PTX-814)

388. The 20 different samples from two different exhibit batches of Sigmapharm's 20 mg tablets yielded consistent results. (Morin Tr. 387-88; PTX-593; PTX-594; PTX-595; PTX-596; PTX-814)

389. Dr. Morin did not observe a single peak associated with claimed crystalline vortioxetine HBr in any of the "untreated" samples he tested. (Morin Tr. 381-82, 387-88; Myerson Tr. 955-57, 963, 969)

390. Samples that Dr. Morin destroyed with his stress test treatments were converted to a caking compound; they were paste-like instead of being a powder, sticky to the touch with gloves, having no flowability, and could not be poured into capillary tubes for S-XRPD – they had to be smeared on glass rods instead. (Morin Tr. 447-48, 449; Hollingsworth Tr. 1464)

391. Even in the samples of Sigmapharm's 20 mg tablets that produced caking and stickiness at the 50% relative humidity threshold, Dr. Morin did not observe any of the four characteristic peaks of the alpha form or beta form of crystalline vortioxetine HBr. (Morin Tr. 455-58; PTX-814)

392. Plaintiffs admit there is "no evidence that any defendant will try to sell a cakey or sticky tablet." (Closing Argument Tr. 2126-27; *see also* Tr. 1380)

393. Dr. Morin's tablet-destroying stress test treatments included, as one example, a combination of 40º C and 60% RH, a heat index of more than 135 ºF, which would not reflect normal "market conditions" for sale or storage of Sigmapharm's ANDA Products. (Myerson Tr. 958-60)

394. Dr. Myerson testified that what he considered to be evidence of crystalline vortioxetine HBr appeared only in samples of Sigmapharm's 20 mg tablets and Drug Product Intermediate subjected to Dr. Morin's tablet-destroying stress test treatments, and not in any tablets that had not been destroyed in that manner, and he attributed the evidence of crystalline vortioxetine HBr to the tablet-destroying stress test treatments by Dr. Morin. (Myerson Tr. 963-64)

395. Dr. Morin tested, and Dr. Myerson testified, only as to Sigmapharm's 20 mg tablet, not Sigmapharm's 10 mg tablet. (Myerson Tr. 954-55) Sigmapharm's 20 mg and 10 mg

ANDA products differ not only in the amount of API; the 10 mg also has less povidone and more mannitol and microcrystalline cellulose, the latter two diluents which are crystalline materials. (Myerson Tr. 939-42; DTX-1532 at 12) "Mannitol is an excipient of choice for moisture sensitive drugs as it is non-hygroscopic." (DTX-1532 at 12)

396. Dr. Morin admits that he did not do any placebo tests to identify excipient peaks, or peaks that excipients might form after his tablet-destroying stress test treatments (Morin Tr. 458), even though excipient peaks could have coincided with the peak values for crystalline vortioxetine HBr.

397. Plaintiffs' counsel shipped Sigmapharm's 20 mg tablets to Dr. Morin on July 29, 2019, and September 27, 2019, in pill containers different from Sigmapharm's original container (i.e., a HDPE bottle with a heat induction seal). (Myerson Tr. 953-54; Hollingsworth Tr. 1457-58; PTX-1790)

398. Dr. Morin was not provided with samples for testing until after their two-year expiration. (Myerson Tr. 689; Hollingsworth Tr. 1455-57, 1467-68; PTX-421; PTX-422 at 33-35, 38, 52-57)

399. Plaintiffs admit there is no evidence explaining why they delayed testing until after Sigmapharm's samples had expired. (Closing Argument Tr. 2124-25)

400. Plaintiffs and Dr. Morin handled all samples of Sigmapharm's 20 mg tablets, including all "untreated" samples, improperly, including by (i) tampering with the storage container specified in Sigmapharm's ANDA, not only opening the container and removing the foil moisture barrier but also removing Sigmapharm's 20 mg tablets from their container entirely; (ii) storing Sigmapharm's 20 mg tablets (presumably in the pillbox depicted in Dr.

Morin's photographs, because there is no evidence to the contrary) under undisclosed conditions in a lawyer's custody with no approved closure or foil seal or desiccant or any other protection for the tablets; (iii) allowing them to expire, exceeding their proposed shelf life; (iv) shipping them to Dr. Morin under unspecified conditions; and (v) subjecting them to Dr. Morin's preparation process that included freezing ground-up tablets for days at -20 ºC (-4 ºF) before he tested them. (Morin Tr. 358-60, 452-53; Hollingsworth Tr. 1455-61; DTX-1491; DTX-1518 at 69; DTX-1537-39; DTX-1523-28; DTX-1499; PTX-1486; PTX00593; PTX00597)

401. Before subjecting the samples to his treatments, Dr. Morin placed them in a locker at his facility at "ambient relative humidity," sometimes for many days. (Morin Tr. 358-59, 433-34, 453)

402. Dr. Morin carried out his stress tests not only outside the ANDA container closure system but outside any container whatsoever, in open Eppendorf tubes that were placed in hot and humid chambers. (Morin Tr. 414-15, 453)

403. Plaintiffs subjected samples of Sigmapharm's expired tablets to treatment outside Sigmapharm's ANDA specification, even though Plaintiffs' "untreated" samples of Sigmapharm's expired tablets had already been through Sigmapharm's manufacturing process and showed no evidence of crystalline vortioxetine HBr. (Hollingsworth Tr. 1467-68, 1471-72, 1472)

404. Stability studies and stress testing are two different things, discussed in two different sections of the WHO guidance document Plaintiffs rely on. (Myerson Tr. 633) Dr. Myerson agreed that "Dr. Morin studies weren't stability studies . . . he did stress studies." (Myerson Tr. 636)

405. Sigmapharm performed long-term and accelerated stability studies of its ANDA Products and Drug Product Intermediate, which showed no evidence of claimed crystalline vortioxetine HBr. (Hollingsworth Tr. 1468-69; DTX-1546; DTX-1534; DTX-1553; DTX-1554; DTX-1555; DTX-1556; DTX-1557; DTX-1558; DTX-1559; DTX-1560; DTX-1561; DTX-1562; DTX-1563; DTX-1564; DTX-1565; DTX-1566; DTX-1567; DTX-1568; DTX-1569; DTX-1570)

406. Dr. Hollingsworth received samples of Sigmapharm's ANDA Products in their original packaging, sealed with a heat induction foil seal under the cap, and transported them from Manhattan, Kansas to Chicago, Illinois by airline in his carry-on luggage at "ambient conditions." (Myerson Tr. 1001-02)

407. Dr. Hollingsworth conducted a controlled S-XRPD experiment whereby he performed testing on near-expired, representative samples of Sigmapharm's 10 and 20 mg ANDA Products from each exhibit batch and their respective placebos. (Hollingsworth Tr. 1443-45, 1447-54, 1461, 1461-62, 1473; DTX-1498 at 3, 15, 20, and 29-31) He did not observe any claimed forms of crystalline vortioxetine HBr in any of the samples he tested (Hollingsworth Tr. 1461-62), and Plaintiffs confirmed his findings repeatedly during trial. (Myerson Tr. 957, 1003-04; Closing Argument Tr. 2124-25; DTX-1498 at 2-3)

408. Sigmapharm's expert Dr. Hollingsworth testified that Sigmapharm's ANDA Products and Drug Product Intermediate do not infringe Claims 1-3 of the '684 Patent, Claims 2-7 of the '630 Patent, and Claims 4-5 of the '096 Patent (the "crystalline claims"). (Hollingsworth Tr. 1396-1411, 1435-73, 1403; 1473; DTX-1498 at 20, 29-31; PTX-12; PTX-15; PTX-17)

409. The parties agree that Dr. Morin's testing of expired, "untreated" samples of Sigmapharm's 20 mg tablets and Drug Product Intermediate and Dr. Hollingsworth's testing of near-expired samples of Sigmapharm's ANDA Products both showed no evidence of any crystalline vortioxetine HBr in Sigmapharm's ANDA Products. (Morin Tr. 381-82, 387-88; PTX-595; PTX-596; PTX-814; Hollingsworth Tr. 1449-51, 1453, 1455, 1452; DTX-1498 at 3, 20, 29-31; *see also* Myerson Tr. 955-57, 1003-04 (testifying that "peak positions all appear to be identical" between Dr. Hollingsworth's data and Dr. Morin's data); Myerson Tr. 968-69 ("Q. And when the representative untreated Sigmapharm tablets were tested, the four characteristic peaks of the claims of the asserted patents or the alpha form or the beta form are just not there; correct? A. Correct.")

410. Plaintiffs' expert, Dr. Myerson, agreed that Dr. Morin's testing of samples he called "untreated" – like Sigmapharm's own internal testing, and testing by Sigmapharm's expert, Dr. Hollingsworth – all showed no evidence of any crystalline vortioxetine HBr but were, instead, consistent with amorphous material. (Myerson Tr. 955-57, 968-69)

e. Zydus

411. The vortioxetine hydrobromide in Zydus' proposed ANDA Product is in the form of an amorphous solid dispersion. (Sacchetti Tr. 1596; DTX-556; PTX-429 at 8) The use of amorphous solid dispersions is well established in the literature. (Sacchetti Tr. 1596; DTX-1292 at 28-37) However, when exposed to higher temperatures and higher humidity outside of their appropriate container closure system, amorphous solid dispersions can be destabilized, leading to crystallization. (Sacchetti Tr. 1596)

412. Zydus' manufacturing process introduces mechanical forces including compaction and compression as well as atmospheric humidity up to 50% and temperatures as

high as 40 to 50°C. (Myerson Tr. 606-08; PTX-739 at 2; PTX-704 at 3-5)

413. Zydus' drug substance specification allows Zydus' drug substance to absorb up to 3% water, and Zydus' in-process specification allows its tablets to absorb up to 6% water. (Myerson Tr. 604-06; PTX-429 at 19; PTX-729 at 3; PTX-730 at 3; PTX-731 at 3; PTX-732 at 3; PTX-733 at 3; PTX-734 at 3; PTX-727 at 2; PTX-728 at 2; PTX-2033 at 2; D.I. 985 Ex. 1J ¶¶ 43, 48-50) This indicates that Zydus' ASD is exposed to moisture and permitted to absorb water.

414. Zydus' drug substance requires storage under nitrogen at 2-8°C because at higher temperatures it can convert to crystalline forms. (Myerson Tr. 603; PTX-428 at 30-33)

415. Zydus recognizes that its drug substance is highly hygroscopic and found during development that temperature and/or the presence of water can change Zydus' amorphous form to a crystalline form. (Singh Tr. 1042-44; Sacchetti Tr. 1632)

416. Pharmaceutical scientists are well aware that they may need to protect drug substances and drug products from the effects of water. (Sacchetti Tr. 1594-95)

417. The following are commonly used to protect tablets from deleterious humidity: (1) desiccants; (2) tablet coatings; and (3) specialized packaging and container closure systems. (Sacchetti Tr. 1594-95; DTX-527 at 4-5; DTX-545 at 8) If approved, Zydus would use all three of these to protect its proposed ANDA Product from humidity, as set out in its ANDA. (Sacchetti Tr. 1595; DTX-534; PTX-429 at 6)

418. During development, Zydus detected the two most intense gamma peaks at 11.82° 2θ and 4.53° 2θ in more than a dozen development batches of its ANDA Product, including untreated samples, and at several different temperature and humidity conditions, including long-term stability conditions (25° C and 60% RH). (Myerson Tr. 613-14; PTX-759 at 4; *see also*

PTX-740; PTX-741; PTX-760; PTX-761; PTX-762; Myerson Tr. 611-13, Kesevan Tr. 1029-41; PTX-745 at 521-27; PTX-746; PTX-748; PTX-749; PTX-750) In several cases, Zydus employees labelled the peak at 11.82° 2θ with the Greek letter for gamma. (Myerson Tr. 611-13; Kesevan Tr. 1029-41; PTX-745 at 521-27; *see also* PTX-746; PTX-748; PTX-749; PTX-750)

419. The research and development samples relied on by Dr. Myerson are composed of different ingredients than Zydus' proposed ANDA Product, including different excipients and an amorphous solid dispersion of vortioxetine hydrobromide in a different polymer than in Zydus' proposed ANDA Product. (Myerson Tr. 790-96; PTX-183 at 39-40; PTX-429 at 87; PTX-1615 at 19) They are not representative of what the FDA would approve and what Zydus would sell. (Sacchetti Tr. 1598-99)

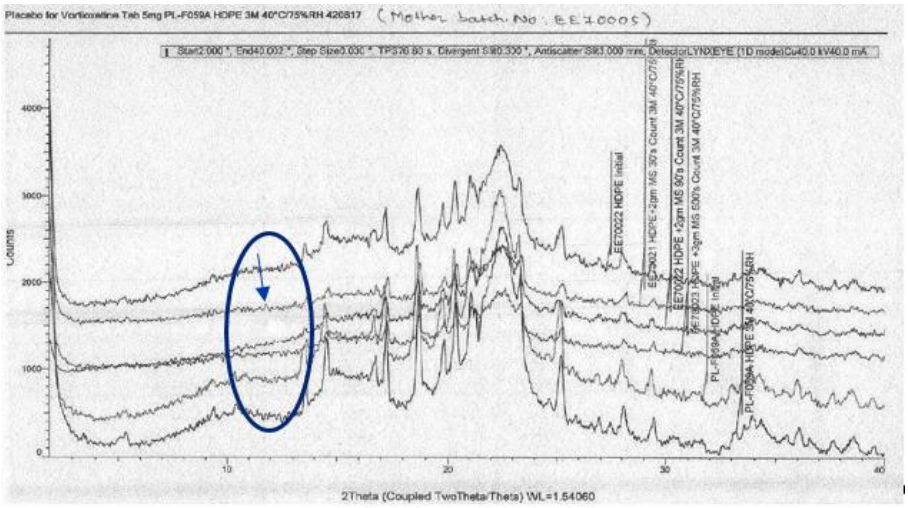
420. Zydus performed a polymorphic study on an exhibit batch of its drug product in which Plaintiffs allege it determined that a crystalline peak at 11.82° 2θ is "indicative and discriminatory" of the gamma form of vortioxetine HBr characterized by FIG. 4 of the asserted patents and XRPD peaks at 11.82, 16.01, 17.22, and 18.84 ±0.1° 2θ. (Myerson Tr. 609-10; Kesevan Tr. 1027-28; Sacchetti Tr. 1631; PTX-4395 at 20)

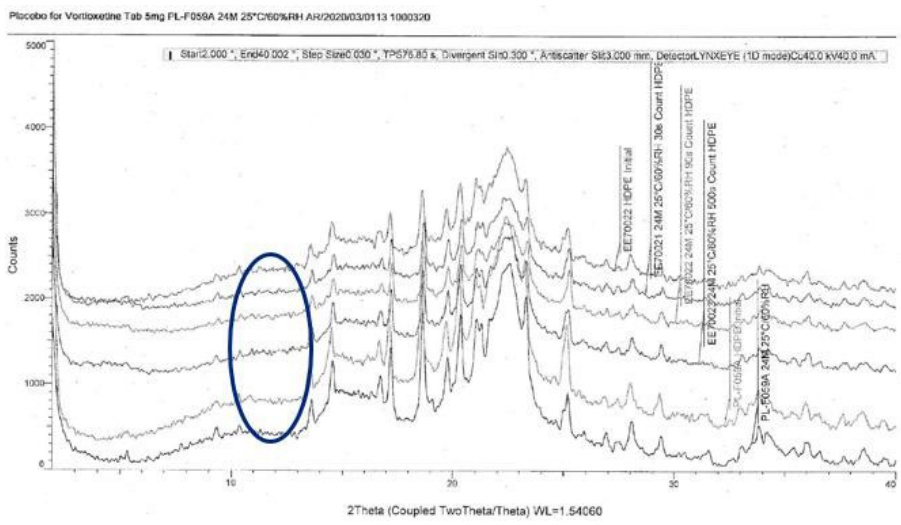
421. Zydus' XRPD software detected the XRPD peak at 11.82° 2θ that is allegedly "indicative and discriminatory" of the gamma form in exhibit batch EE70021 of its ANDA Product that was subjected to accelerated stability conditions of 40° C / 75% RH for three months. (Myerson Tr. 610-11; Sacchetti Tr. 1630-31; PTX-748 at 337-38)

422. The exhibit batch in which Zydus detected an alleged gamma peak at 11.82° 2θ was made exactly the way Zydus' product will be made if it is approved and sold. (Myerson Tr. 611)

423. Zydus did not identify a peak at 11.82° 2θ as evidence that the gamma form or any other crystalline form of vortioxetine is present in a sample. (Sacchetti Tr. 1631-32; PTX-4395 at 25) Instead, Zydus identified noninterfering peaks from various crystalline forms of vortioxetine not seen in the placebo tablet to determine whether the amorphous samples contain crystalline material of any kind. (Sacchetti Tr. 1631-32; PTX-4395 at 25)

424. In examining Zydus' internal testing, Dr. Myerson has placed undue weight on a single feature present in a single diffractogram (top figure below) that does not appear to be a peak. (Sacchetti Tr. 1618-23; DTX-541 at 4) In the second diffractogram (EE70021, 40° C, 75% RH), Dr. Myerson relies solely on the peak list to point at a feature near 11.82° 2θ (*see* arrow in top figure), which upon visual inspection of the diffractogram appears be mislabeled baseline noise. (Sacchetti Tr. 1621-22; DTX-541 at 4) A scientist, looking for repetition and reproducibility, would not attribute noise in a single diffractogram, that did not recur in any of Zydus' myriad testing, to crystalline material. (Sacchetti Tr. 1618-22; DTX-541; PTX-703; PTX-4395)





425. Zydus' internal testing shows that the vortioxetine hydrobromide in its proposed ANDA Product remains amorphous throughout its two-year expiry period and under accelerated conditions. (Sacchetti Tr. 1616-17; DTX-541; PTX-703; PTX-4395)

426. Zydus performed polymorph XRPD studies on 12 exhibit batches in three bottle configurations at two years under long-term conditions (25° C / 60% RH) and three months at accelerated conditions (40° C / 75% RH), all of which confirmed that its API remained amorphous under these conditions. (Sacchetti Tr. 1616-17; DTX-541; PTX-703; PTX-4395) Unlike Dr. Morin's testing, all of these studies included placebo controls, which is the standard of science. (Sacchetti Tr. 1616-17; DTX-541; PTX-703; PTX-4395)

427. Dr. Morin tested 11 samples of batch number VTA1ARJ01D of Zydus' drug substance. (Morin Tr. 364, 371; PTX-817) Two of the drug substance samples were untreated. (Morin Tr. 364; PTX-817) The remainder of the samples were exposed to the following treatment conditions for varying lengths of time: (1) 22° C / 75% RH; (2) 40° C / 30% RH; and (3) 40° C / 75% RH. (PTX-817)

428. Batch number VTA1ARJ01D is an exhibit batch submitted to the FDA as

representative of the drug substance in Zydus' ANDA Product. (DTX-535; PTX-428 at 16)

429. Dr. Morin did not detect any crystalline forms in the untreated samples of Zydus' drug substance. (Morin Tr. 364-65)

430. Dr. Morin detected the gamma form of vortioxetine HBr in samples of exhibit batches of Zydus' drug substance that were exposed to 40° C / 75% RH. (Morin Tr. 365-66; PTX-1462 at 10-12) Dr. Morin also detected the gamma form of vortioxetine HBr in samples of exhibit batches of Zydus' drug substance that were exposed to 22° C / 75% RH after one day of treatment. (Morin Tr. 366; PTX-1462 at 4-6)

431. Dr. Morin tested 21 samples of batch nos. EE70060 and EE70054 of Zydus' drug product. (Morin Tr. 367, 371; PTX-817) Three of the drug product samples were untreated. (PTX-817) The remaining samples were exposed to the following treatment conditions: (1) 22° C / 50% RH; (2) 22° C / 60% RH; (3) 22° C / 75% RH; (4) 30° C / 60% RH; (5) 40° C / 60% RH; and (6) 22° C / 60% RH. (PTX-817)

432. Dr. Morin detected the gamma form of vortioxetine HBr – including four XRPD Peaks at 11.82, 16.01, 17.22, and 18.84 ± 0.1° 2θ – in all 21 samples of Zydus' drug product he tested, including all three untreated samples. (Morin Tr. 367-70; Myerson Tr. 617-18; PTX-822; PTX-1462) With treatment, the gamma peaks grew in number and intensity over time. (Morin Tr. 368-69)

433. Zydus' expert, Dr. Mark Sacchetti, agreed that Dr. Morin detected the gamma form of vortioxetine HBr in at least one exhibit batch sample of Zydus' untreated drug product as well as an exhibit batch sample of Zydus' drug product exposed to 22° C / 50% RH. (Sacchetti Tr. 1625, 1627-28)

434. None of the samples tested by Dr. Morin were truly "untreated." (Sacchetti Tr. 1628-29) Rather, all samples were expired and subjected to shipping and handling conditions that would violate the FDA-approved storage and handling conditions set forth in Zydus' ANDA, including removal from the proposed container closure system and exposure to extreme temperatures and humidity, all before receipt by Dr. Morin. (Morin Tr. 403-11; Myerson Tr. 801-02; Sacchetti Tr. 1628-29; DTX-535; PTX-821 at 1, 8, 10, 14, 16, 20-21, 25-26)

435. Dr. Morin's sample preparation methods were likely to induce crystallization of Zydus' API within Zydus' proposed ANDA products. (Sacchetti Tr. 1606-07) Dr. Morin ground Zydus' proposed ANDA product samples, filled the resulting powder into capillary tubes at 22° C up to 25% RH, and placed the sealed capillaries in a freezer for storage. (Sacchetti Tr. 1606-07) Cooling air from 22° C at 25% RH to -20 °C, as Dr. Morin did during storage, produces supersaturated relative humidity, which could have induced crystallization. (Morin Tr. 414; Sacchetti Tr. 1606-07)

436. Dr. Morin exposed the expired tablets in open Eppendorf tubes to temperature and humidity conditions outside of Zydus' required storage and handling conditions. (Sacchetti Tr. 1614-16; DTX-534; DTX-544 at 3)

437. The samples that Dr. Morin tested were both expired and mishandled. (Morin Tr. 403-11; Myerson Tr. 799, 801-02; Sacchetti Tr. 1599-1600, 1628-29; DTX-535; DTX-538; PTX-821 at 1, 8, 10, 14, 16, 20-21, 25-26) Plaintiffs waited at least five months after the tablets expired before they arranged to ship the tablets to Dr. Morin, who tested the tablets about a month later. (Sacchetti Tr. 1599-1600; PTX-817 at 2-3; PTX-1493 at 1-2)

438. Zydus' proposed ANDA Product and API samples were tested at least six months

past expiry or retest date. (Sacchetti Tr. 1599-1600; DTX-535 at 5; DTX-538 at 25, 33; PTX-817 at 2-3) It is undisputed that Plaintiffs received Zydus' samples over a year before testing was undertaken, well prior to their expiration. (Sacchetti Tr. 1599-1601; DTX-535 at 5; DTX-538 at 25, 33; DTX-542; PTX-817 at 2-3; PTX-1493 at 1-2, 4) It is difficult to draw conclusions in Plaintiffs' favor from Dr. Morin's testing because it is not clear the samples tested were representative of Zydus' proposed ANDA Product. (Myerson Tr. 800-03; Sacchetti Tr. 1602-03; DTX-554; DTX-564)

439. Dr. Morin did nothing to determine whether Plaintiffs' shipping and handling or his sample preparation methods induced crystallization. (Morin Tr. 402-03; Myerson Tr. 802)

440. It is uncontested that the reference samples of Zydus' API tested by Dr. Morin showed no evidence of crystalline material. (Sacchetti Tr. 1604-05; PTX-819 at 5)

441. Dr. Morin and Dr. Myerson inaccurately attribute the peak at 18.4° 2θ to the gamma form of vortioxetine hydrobromide, even though it overlaps with a placebo peak. (Sacchetti Tr. 1610-12)

B. Invalidity

442. No challenge to the validity of the Asserted Claims of either of the Crystalline Form Patents was presented at trial.

X. Facts Related To Disputes Concerning The Process Patents

A. Infringement

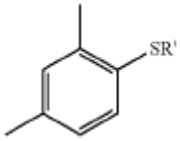
443. Zydus has admitted infringement of the '575 Process Patent. (D.I. 985 Ex. 1J ¶¶ 65-66)

444. Plaintiffs and Lupin went to trial over whether Lupin's manufacturing process infringes Claim 12 of the '626 Process Patent, both literally and under the doctrine of

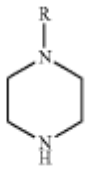
equivalents. (MacMillan Tr. 201)

445. The ’626 patent is a process patent covering a specific palladium-catalyzed process for the making of vortioxetine. (PTX-19 at Claim 12)

446. Claim 1 specifies “reacting” Compound II with Compound III and Compound IV. (PTX-19 at Claim 1)

447. Compound II is 

wherein R’ represent hydrogen or a mono-valent metal ion. (PTX-19 at Claim 1) When R’ represents a hydrogen, it is a thiol. (Suryanarayanan Tr. 1846; PTX-19) When R’ represents a mono-valent metal ion, it is a thiolate. (Suryanarayanan Tr. at 1846; PTX-19)

448. Compound IV is 

wherein R represents hydrogen or a protecting group. (MacMillan Tr. 292-93)

449. Lupin manufactures the vortioxetine HBr present in its ANDA Product under DMF No. 031507 in Tarapur India. (D.I. 985 Ex. 1C ¶ 69)

450. Lupin’s ANDA describes the same synthetic process as described in Lupin’s DMF for producing vortioxetine HBr. (D.I. 985 Ex. 1C ¶ 77; *see also* MacMillan Tr. 248-50)

451. In a palladium catalyzed cross-coupling reaction, two compounds react to form a product via oxidative addition and reductive elimination when exposed to a palladium catalyst. (MacMillan Tr. 202-03; Micalizio Tr. 1852-54)

452. Both Plaintiffs' expert, Dr. MacMillan, and Lupin's expert, Dr. Micalizio, testified that as part of a palladium catalyzed cross-coupling reaction, a POSA would understand that the two compounds react with the palladium catalyst to form different intermediates before yielding the final product. (MacMillan Tr. 202-03; Micalizio Tr. 1573, 1852-54)

453. The palladium catalyst drives the cross-coupling reaction, but is not consumed and is therefore not a reactant. (MacMillan Tr. 203, 295-96) A palladium-catalyzed cross-coupling reaction can occur in a one-pot synthesis where all reactants are mixed together at the start of the reaction or process (as recited in Claim 3 of the '626 Patent) or via a two-pot synthesis where two compounds first react and then their reaction product reacts with a third compound (as recited in Claim 2 of the '626 Patent). (MacMillan Tr. 205-07; PTX-19 at 15:1-3, Claims 2-3)

454. The process of Claim 12 is not limited to a one-pot synthesis. (MacMillan Tr. 208, 214)

455. The process of Claim 12 involves two distinct palladium catalyzed cross-coupling reactions. (MacMillan Tr. 208-09)

456. The process of Claim 12 results in a compound of Claim 1 or a pharmaceutically acceptable salt thereof. (PTX-19) That compound may be vortioxetine or its pharmaceutically acceptable salt, vortioxetine HBr. (MacMillan Tr. 249)

457. The process of Claim 12 involves reacting compound II with a compound of formula III and compound IV (the formula of each is specified in the claim), in the presence of a solvent, a base, a palladium catalyst consisting of a palladium source and rac-BINAP, at a temperature of between 60º C and 130º C. (PTX-19)

458. Compound II recited in Claim 1 can either be a thiol wherein R' is a hydrogen or a thiolate wherein R' is a mono-valent ion. (PTX-19) The thiol or thiolate of compound II can be introduced into the reaction described in Claim 12 by various methods. For example, the thiol or thiolate can be directly added, or charged, to the reaction, or the thiol or thiolate can be generated from a [redacted]. (MacMillan Tr. 209-10)

459. Dr. MacMillan applied the plain and ordinary meaning of all terms in Claim 12 of the '626 Patent in his infringement analysis. (MacMillan Tr. 211)

460. The process described in Lupin's ANDA and DMF manufactures vortioxetine HBr or a pharmaceutically acceptable salt (MacMillan Tr. 248-51; PTX-237 at 3, 6, 24, 27; PTX-215 at 3, 8, 10; D.I. 985 Ex. 1C ¶¶ 69-70, 75-80) and occurs in the presence of a [redacted] at a temperature between 60° C and 130° C. (MacMillan Tr. 270-72; PTX-237 at 4-5, 20; D.I. 985 Ex. 1C ¶¶ 73-74)

461. Lupin's process for the manufacture of vortioxetine HBr occurs in Stages I-III, with Stage I further divided into steps A, B, and C. (PTX-237 at 3-6; D.I. 985 Ex. 1C ¶ 70; MacMillan Tr. 252)

462. In Stage I, Step A of Lupin's process, [redacted]. (D.I. 985 Ex. 1C ¶ 71)

463. In Stage I, Step B of Lupin's process, [redacted] (D.I.

985 Ex. 1C ¶ 73)

464. Within this step, Lupin's process utilizes [redacted], which falls under the genus of a compound of formula III of Claim 1 of the '626 Patent, in the presence of [redacted] (MacMillan Tr. 264-65, 270-72; PTX-237 at 4, 20; D.I. 985 Ex. 1C ¶ 73)

465. In Stage I, Step C of Lupin's process, [redacted]. (MacMillan Tr. 265, 270-72; PTX-237 at 5, 20; D.I. 985 Ex. 1C ¶ 74)

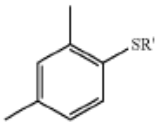
466. Within this step, Lupin's process utilizes [redacted]. (MacMillan Tr. 265, 270-72; PTX-237 at 5, 20; D.I. 985, Ex. 1C ¶ 74)

467. Lupin prepares the pharmaceutically acceptable salt of vortioxetine, vortioxetine HBr, in Stage II of its process. (D.I. 985 Ex. 1C ¶ 75)

468. The vortioxetine HBr produced in Stage II of Lupin's process is [redacted] does not make any material changes to the vortioxetine HBr synthesized in Stage II, as the molecular formula and chemical bonds of vortioxetine HBr are unaltered. (D.I. 985 Ex. 1C ¶ 76)

469. None of the processes described in Lupin's ANDA for formulation of Lupin's ANDA Product make any material changes to the vortioxetine HBr, including any changes to the

chemical bonds of vortioxetine HBr manufactured by Lupin according to DMF No. 031507. (MacMillan Tr. 250)

470. 2,4-dimethylthiophenol is a compound of compound II () of Claim 1 (and therefore of Claim 12) of the '626 Patent wherein R' represents hydrogen. (MacMillan Tr. 253; Micalizio Tr. 1838)

471. Both sides' experts agreed on the following specific differences between VRT-I and Compound II. (Micalizio Tr. 1844-47) VRT-I is [redacted] (MacMillan Tr. 284; Micalizio Tr. 1846) VRT-I [redacted]. (MacMillan Tr. 284; Micalizio Tr. 1845) VRT-I and Compound II do [redacted] (MacMillan Tr. 284) They have different electronic structures. (MacMillan Tr. 284; Micalizio Tr. 1842, 1846-47) The bond strengths between the [redacted] are stronger than the bond strengths between the sulfur and the hydrogen (Compound II). (MacMillan Tr. 284)

472. A POSA would understand that VRT-I does not and cannot [redacted] (MacMillan Tr. 257-58, 293-94)

473. Dr. Micalizio admitted that the [redacted]. (Micalizio Tr. 1849, 1851-52; MacMillan Tr. 262)

474. In Stage I, Step B, VRT-I is exposed to the [redacted]

[redacted]. (MacMillan Tr. 255; PTX-237 at 4, 20) Under these conditions, the [redacted] and forms the thiol or thiolate of compound II of the '626 Patent. (MacMillan Tr. 255-58, 265-69, 289) Stated another way, [redacted] of compound II which is formed during Lupin's process. (MacMillan Tr. 255-56)

475. The generation of compound II of the '626 Patent following the [redacted] is further confirmed by Lupin's own documents. An internal study representative of Lupin's process showed that VRT-I is [redacted] (MacMillan Tr. 260-61, 291-92; PTX-272 at 1 ("[redacted]")) Lupin's study also stated that [redacted] (PTX-272 at 1; MacMillan Tr. 261-62)

476. Following [redacted] Lupin's process for the preparation of vortioxetine HBr proceeds according to the reaction conditions described in Claim 12 of the '626 Patent. (*See, e.g.,* MacMillan Tr. 248-51, 264-65, 270-72; PTX-237 at 3-6, 20, 24, 27; PTX-215 at 3, 8, 10; D.I. 985 Ex. 1C ¶¶ 69-80)

477. [redacted] aside, Lupin's in-process specification confirms that its process will, in fact, react compound II with compound III in Stage I, Step B. After Stage I, Step A, not more than [redacted] may be present at the beginning of Stage I, Step B to react with [redacted] and generate VRT-II. (D.I. 985 Ex. 1C ¶ 72; PTX-225 at 1; PTX-237 at 19; MacMillan Tr. 254, 263-64, 285-88, 295)

478. The [redacted] in Stage I, Step B of Lupin's synthesis is described in

the literature. The reaction depicted in Scheme 1 of Wager *et al.* [redacted] of a [redacted] of compound II of the '626 Patent. (MacMillan Tr. 258-60; PTX-1436 at 2; *see also* PTX-1435 at 23 ([redacted]))

479. Lupin's in-process specification also confirms that Lupin will, in fact, react compound II with compounds III and IV in Stage I, Step C. After Stage I, Step B, not more than [redacted] content may be present at the beginning of Stage I, Step C to react with [redacted]. (MacMillan Tr. 267-69, 287-88; PTX-225 at 1) Because up to [redacted] may not react in Stage I, Step B, up to [redacted] may also be present in Stage I, Step C of Lupin's process and react with [redacted] to form VRT-III. (MacMillan Tr. 267-69, 287-88)

480. Plaintiffs and Lupin dispute the plain and ordinary meaning of "reacting" recited in Claim 1 of the '626 Patent.

481. Dr. MacMillan and Dr. Micalizio agree that the term is "ubiquitous" in the field of chemistry. (MacMillan Tr. 212-13; Micalizio Tr. 1568)

482. The specification of the '626 Patent does not provide a definition for "reacting." (PTX-19)

483. Neither the applicants nor the Examiner defined the term "reacting" during the prosecution of the patent application that led to the issuance of the '626 Patent.

484. At trial, Lupin's expert, Dr. Micalizio, testified that the plain and ordinary meaning of "reacting" must be understood to mean "the specified chemicals are added to the reaction vessel at the beginning of the process as starting material." (Micalizio Tr. 1568-69) Dr.

Micalizio further testified that "the specified chemicals" in his redefinition of "reacting" refer to compounds II, III, and IV; "not *in situ* intermediates." (Micalizio Tr. 1566-67)

485. However, a POSA would understand the plain and ordinary meaning of "reacting" is "the changing of a reactant(s) to product(s)." (MacMillan Tr. 212-13)

486. The transition "comprising" immediately precedes "reacting" in Claim 1 of the '626 Patent and Dr. MacMillan confirmed that a POSA would understand the process of Claim 1 is "not exclusively restricted to these" claimed elements. (MacMillan Tr. 214; PTX-19 at Claim 1) Claims 2 and 3 of the '626 Patent also provide support for the plain and ordinary meaning of "reacting" by describing, respectively, either a two-pot or one-pot synthesis. (MacMillan Tr. 213-14; PTX-19 at Claims 2-3)

487. Nothing in the specification or prosecution history of the '626 Patent alters the plain and ordinary meaning of "reacting." (MacMillan Tr. 214-15)

488. The 2004 Fifth Edition of the Oxford Dictionary of Chemistry defines "chemical reaction" as "[a] change in which one or more chemical elements or compounds (the *reactants*) form new compounds (the *products*)." (PTX-1432 at 3; *see also* MacMillan Tr. 215-16)

489. Lupin's invalidity expert, Dr. Trevor Laird, agreed with the plain and ordinary meaning of "reacting" as used in the '626 Patent and consistent with Dr. MacMillan's testimony. (MacMillan Tr. 218) (quoting Dr. Laird's deposition testimony)

490. Dr. Micalizio's latest "plain and ordinary" meaning of "reacting" rewrites Claim 1 in a way that transforms Claim 1 into Claim 3. Dr. Micalizio's inclusion of "added" into Claim 1 requires that compounds II, III, and IV be "added . . . at the beginning of the process as starting material." (Micalizio Tr. 1568-69) Claim 3 recites "compound II, compound III and compound

IV are mixed together at the start of the process." (PTX-19 at claim 3)

491. A POSA would refer to the action of "adding" compounds to a reaction vessel as "charging" not "reacting." (MacMillan Tr. 216)

492. Both Dr. MacMillan and Dr. Micalizio agreed that a POSA would understand that when two compounds react via a palladium-catalyzed cross-coupling reaction, such as the one claimed by the '626 Patent, palladium-compound intermediates are formed. (MacMillan Tr. 202-03; Micalizio Tr. 1573, 1852-54) Moreover, and contrary to Dr. Micalizio's testimony (Micalizio Tr. 1568), requiring direct interaction between compounds II and IV would not result in the formation of the claimed product.

B. Invalidity

493. Lupin did not challenge the validity of the Asserted Claim of the '626 Process Patent.

494. At trial, Zydus contended that Claim 3 of the '575 Process Patent is invalid due to obviousness based on the same six prior art references relied on by Defendants in connection with their invalidity challenge to the Compound Patents, and optionally further in view of GB '711. (Lepore Tr. 1915; D.I. 1011 at 23)

495. Dr. Lepore admitted that any evidence regarding the purported obviousness of Claim 3 is identical to the evidence that the asserted claims of the Compound Patents are allegedly obvious. (Lepore Tr. 1914-15)

496. The priority date for Claim 3 of the '575 Patent is Oct. 4, 2001. (DTX-242 at 1)

497. GB '711 was identified on the face of the '575 Patent (and on the face of the '884 Patent) as considered by the USPTO during prosecution. (PTX-10; DTX-242 at 1)

498. GB '711 describes a broad genus of phenoxy compounds having the structure of

formula I, and reports that these compounds may be useful in the treatment of glucid and lipid metabolism disorders. (DTX-258)

499. GB ’711 does not disclose any compounds that may have any use as an antidepressant. (Lepore Tr. 1961; DTX-258)

500. GB ’711 does not disclose 1-[2-(2,4-DMPS)P]P. (Lepore Tr. 1961)

501. GB ’711 discloses ethers that correspond to Dr. Lepore’s biarylether piperazine motif. GB ’711 also discloses the reaction of a biarylether aniline with a bis(halo)ethyl amine to form biarylether piperazines, which are encompassed by the biarylether piperazine lead motif. (Lepore Tr. 1902-03, 1914-15; DTX-258 at 1-3)

502. However, GB ’711 does not disclose any biological activity data. Nor does it offer any teaching, suggestion, or motivation to modify the disclosed compounds in order to potentially achieve antidepressant activity, or provide any need to modify or improve upon these compounds. (DTX-258)

503. Dr. Lepore’s obviousness opinion with respect to the asserted claims of the Compound Patents concludes with a genus of compounds that includes 1-[2-(2,4-DMPS)P]P. (*See* Lepore Tr. 1934-35, 2038-39; Reider Tr. 2053-54) Dr. Lepore’s obviousness opinion regarding Claim 3 of the ’575 Patent, however, is premised on a POSA specifically seeking to synthesize 1-[2-(2,4-DMPS)P]P through a specific process. (Lepore Tr.. 1915; DTX-256 at 2; DTX-258 at 1-3; DTX-367 at 2, 12, 32; DTX-378 at 2)

504. Neither Planas (DTX-371 at 1) nor Pinder (DTX-259) discloses any synthetic methods at all. (Lepore Tr. 1958-59)

505. Jílek and Kopicová disclose methods of making piperazine-containing compounds

by adding an already formed piperazine; not a compound of formula IVa or a bis(chloro or bromo)ethyl amine as required by Claim 3. (DTX-257 at 8; DTX-349 at 7)

506. Neither ES '127 nor GB '711 discloses a phenylthiol aniline or reaction between a phenylthiol aniline and a bis(halo)ethyl amine. (Lepore Tr. 1960-61; DTX-256; DTX-258)

507. WO '678 discloses a piperazine-containing secondary amine of formula III that can be prepared by either reacting an aniline with a bis(2-chloroethyl)amine hydrochloride or by using a multistep synthesis. (Reider Tr. 2065-66; DTX-367 at 14)

508. Neither Zydus nor Dr. Lepore provides any reason why a POSA would prepare a piperazine-containing secondary amine of formula III by reacting an aniline with a bis(2-chloroethyl)amine and not the disclosed multistep synthesis.

509. Dr. Lepore never testified that WO '678 discloses the synthesis of 1-[2-(2,4-DMPS)P]P by reacting an aniline with a dihaloethylamine. Nor did Dr. Lepore testify that Formula III of WO '678 encompasses Example 3 of GB '711.

510. Dr. Lepore has not offered any reasoning or explanation as to why a POSA would have a reasonable expectation to successfully formulate 1-[2-(2,4-DMPS)P]P according to Claim 3 of the '575 Patent. His opinion is conclusory. (Lepore Tr. 1915)

XI. Facts Relating To Induced And Contributory Infringement Of The Sexual Dysfunction Patent

A. Claims Requiring Crystalline Forms Are Not Infringed

511. Plaintiffs have asserted that Alembic, Lupin, and Sigmapharm infringe Claims 4 and 5 of the '096 patent, which require the beta form of vortioxetine. (PTX-17 at 20:48-53) As the Court is not persuaded that the proposed ANDA Products of Alembic, Lupin, and Sigmapharm contain crystalline forms of vortioxetine, it necessarily follows that Plaintiffs have

not proven infringement of Claims 4 or 5 of the Sexual Dysfunction Patent.

B. TESD And Antidepressants

512. Treatment Emergent Sexual Dysfunction ("TESD") is alternatively referred to as Sexually Related Adverse Events ("SRAE"). (Clayton Tr. 1082, 1103, 1164)

513. TESD is a term used for sexual dysfunction that is caused by an antidepressant and not caused by the MDD. (Clayton Tr. 1163-64)

514. TESD is a long-term side effect that generally does not resolve on its own and often results in reduced quality of life and relationship problems for patients. (Clayton Tr. 1098, 1154-55; Mattingly Tr. 859-61; PTX-134 at 1-2) Clinicians are motivated to address TESD because it negatively impacts patient quality of life and can lead to noncompliance and/or discontinuation of antidepressant treatment. (Clayton Tr. 1093-94; PTX-72 at 1; PTX-135 at 2, 4; PTX-126 at 8)

515. SSRI, SNRIs, TCAs, MAOIs, and NRIs are all associated with high rates of sexual dysfunction. (Clayton Tr. 1086; Mattingly Tr. 839-40, 846, 861; Rothschild Tr. 1713; PTX-17 at 17, 20; PTX-71 at 1; PTX-72 at 1; PTX-117 at 5; PTX-119 at 3; PTX-123 at 4; PTX-125 at 22; PTX-126 at 17; PTX-127 at 2; PTX-129 at 11; PTX-132 at 10; PTX-134 at 2–3; PTX-135 at 5-8; PTX-1046 at 1; PTX-1399 at 5; PTX-1400 at 1; PTX-1410 at 3; PTX 1417 at 2; PTX-1418 at 1-2)

516. Clinicians are aware, and have been aware for decades (at least since 2000), that SSRIs, SNRIs, NRIs, and TCAs cause sexual dysfunction from the published literature, lectures and conferences, drug labels, available study/trial data, and their own clinical experience. (Clayton Tr. 1087; Rothschild Tr. 1713; Mattingly Tr. 839-40, 846, 861) For example, the 2000 and 2010 APA Guidelines explain that sexual dysfunction is a frequent and troublesome side

effect of SSRIs, SNRIs, and TCAs. (Clayton Tr. 1088; PTX-125 at 22; PTX-126 at 17)

517. The Clayton 2002 point prevalence study of over 6,000 patients treated with an antidepressant monotherapy found that sexual dysfunction – specifically, sexual dysfunction that impacts all phases of the sexual response cycle – is a class effect of SSRIs and SNRIs, affecting approximately 40% of patients. (Clayton Tr. 1089-90; PTX-117 at 5) Clayton 2006 found even higher rates of sexual dysfunction (over 90%) for patients taking an SSRI or SNRI, as judged by dysfunction in at least one phase of the sexual response cycle. (Clayton Tr. 1090-91; PTX-1399)

518. In Montejo 2001, over 38% of patients who experienced TESD rated themselves as concerned enough about sexual dysfunction to discontinue their antidepressant therapy. Another third of patients indicated that while they did not intend to discontinue their antidepressant, they and/or their partners were concerned and distressed about the sexual dysfunction. (Clayton Tr. 1094-95; PTX-123 at 3, 6) Montejo 2001 reflects sexual dysfunction induced by the antidepressants, as it only included patients who had normal sexual functioning prior to taking an antidepressant. (PTX-123 at 4)

519. According to Ashton, sexually related adverse events – specifically "couldn't have an orgasm" (20%) and "lost interest in sex" (20%) – were among the top four reasons for noncompliance with an antidepressant prescription, and sexually related adverse events were among the side effects patients identified as extremely difficult to tolerate, specifically "unable to have an erection" (25%), "difficulty reaching orgasm" (24%), and "lost interest in sex" (~19%). (PTX-124 at 6-7; Clayton Tr. 1095-96) When patients were asked what improvements they wanted to see in antidepressant drugs, eliminating sexually related adverse events (34%) was in the top three desired improvements. (Clayton Tr. 1096-97; PTX-124 at 6)

520. A recognized and common strategy for managing TESD in an MDD patient is to substitute an antidepressant known to cause less TESD than the antidepressant that induced the patient's sexual dysfunction. (Clayton Tr. 1097) The 2000 and 2010 APA Guidelines recommend this strategy. (PTX-125 at 31; PTX-126 at 16; Clayton Tr. 1100-01)

C. Rates Of TESD May Vary Among Antidepressants

521. Montejo 2001 reported high rates of sexual dysfunction in patients treated with SSRIs and SNRIs (citalopram (72.7%), paroxetine (70.7%), venlafaxine (67.3%), sertraline (62.9%), and fluoxetine (57.7%)). (Clayton Tr. 1094; PTX-123 at 4)

522. Serretti & Chiesa is a meta-analysis comparing the rates of TESD for 16 antidepressants. (PTX-1410) All studies included in the meta-analysis used a method of direct inquiry, such as a sexual function questionnaire, to assess the rate of sexual dysfunction. (PTX-1410 at 1-2; Clayton Tr. 1091) In the meta-analysis, the SSRI with the lowest rate of TESD was escitalopram (approximately 40%); all other SSRIs had a TESD rate of 70-80%. (Clayton Tr. 1092; PTX-1410 at 3) The rate of TESD for the SNRI venlafaxine was approximately 80% and the TCA imipramine had a TESD rate over 40%. (Clayton Tr. 1092; PTX-1410 at 3)

523. The placebo adjusted rates of TESD for antidepressants approved for MDD in the U.S. from the Serretti & Chiesa meta-analysis are:

Antidepressant	Serretti & Chiesa Placebo Adjusted Incidence of TESD (%)
Sertraline (SSRI)	66.10%
Venlafaxine (SNRI)	65.63%
Citalopram (SSRI)	64.39%
Paroxetine (SSRI)	57.28%
Fluoxetine (SSRI)	56.40%
Imipramine (TCA)	30.24%
Phenelzine (MAOI)	27.46%
Duloxetine (SNRI)	27.40%
Escitalopram (SSRI)	22.84%
Mirtazapine	10.28%

(Clayton Tr. 1108-09; PTX-1410; PTX-1369 at 1; SF ¶¶ 50, 52-53, 57)

524. Clayton 2002 reported a non-placebo adjusted TESD rate of 20-30% for nefazodone, bupropion SR, and bupropion IR, as measured by the Changes in Sexual Functioning Questionnaire ("CSFQ"). (PTX-117 at 5)

525. Alvarez describes a clinical trial that found that patients treated with 5 and 10 mg of vortioxetine reported placebo like levels of sexually related adverse events. (PTX-136 at 8)

526. Jacobsen 2015 reported the results of Plaintiffs' own 318 Superiority Study. (*See* PTX-127; *see also infra* ¶ 543)

527. Jacobsen 2019 reported the results of Plaintiffs' own 4001 Superiority Study. (*See* PTX-1417; *see also infra* ¶ 543)

528. Baldwin is a meta-analysis of 11 clinical trials of vortioxetine which found that vortioxetine had placebo-like levels of voluntarily reported sexually related adverse events. (PTX-144 at 1, 6-7)

529. The placebo-adjusted Arizona Sexual Experiences Scale ("ASEX") TESD rates for vortioxetine are similar to or lower than the placebo-adjusted TESD rate for mirtazapine, which Dr. Rothschild testified is well-understood by clinicians to have a low rate of TESD.

(Rothschild Tr. 1712-13)[13]

530. The authors of the Khin (PTX-71) and Kronstein (PTX-72) articles cited by Plaintiffs expressly qualified their discussion of ASEX and CSFQ by stating, "It should be emphasized that the FDA does not endorse any particular instrument to assess sexual function in depression trials." (PTX-72 at 2)

531. All in all, the Court finds that some – but not nearly all – clinicians would believe that vortioxetine has a lower incidence of TESD than some other antidepressants. (*See generally* Clayton Tr. 1134) A POSA would be aware of Plaintiffs' belief in vortioxetine's low incidence of TESD from the Trintellix label, Plaintiffs' Superiority Studies, other academic literature, and discussions at academic events. Plaintiffs did not, however, persuade the Court that there is a consensus among POSAs, or the FDA, that vortioxetine in fact has a lower incidence of TESD that most other antidepressants.

D. Clinicians Prescribe Vortioxetine To MDD Patients Experiencing TESD

532. A patient may be prescribed vortioxetine for multiple reasons, including efficacy, treatment of cognitive impairment, and TESD experienced on an SSRI, SNRI, or TCA. (Mattingly Tr. 846-47)

533. Clinicians understand that vortioxetine can be administrated to a patient who previously received or is still receiving an SSRI, SNRI, or TCA. There is no contraindication or prohibition in Trintellix's or Defendants' Prescribing Information on the use of vortioxetine to treat such patients or on the co-administration of vortioxetine with an SSRI, SNRI, or TCA.

[13] The ASEX includes five questions pertaining to five aspects of sexual function: (1) sex drive; (2) ease of arousal; (3) ability to achieve erection (men) and lubrication (women); (4) ease of reaching orgasm; and (5) orgasm satisfaction. (PTX-2958 at 7)

(Rothschild Tr. 1714, Clayton Tr. 1137; PTX-4565 (Lupin) at 1, 3-4; PTX-4363 (Sigmapharm) at 1, 5; PTX-4566 (Macleods) at 2, 5; PTX-4567 (Alembic) at 3, 7; DTX-1933 (Zydus) at 1, 6; DTX-1169 (Sandoz) at 1, 4) Such co-administration often occurs during cross-titration. (Clayton Tr. 1100)

534. Trintellix is used for, among other things, treatment of MDD in patients who have ceased or reduced, or have to cease or reduce, use of an SSRI, SNRI, or TCA due to sexually related adverse events. (Mattingly Tr. 846; Clayton Tr. 1125)

E. Plaintiffs' Studies And The Trintellix Label

535. In Phase II clinical studies undertaken by Lundbeck and Takeda, a significant number of patients (8%) in the venlafaxine group spontaneously reported sexually related adverse events, while spontaneous reports of sexual dysfunction with vortioxetine 5 mg (1%) and 10 mg (1%) were comparable to placebo (2%). (PTX-2957 at 41-42; Dragheim Tr. 116-17) Pooled data from ten short-term Phase II/III studies demonstrated that Trintellix had a low incidence of sexually related adverse events compared to two widely used antidepressants: duloxetine and venlafaxine. (PTX-149 at 15; Dragheim Tr. 116-17, 120-22)

536. At the FDA's request, Plaintiffs added the ASEX to prospectively assess sexual dysfunction in the Phase III clinical trials for vortioxetine. (PTX-2958 at 4-5) The rate of sexual dysfunction reported with the ASEX for vortioxetine was not statistically significantly different than placebo. (Dragheim Tr. 124; PTX-4475 at 10; PTX-1419 at 10)

537. The FDA originally approved Trintellix® on September 30, 2013, under the name Brintellix®. (SF ¶¶ 32-33; Peck Tr. 1317-18)

538. As originally approved in 2013, the Brintellix® Prescribing Information contained the portions of Section 6.1 titled "Voluntarily Reported Adverse Reactions of Sexual

Dysfunction" and "Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline." (PTX-87 at 18; Peck Tr. 1317-19)

539. The USPTO issued the '096 Patent on March 8, 2016. (PTX-17 at 1) Takeda did not list the '096 Patent in the Orange Book within 30 days of when the USPTO issued that patent. (SF ¶ 202; Peck Tr. 1319, 1322)

540. At the time the '096 Patent issued in 2016, the Trintellix® Prescribing Information contained the same subparts of Section 6.1 titled "Voluntarily Reported Adverse Reactions of Sexual Dysfunction" and "Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline" that had been present in the label since it was originally approved in 2013. (Peck Tr. 1319-20; DTX-1164 at 10)

541. Over two years later, on October 19, 2018, FDA approved the following additions to the Trintellix® Prescribing Information: (1) a subpart within "Clinical Studies" (Section 14) entitled "Prospective Evaluation of Treatment Emergent Sexual Dysfunction (TESD)"; and (2) a sentence within "Clinical Studies Experience" (Section 6.1) under the "Sexual Dysfunction" subpart that cross-references the addition to Section 14. (Peck Tr. 1321-22; DTX-1080 at 14, 29-30; DTX-514 at 1-2; Rothschild Tr. 1646) These two additions are collectively referred to as the "TESD comparative information."

542. Only on November 13, 2018, after the TESD comparative information was added to the Trintellix® label, did Plaintiffs ask FDA to list the '096 Patent in the Orange Book. (Peck Tr. 1322)

543. In the current version of the Trintellix® Prescribing Information, Section 14 contains data from the two superiority studies conducted by Plaintiffs: the 318 Superiority Study

and the 4001 Superiority Study. (Clayton Tr. 1110, 1113; PTX-4475 at 26-28; PTX-1419 at 24-26;) The results of the 318 Superiority Study were also published in Jacobsen 2015. (PTX-127; Clayton Tr. 1110-11) The results of the 4001 Superiority Study were published in Jacobsen 2019. (PTX-1417; Clayton Tr. 1115)

544. In the 318 Superiority Study, MDD patients with adequately treated MDD, who were experiencing TESD on citalopram, sertraline, or paroxetine, were randomized to receive vortioxetine or escitalopram. (PTX-4475 at 26; PTX-1419 at 24; PTX-127 at 2-3; Clayton Tr. 1111) Most of the vortioxetine patients (65.6%) in the study were prescribed the 20 mg dose. (Dragheim Tr. 125; PTX-4475 at 26; PTX-1419 at 24)[14]

545. The primary endpoint of the 318 Superiority Study was the change in the CSFQ score from baseline. (Clayton Tr. 1111; PTX-127 at 4) The CSFQ is a validated questionnaire developed by Dr. Clayton which is now widely used by clinicians and accepted by FDA. (Clayton Tr. 1082, 1101-02; PTX-71 at 2; PTX-72 at 2) Higher scores on the CSFQ indicate higher sexual functioning. (PTX-127 at 4; PTX-4475 at 26; PTX-1419 at 24)

546. Patients in the 318 Superiority Study who were switched to vortioxetine experienced an 8.8 point increase in CSFQ score, compared to a 6.6 point increase in CSFQ score seen in patients switched to escitalopram. (Clayton Tr. 1111; PTX-4475 at 27; PTX-1419 at 24; PTX-127 at 6-7) The 2.2 point additional increase in CSFQ score with vortioxetine was statistically significant and clinically meaningful – as the Trintellix label states. (PTX-4475 at 26; PTX-1419 at 24; PTX-127 at 6-7; Clayton Tr. 1111-13) Both vortioxetine and escitalopram

[14] Plaintiffs' sales data shows that the 20 mg dose of vortioxetine accounted for 43.3-46.6% of actual monthly sales in each month from September 2016 to October 2019. (*See* Rothschild Tr. 1724-25)

maintained efficacy in treating the patients' depression. (Dragheim Tr. 126; PTX-127 at 8)

547. FDA found that "the study design of study 318 [was] reasonable." (PTX-80 at 7)

548. In the 4001 Superiority Study, healthy control subjects were randomized to receive vortioxetine 10 mg, vortioxetine 20 mg, paroxetine 20 mg, or placebo. (Clayton Tr. 1113-14; PTX-1417 at 2) The CSFQ was used to measure changes in sexual functioning. (Clayton Tr. 1114; PTX-1417 at 3; PTX-4475 at 27; PTX-1419 at 25)

549. In the 4001 Superiority Study, there was no difference in CSFQ scores between the 10 mg and 20 mg vortioxetine groups and placebo, but there was a statistically significant difference between paroxetine 20 mg and placebo. (Clayton Tr. 1114-15; PTX-4475 at 27; PTX-1419 at 25; PTX-1417 at 4-5) TESD with 10 mg vortioxetine was statistically significantly less than paroxetine. (PTX-1417 at 4)

550. In the 4001 Superiority Study, vortioxetine 20 mg was associated with numerically less TESD than paroxetine. (PTX-1417 at 4-5)

551. There is a high bar for adding superiority studies to prescribing information. (Dragheim Tr. 128) FDA rigorously reviews superiority studies presented for inclusion in drug prescribing information. (Dragheim Tr. 126, Peck Tr. 1305; *see generally* PTX-80; PTX-2983) FDA found "no significant review issues" with the 318 and 4001 Superiority Studies and determined that both studies "contribute useful information" about vortioxetine's effect on sexual functioning. (PTX-2983 at 4)

552. Trintellix was the first and remains the only drug with TESD superiority study data in its prescribing information. (Dragheim Tr. 128; Clayton Tr. 1161-62)

F. The Claimed Method Of Treatment Is An Approved Use Of Trintellix And Will Be An Approved Use Of Defendants' ANDA Products

553. Use of vortioxetine to treat depression in patients who have previously received an SSRI, SNRI, or TCA and have ceased or reduced, or have to cease or reduce, using that medication due to sexually related adverse events is an approved use of Trintellix and Defendant's ANDA Products. (Peck Tr. 1302-03, 1311, 1313)

554. FDA approved of the inclusion of the 318 and 4001 Superiority Studies in the Trintellix Prescribing Information because the studies relate to an approved use of vortioxetine. (Peck Tr. 1307-08, 1310-11)

555. FDA guidance states that physicians should consider labeling in its entirety for individual prescribing decisions. (Peck Tr. 1306; PTX-60 at 5) The Indications and Usage section should be "concisely written," and essential details that enable safe and effective use of the drug should be distributed across different sections of the labeling, including the clinical studies section. (PTX-60 at 5; Peck Tr. 1306-07) The Clinical Studies section should include "studies that demonstrate effectiveness of the drug for its approved indication. (PTX-58 at 5) If clinical studies imply effectiveness for unapproved uses, however, FDA Guidance instructs that those studies "should usually not be included in the clinical studies section." (PTX-58 at 6; *see also* Peck Tr. 1307-08) FDA would not have approved the inclusion of the 318 and 4001 Superiority Studies if such studies implied effectiveness for an unapproved use.

556. Takeda's promotional materials explain that "for MDD patients with SSRI-induced sexual dysfunction, a switch to Trintellix resulted in statistically superior improvement in treatment-emergent sexual dysfunction" and maintained antidepressant efficacy. (PTX-1704 at 3-4; Peck Tr. 1315) If marketing materials promote a use that is not approved for use in the

label, FDA will invoke an enforcement action against the company. (Peck Tr. 1315) FDA has not instituted any such enforcement action against Takeda's promotion. (Peck Tr. 1315)

557. Omission of the 318 and 4001 Superiority Studies from Section 14 does not change the approved uses of Defendants' ANDA products. (Peck Tr. 1312) Defendants have not narrowed the Indications in their Prescribing Information. Defendants' ANDA Products will be used to treat MDD patients. The use of vortioxetine to treat patients with MDD who were taking an SSRI, SNRI, or TCA and have ceased or reduced or have to cease or reduce the medication due to sexually related adverse events is within the approved indication and use. (Peck Tr. 1313)

G. Defendants' Proposed Labels

558. If approved, Defendants' ANDA Products will be prescribed to treat, among other things, MDD in patients who were taking an SSRI, SNRI, or TCA that was ceased or reduced, or has to be ceased or reduced, due to sexually related adverse events. (Clayton Tr. 1125-27, 1135; *see also* Mattingly Tr. 846-48) Dr. Clayton testified that she would prescribe generic versions of Trintellix in this way. (Clayton Tr. 1125-26)

559. Each Defendant's proposed prescribing information contains only one indication, which is "the treatment of major depressive disorder (MDD) in adults." (SF ¶ 232; PTX-4363 at 3 (Sigmapharm); PTX-4565 at 2 (Lupin); PTX-4566 at 4 (Macleods); PTX-4567 at 5 (Alembic); DTX-1169 at 2 (Sandoz); DTX-1933 at 4 (Zydus); Rothschild Tr. 1646-47) Defendants' prescribing information may also be referred to as "labels" or "package inserts."

560. Zydus' proposed prescribing information (DTX-1933) is representative of Defendants' proposed prescribing information relevant to Plaintiffs' allegations of infringement. (*See* Peck Tr. 1341; Rothschild Tr. 1649; Rheinstein Tr. 2115; 21 C.F.R. § 314.105(d); 21 C.F.R.

§ 314.127(a)(7)) There are no material differences among the respective Defendants' proposed prescribing information with respect to the issues pertinent to non-infringement of Claim 1 of the '096 Patent, which is the parent of all the asserted claims. (*See, e.g.*, DTX-1933 (Zydus))

561. Zydus' proposed prescribing information carves out two sets of information from Trintellix's label, specifically in Sections 6.1 and 14. (*Compare* PTX-4475 at 9, 23-24, 26-28, *with* DTX-1933 at 11, 25-30; DTX-507 at 22-23; DTX-514 at 1-2) Those two sets of carve outs relate to: (1) cognitive impairment information in Section 14; and (2) TESD comparative information in Sections 6.1 and 14.

562. FDA has tentatively approved the similar proposed prescribing information for Sandoz and Alkem, and Defendant Alkem has been dismissed from the case. (SF ¶ 236; PTX-1196 (comparing Trintellix label with Alkem label); DTX-1169; Rheinstein Tr. 2113; D.I. 983)

563. With the exception of Sandoz, those same two sets of carve outs are also made in all other Defendants' proposed prescribing information. (SF ¶ 232; Rheinstein Tr. 2115; *compare* PTX-1196 at 21-22, 47-51, *with* PTX-4363 at 10, 27-28 (Sigmapharm); PTX-4565 at 8, 23-24 (Lupin); PTX-4566 at 9, 21 (Macleods); PTX-4567 at 12, 28-29 (Alembic); DTX-1169 at 8, 20-21 (Sandoz); DTX-1933 at 11, 29-30 (Zydus))

564. Sandoz's proposed prescribing information only carves out the TESD comparative information, i.e., the second set of carve outs. (DTX-1169 at 8, 20-21)[15]

565. In response to Plaintiffs' Citizen Petition, the FDA determined that Defendants'

[15] Sandoz's prescribing information does not contain the first set of carve outs related to cognitive impairment because Sandoz submitted a Paragraph III certification for the '910 Patent and that patent is no longer asserted against Sandoz. (D.I. 908, 909, 942, 991; 21 U.S.C. § 355(j)(2)(A)(vii)(III))

carve-outs of the TESD information from Section 14 and reference to that in Section 6.1 is proper. (DTX-507; DTX-514; Rheinstein Tr. 2113-15)

566. In the July 18, 2019 Citizen Petition decision, FDA noted that the comparative data with escitalopram in Section 14 showed that the "more than half (52.1%) of patients who took vortioxetine experienced a return to normal CSFQ scores, indicating that approximately 48% of patients continued to experience sexual dysfunction, and some experienced a worsening of sexual dysfunction." (DTX-514 at 17)

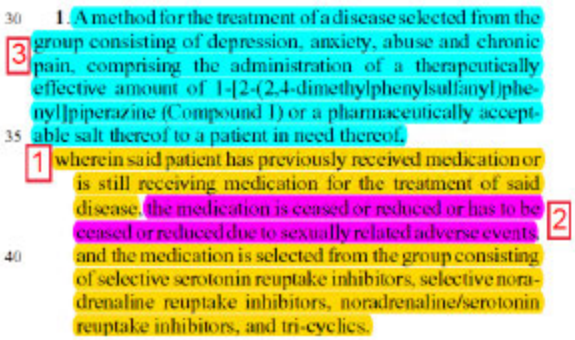
567. FDA has also observed that Plaintiffs' claims that the incidence of sexual dysfunction was lower for vortioxetine than for other SSRIs did not apply to the 20 mg dose of vortioxetine. FDA observed, "[P]rescribers would understand to prescribe the recommended dose of 20 mg/day to provide greater efficacy in treating MDD, but at that recommended dose, vortioxetine did not show a lower incidence of sexual dysfunction." (DTX-514 at 16)

H. The Asserted Claims And The Claim Limitations

568. Claim 7 of the '096 Patent is asserted against Alembic, Lupin, Macleods, Sandoz, Sigmapharm, and Zydus, and Claims 4 and 5 of the '096 Patent are asserted against Alembic, Lupin, and Sigmapharm. (D.I. 987 Ex. 4A (Alembic) ¶¶ 7-10, Ex. 4C (Lupin) ¶¶ 7-10, Ex. 4D (Macleods) ¶¶ 7-10, Ex. 4F (Sandoz) ¶¶ 1-4, Ex. 4G (Sigmapharm) ¶¶ 7-10, Ex. 4J (Zydus) ¶¶ 6-9)

569. Claim 7 depends from Claim 6, which in turn depends from Claim 1.

570. The method of Claim 1 of the '096 Patent can be divided into what Dr. Rothschild characterized as "three key steps." (Rothschild Tr. 1644-45) In the reproduction of Claim 1 below, each key step is shaded in a different color and numbered chronologically in the order in which they must occur to perform the claimed method.



571. Neither asserted Claims 4, 5, and 7, nor their parent Claims (1, 3, and 6), requires that vortioxetine be effective to reduce TESD. (PTX-17 at 20:30-59; Rothschild Tr. 1695)

572. Defendants' ANDA Products are to be administered orally once daily. (Clayton Tr. 1124; SF Ex. 1 ¶ 227 & Ex. 1A ¶ 21 (Alembic), Ex. 1G ¶ 15 (Sigmapharm), Ex. 1F ¶ 17 (Sandoz), Ex. 1C ¶ 37 (Lupin), Ex. 1J ¶ 8 (Zydus); PTX-4566 (Macleods) at 2, 4)

573. Defendants seek to import, sell, and/or offer to sell their ANDA Products in the U.S. (Clayton Tr. 1139; D.I. 844 ¶ 69 (Alembic); D.I. 853 ¶ 54 (Lupin); D.I. 857 ¶¶ 50-52 (Macleods); D.I. 849 ¶ 48 (Sandoz); D.I. 835 ¶ 42 (Sigmapharm); D.I. 865 ¶ 72 (Zydus))

574. All Defendants are seeking approval of their ANDA Products for one indication: "the treatment of major depressive disorder (MDD) in adults." (PTX-4475 (Trintellix) at 1; PTX-4566 at 2 (Macleods); PTX-4567 at 3 (Alembic); PTX-4565 at 2 (Lupin); PTX-4363 at 1 (Sigmapharm); DTX-1933 at 1 (Zydus); DTX-1169 at 1 (Sandoz))

575. All Defendants seek approval for vortioxetine tablets in 10 mg and 20 mg dosage strengths; Alembic, Lupin, and Sandoz also seek approval for 15 mg tablets; and Alembic, Lupin, Macleods, Sandoz, and Zydus also seek approval for 5 mg tablets. (D.I. 985 Ex. 1A ¶¶ 1-2 (Alembic), Ex. 1C ¶¶ 36-37, 39 (Lupin), Ex. 1D ¶ 1 (Macleods), Ex. 1F ¶¶ 1-2 (Sandoz), Ex. 1G ¶¶ 1-2 (Sigmapharm), Ex. 1J ¶¶ 7-8 (Zydus)) These are all indisputably therapeutically

effective amounts. (SF ¶¶ 230-35)

576. Defendants have represented to the FDA that their ANDA Products are bioequivalent to Trintellix. (SF ¶ 230, Ex. 1A (Alembic) ¶ 16, Ex. 1C (Lupin) ¶ 44, Ex. 1D (Macleods) ¶¶ 12, 34-35, Ex. 1G (Sigmapharm) ¶¶ 7-8, Ex. 1J (Zydus) ¶¶ 16–17, Ex. 1F (Sandoz) ¶¶ 12-13)

I. Induced Infringement

577. Dr. Clayton's opinions of induced infringement are based on four sections of Defendants' proposed prescribing information: Sections 2.5, 5.2, 6.1, and 7.1. (Clayton Tr. 1135-38)

1. Section 6.1

578. The "Adverse Reactions" section (Section 6) is the only section of Defendants' proposed Prescribing Information relied upon by Plaintiffs that mentions sexual dysfunction or TESD. (*Compare* DTX-1933 at 11-12 (6.1), *with* DTX-1933 at 5 (2.5); 1933 at 8-9 (5.2); DTX-1933 at 14-15 (7.1); Rothschild Tr. 1647; Clayton Tr. 1176)

579. The portion of the Adverse Reactions section (Section 6.1) that Plaintiffs rely upon is reproduced in full below:

Sexual Dysfunction

Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

Voluntarily Reported Adverse Reactions of Sexual Dysfunction

In the MDD 6 to 8 week controlled trials of vortioxetine, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in vortioxetine 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in vortioxetine 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their self-reported ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed treatment-emergent sexual dysfunction when treated with vortioxetine or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

Table 3
ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	Vortioxetine 5 mg/day N=65:67†	Vortioxetine 10 mg/day N=94:86†	Vortioxetine 15 mg/day N=57:67†	Vortioxetine 20 mg/day N=67:59†	Placebo N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

*Incidence based on number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

† Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

(DTX-1933 at 11-12)

580. None of the information in the above portion of the Adverse Reactions section (Section 6.1) suggests that Defendants' ANDA Products will result in less TESD than any other medication. (Rothschild Tr. 1646)

581. Pursuant to 21 U.S.C. § 505(j)(2)(A)(viii), all Defendants have omitted, or "carved out," all of the TESD comparative information from their proposed prescribing information, i.e., the subpart of Section 14 of the Trintellix® Prescribing Information that

summarizes TESD clinical data, and the one-sentence cross-reference to that data in Section 6.1. (*Compare* PTX-4475 at 9, 26-28, *with, e.g.*, PTX-4363 at 10, 28 (Sigmapharm); PTX-4565 at 8, 24 (Lupin); PTX-4566 at 9, 21 (Macleods); PTX-4567 at 12, 29 (Alembic); DTX-1169 at 8, 21 (Sandoz); DTX-1933 at 11, 30 (Zydus))

582. The only information related to TESD in Defendants' proposed prescribing information appears in the "Adverse Reactions" section. (DTX-1933 at 10) That information includes the same two subsections in Section 6.1, titled "Voluntarily Reported Adverse Reactions of Sexual Dysfunction" and "Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline," that were present in the Trintellix® Prescribing Information for five years before Plaintiffs listed the '096 Patent in the Orange Book. (Peck Tr. 1319-22; DTX-1164 at 10; SF ¶ 202; PTX-4363 at 10-11 (Sigmapharm); PTX-4565 at 8-9 (Lupin); PTX-4566 at 9-10 (Macleods); PTX-4567 at 12-13 (Alembic); DTX-1169 at 8-9 (Sandoz); DTX-1933 at 11-12 (Zydus))

583. The "Voluntarily Reported Adverse Reactions of Sexual Dysfunction" subsection under Section 6.1 – of both Trintellix's and Defendants' Prescribing Information – reports that in the Phase II/III MDD 6- to 8-week controlled trials of vortioxetine, sexually related adverse events were reported at rates of 3%, 4%, 4%, and 5% for male patients receiving vortioxetine 5 mg, 10 mg, 15 mg, and 20 mg, respectively; <1%, 1%, <1%, and 2% for female patients receiving vortioxetine 5 mg, 10 mg, 15 mg, and 20 mg, respectively; and <1% for patients in the placebo group. (PTX-4475 (Trintellix) at 9; PTX-4566 (Macleods) at 9; PTX-4567 (Alembic) at 12; PTX-4565 (Lupin) at 8; PTX-4363 (Sigmapharm) at 10-11; DTX-1169 (Sandoz) at 8; DTX-1933 (Zydus) at 11-12) According to Dr. Clayton, this data informs clinicians that vortioxetine

has a very low, placebo-like rate of sexually related adverse events. (Clayton Tr. 1104)

584. The "Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline" subsection of Section 6.1 includes data reported using the ASEX. The ASEX data in Section 6.1 reports the incidence of TESD that developed in patients without sexual dysfunction at baseline. (SF ¶ 235; PTX-79 at 9; PTX-4475 at 10; PTX-1419 at 10; PTX-4565 (Lupin) at 8-9; PTX-4363 (Sigmapharm) at 11; PTX-4566 (Macleods) at 9-10; PTX-4567 (Alembic) at 12-13; DTX-1933 (Zydus) at 12; DTX-1169 (Sandoz) at 8-9) The following table appears in this section of Section 6.1:

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	TRINTELLIX 10 mg/day N=94:86†	TRINTELLIX 15 mg/day N=57:67†	TRINTELLIX 20 mg/day N=67:59†	Placebo N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

* Incidence based on number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

† Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

585. There is nothing in Defendants' proposed prescribing information that compares the rate of TESD for vortioxetine with the rate of TESD for any other drug. (DTX-1933 at 11-12, 30)

586. There is nothing in Defendants' proposed prescribing information that refers to patients who previously received another medication for the treatment of depression. (DTX-1933 at 11-12, 30)

587. There is nothing in Defendants' proposed prescribing information that refers to patients who previously received SSRIs, SNRIs, sNRIs or TCAs for the treatment of depression. (DTX-1933 at 11-12, 30)

588. There is nothing in Defendants' proposed prescribing information that refers to patients who previously took another medication for the treatment of depression and who had to cease or reduce that medication due to TESD. (DTX-1933 at 11-12, 30)

589. There is nothing in Defendants' proposed prescribing information that refers to a patient who previously took an SSRI, SNRI, sNRI, or TCA for the treatment of depression and who had to cease or reduce that medication due to sexually related adverse events. (DTX-1933 at 11-12, 30)

590. Dr. Rothschild explained how the prescribing information for an early SSRI, fluoxetine (Prozac®), had similarly low numbers of spontaneously-reported sexual dysfunction, but subsequent studies showed the frequency of TESD was much higher. (Rothschild Tr. 1649-50; DTX-373 at 21 ("[D]ecreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo)"); PTX-1410 at 3 (over 70% rate of total sexual dysfunction with fluoxetine ("flu")))

591. The second subpart of Section 6.1, titled "Adverse Reactions of Sexual Dysfunction in Patients with Normal Sexual Functioning at Baseline," will not encourage clinicians to prescribe vortioxetine in patients that have ceased or reduced or have to cease or reduce another antidepressant due to TESD, for reasons including that the rates of TESD reported in this subpart of Section 6.1 are not unusually low, particularly for the recommended 20 mg dose. (DTX-1933 at 4 (2.1); DTX-514 at 16; Rothschild Tr. 1650-51, 1724-25; PTX-4475 at 1)

592. For the 20 mg dose, the data in Section 6.1 shows that between 29%-34% of patients taking vortioxetine experienced sexually related adverse events. (DTX-1933 at 11-12)

This is more than double the placebo rate for men and 14% higher for women. (Rothschild Tr. 1650-51) Dr. Rothschild explained that a clinician would take away from this data that "a third of the patients will be in my office complaining about sexual dysfunction." (Rothschild Tr. 1651)

593. Further, at the beginning of Section 6.1, Defendants' proposed prescribing information expressly instructs clinicians not to compare the rates of adverse events for vortioxetine to other drugs. (Rothschild Tr. 1652-53) Specifically, Defendants' proposed prescribing information states in relevant part:

> **6.1 Clinical Studies Experience**
> Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug.

(DTX-1933 at 10)

594. Dr. Clayton agreed that it is inappropriate to compare the outcomes for two different agents that have been investigated in two different clinical trials, stating "there are so many other variables that can contribute; what sites were used, the design of the trial, the interventions used, et cetera. That's why we don't do that." (Clayton Tr. 1174-75; *see also* Rothschild Tr. 1661-62)

595. Even Plaintiffs acknowledged to the FDA that the adverse event data in Section 6.1 might discourage prescribers from administering vortioxetine to reduce TESD, asserting that

> a prescriber viewing the ASEX data shown in Table 3 of the TRINTELLIX labeling might reach the incorrect conclusion that vortioxetine is associated with a high rate of sexual dysfunction because the incidence reported in Table 3 ranges from 16 to 34 percent.

(DTX-507 at 12)

596. In a survey of 30 clinicians who were asked about the ASEX data that now

appears in Section 6.1, Table 3, of Defendants' proposed prescribing information, only one psychiatrist was even familiar with ASEX. (DTX-1138 at 5, 10, 20) Clinicians found "it difficult to compare vortioxetine; they are not knowledgeable about this scale and do not have this data for other antidepressants." (DTX-1138 at 10; *see also* Dragheim Tr. 144-47)[16]

597. In denying a Citizen Petition filed by Lundbeck and Takeda, the FDA concluded that clinicians will consider the ASEX data in Section 6.1 of Defendants' Prescribing Information when making prescribing decisions and will understand how to use the placebo rate to adjust and assess the vortioxetine ASEX rates. (DTX-514 at 12-13) The FDA stated that it is "appropriate to assume that prescribers will read the remaining labeling" which will include the ASEX data. The FDA explained that prescribers reviewing the ASEX data will consider the rates of sexual dysfunction for placebo. (DTX-514 at 12-13; Peck Tr. 1365-66) The FDA also commented that even with the Section 14 studies omitted "physicians will continue to consider

[16] Plaintiffs move to strike DTX-1138, entitled "Report of Findings from Individual Depth Interviews with Primary Care Physicians and Psychiatrists." According to the report, its purpose is to solicit feedback from target physicians on four aspects of a draft label to optimize the FDA submission. (DTX-1138 at 3) Having considered the parties' arguments (*see* D.I. 1047 n. 22; D.I. 1054 at 41-44; D.I. 1065; D.I. 1068), the Court will deny Plaintiffs' request. The report evidences no indicia of untrustworthiness, and Plaintiffs' contention to the contrary is unpersuasive, particularly given that ***Plaintiffs*** commissioned the report. *See Bodeans Cone Co. L.L.C. v. Norse Dairy Sys. L.L.C.,* 678 F. Supp. 2d 883, 904 (N.D. Iowa 2009) ("It is difficult for the court to take seriously 'trustworthiness' challenges to a survey made by the very party that commissioned and used the survey in the first instance, albeit not for purposes of the present litigation.").

The Court further finds DTX-1138 meets the probativeness requirement. Defendants took the position that DTX-1138 became relevant upon the addition of induced infringement to the case in June 2020. (D.I. 801) The Court permitted Plaintiffs to add induced infringement at that time, nearly six months after the close of fact discovery (D.I. 634), in part based on assurances from Plaintiffs that doing so would not prejudice Defendants (D.I. 728 at 3; *see also* D.I. 1065 at 3). Under these circumstances, striking the exhibit now would be inappropriate. Instead, DTX-1138 has been admitted and will be given appropriate weight.

the potential for TESD as one of many factors in choosing a treatment approach for MDD." (DTX-514 at 19-20)

2. Other Sections of Defendants' Labels

598. Sections 2.5, 5.2 and 7.1 of Defendants' proposed prescribing information do not mention sexual dysfunction or TESD. (DTX-1933 at 5 (2.5); 1933 at 8-9 (5.2); DTX-1933 at 14-15 (7.1); Rothschild Tr. 1647; Clayton Tr. 1176)

599. Sections 2.5, 5.2 and 7.1 are each located in sections of Defendants' proposed prescribing information that describe the "bad things that can happen when you mix vortioxetine with other medications, particularly serotonergic medications." (Rothschild Tr. 1653; DTX-1933 at 5 ("2 Dosage and Administration"), 8-9 ("5 Warnings and Precautions"), 14-15 ("7 Drug Interactions"))

600. Section 2.5 of Defendants' Prescribing Information instructs clinicians on how to dose vortioxetine when it is administered concomitantly with the other antidepressants, including fluoxetine and paroxetine, both SSRIs. (PTX-4565 at 3 (Lupin); PTX-4566 at 5 (Macleods); PTX-4567 at 6 (Alembic); DTX-1933 at 5 (Zydus); *see also* PTX-4363 at 4 (Sigmapharm); DTX-1169 at 3 (Sandoz))

601. Section 5.2 cautions against co-administration of vortioxetine with other serotonergic drugs, which include SSRIs, SNRIs, and TCAs. (SF ¶¶ 49-50, 53-57)

602. Section 5.2 of Defendants' Prescribing Information instructs clinicians that "[i]f concomitant use of vortioxetine with other serotonergic drugs, including . . . tricyclic antidepressants, . . . is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome . . . ." (PTX-4565 at 6 (Lupin); PTX-4363 at 8 (Sigmapharm); PTX-4566 at 7 (Macleods); PTX-4567 at 9 (Alembic); DTX-1933 at 8 (Zydus);

DTX-1169 at 6 (Sandoz))

603. Section 7.1 of Defendants' Prescribing Information states, in relevant part:

Other Serotonergic Drugs	
Clinical Impact	Concomitant use of vortioxetine with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Monitor for symptoms of serotonin syndrome when vortioxetine is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of vortioxetine and/or concomitant serotonergic drugs *[see WARNINGS AND PRECAUTIONS (5.2)]*.
Examples	Other SNRIs, SSRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, amphetamines, tryptophan, and St. John's Wort

(PTX-4565 at 10 (Lupin); PTX-4566 at 11 (Macleods); PTX-4567 at 15 (Alembic); DTX-1933 at 14 (Zydus); *see also* PTX-4363 at 13 (Sigmapharm); DTX-1169 at 10 (Sandoz))

604. Sections 2.5, 5.2, and 7.1 of Defendants' Prescribing Information together instruct clinicians that vortioxetine can be administered after or co-administered with serotonergic antidepressants, such as SSRIs, SNRIs, or TCAs. (Clayton Tr. 1137-38)

605. Defendants are not seeking FDA approval for an indication to treat TESD or patients who are taking, or who have previously taken, an SSRI, sNRI, SNRI, or TCA as required by the TESD limitations of claim 1. (DTX-1933 at 4)

606. Defendants' proposed Prescribing Information will not include any indication or instruction for the use of Defendants' Proposed ANDA Products as a replacement therapy for patients who previously took an SSRI, sNRI, SNRI, or TCA. (DTX-1933 at 4)

607. Plaintiffs have not identified any promotional or advertising materials by Defendants that Plaintiffs allege will encourage infringement. (*See* Peck Tr. 1331-32)

608. Plaintiffs have not proven that Defendants intend to induce infringement or that anything they have done or will do in connection with their ANDA Products will cause anyone

to infringe the asserted claims of the ’096 Sexual Dysfunction Patent.

J. Contributory Infringement

609. Plaintiffs allege that Defendants will contributorily infringe Claim 7 of the ’096 Patent.

610. Defendants have conceded or have not contested that they had knowledge of the ’096 Patent. (D.I. 985, Ex. 1C ¶ 102 (Lupin), Ex. 1D ¶ 67 (Macleods), Ex. 1F ¶ 31 (Sandoz); Clayton Tr. 1139-41)

611. Defendants’ ANDA Products are a material part of and integral to the method of treatment of Claim 7 of the ’096 Patent. The method of Claim 7 cannot be practiced without a vortioxetine dosage form. (PTX-17 at 26)

612. If approved, Defendants’ ANDA Products will be considered bioequivalent to Trintellix and approved for the same use and will be offered in therapeutically effective amounts for treating MDD. (SF ¶¶ 230-35; Ex. 1A (Alembic) ¶ 16, Ex. 1C (Lupin) ¶ 44, Ex. 1D (Macleods) ¶¶ 12, 34-35, Ex. 1G (Sigmapharm) ¶¶ 7-8, Ex. 1J (Zydus) ¶¶ 16–17, Ex. 1F (Sandoz) ¶¶ 12-13)

613. Plaintiffs have not shown that Defendants possess the intent required to prove contributory infringement.

614. Furthermore, Defendants’ Proposed ANDA Products, once approved, will have substantial uses other than the uses recited in Asserted Claims 4, 5, and 7 of the ’096 patent. (Rothschild Tr. 1655-59)

615. Dr. Rothschild identified three non-infringing uses: (1) no prior treatment with an antidepressant; (2) prior treatment with an antidepressant other than an SSRI, SNRI, sNRI, or TCA; and (3) a prior antidepressant was not ceased or reduced due to sexually related adverse

events. (Rothschild Tr. 1655, 1656, 1658)

616. Each of Dr. Rothschild's three non-infringing uses is covered by the sole indicated use for Defendants' ANDA Products, which is the treatment of MDD.

617. None of Dr. Rothschild's three non-infringing uses is unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental.

1. Substantial non-infringing use 1

618. SSRIs are by far the most commonly prescribed type of antidepressants and the most commonly prescribed first-line treatment for MDD. (Clayton Tr. 1127-28, 1144; Mattingly Tr. 839; PTX-131 at 12; PTX-1377 at 3) SNRIs are the second-most commonly prescribed AD. (Mattingly Tr. 840; Clayton Tr. 1127, 1144; PTX-131 at 12)

619. Still, many patients of Defendants' ANDA Products will not have been treated with another antidepressant medication prior to being administered vortioxetine and, thus, will not satisfy key step 1. (Rothschild Tr. 1655-56, 1663-64, 1709; Clayton Tr. 1165)

620. While Dr. Clayton testified that she has not prescribed vortioxetine as a first-line treatment for MDD, and is not aware of the physicians or residents with whom she consults doing so (Clayton Tr. 1203-04); and one of Defendants' experts, Dr. Victor Reus, testified that he has not prescribed vortioxetine as a first-line treatment for MDD (Reus Tr. 2003); another of Defendants' experts, Dr. Rothschild, recalled three times he prescribed vortioxetine as a first-line treatment. (Rothschild Tr. 1663, 1715-16)

621. In a video clip published in February 2020, Dr. Clayton publicly instructed that one way to manage TESD associated with antidepressant therapy includes, "[M]aybe from the beginning when you prescribe, if they don't want to experience sexual dysfunction, you start with a medication that's less likely to do that." (Clayton Tr. 1184-85, 1201-02; DTX-1938 at

1:08; DTX-1941)

622. With respect to vortioxetine, Dr. Clayton stated that, where a patient's primary consideration is not wanting to have sexual dysfunction, she would consider starting the patient on vortioxetine from the very beginning instead of first prescribing another antidepressant. (Clayton Tr. 1165-66)

623. Dr. Clayton testified that her current practice of not prescribing vortioxetine first-line is, at least in part, a product of insurance companies not paying for first-line treatment with a branded, non-generic drug. (Clayton Tr. 1165-66, 1203-04) Another of Plaintiffs' experts, Dr. Mattingly, likewise testified that his reason for "[n]ot usually" prescribing vortioxetine first-line is because "insurance companies make me jump through a generic version of it." (Mattingly Tr. 845)

624. SSRIs and SNRIs are inexpensive and are covered as first-line MDD therapies by insurance plans. (Clayton Tr. 1128-29; PTX-1401 at 40-45; PTX-1357 at 38-40) Insurance plans often require treatment with one or even two SSRIs before treatment with a different type of antidepressant. (Clayton Tr. 1128, 1144, 1203-04, Mattingly Tr. 845; PTX-1401 at 40-45; PTX-1357 at 38-40) On each insurance formulary in the record, Tier 1 antidepressants are limited to SSRIs. (PTX-1401 at 40-45 (citalopram and paroxetine); PTX-1357 at 38-40 (citalopram, fluoxetine, and sertraline))

625. Other experts testified that their experiences with insurance companies differed, particularly when it comes to use of generic medications. For example, Dr. Rothschild noted that in his 40 years practicing medicine, pushback from insurance companies "has never happened in my whole career with a generic antidepressant." (Rothschild Tr. 1664; DTX-294) Dr.

Rothschild's opinion that once vortioxetine is generic, there should be no issue with prescribing it first-line (Rothschild Tr. 1663-64), was persuasive.

626. When choosing an antidepressant for a patient, clinicians consider a number of factors, including efficacy, safety, and tolerability; patient preference and concerns; prior response to treatment by the patient or a family member; quantity and quality of the clinical trial data; and cost. (Clayton Tr. 1087-88; PTX-126 at 11; DTX-514 at 3)

2. Substantial non-infringing use 2

627. For those patients who previously took an antidepressant medication, many will have taken an antidepressant that is not in the four classes required in key step 1. (Rothschild Tr. 1656-57; *see also* Clayton Tr. 1172)

628. Many patients who will take one of Defendants' Proposed ANDA Products will not infringe because they will have only taken an antidepressant outside of the four classes of antidepressants recited in Claim 1's key step 1, i.e., "the group consisting of selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors, noradrenaline/serotonin reuptake inhibitors, and tri-cyclics." (Rothschild Tr. 1656-157; PTX-17 at 20:40-43)

629. MAOIs, bupropion, mirtazapine, and nefazodone are all antidepressants that do not fall into the four classes of antidepressants covered by Claim 1. (Rothschild Tr. 1656-57; Clayton Tr. 1172)

630. The most recent APA Guidelines were published in 2010 and list bupropion and mirtazapine as one of several medications that "are optimal for most patients." (PTX-126 at 11; Rothschild Tr. 1656-57; Reus Tr. 1972-73; Clayton Tr. 1088 (relying on PTX-126))

631. Dr. Clayton acknowledged that in her practice, patients to whom she prescribed vortioxetine had previously taken bupropion and mirtazapine. (Clayton Tr. 1172-73)

632. Dr. Rothschild reviewed Plaintiffs' reports for Clinical Study Nos. 12541A (DTX-470), 11984A (DTX-1126), and 11492A (DTX-1122; PTX-2950), each of which involved patients seeking treatment for MDD, and found that approximately 75% of the patients involved in these studies had not taken any of the four claimed antidepressants in the past three months. (Rothschild Tr. 1655-56 (citing DTX-470; DTX-1122; DTX-1126))

633. Plaintiffs cited and relied on each of the three clinical studies cited by Dr. Rothschild during prosecution of the '096 Patent. (DTX-88 at 1341 (listing Study Nos. 11492, 11984, 12541 under table); Dragheim Tr. 137-39)

634. Plaintiffs cited and relied on each of the three clinical studies relied on by Dr. Rothschild to obtain FDA approval of Trintellix®. (*Compare* PTX-149 at 15, *with*, DTX-88 at 1341; PTX-149 at 15 (listing Study Nos. 11492, 11984, and 12541 as part of "Vortioxetine Clinical Program – for US/EU Registration of MDD"); Dragheim Tr. 137-38)

3. Substantial non-infringing use 3

635. Even in those patients who took one of the claimed antidepressants prior to taking vortioxetine, the patient may cease or reduce their prior medication for reasons unrelated to TESD and, thus, not satisfy key step 2, which requires that the "prior medication be ceased or reduced or has to be ceased or reduced due to sexually related adverse events." (Rothschild Tr. 1657-59; PTX-124 at 1, 5; Clayton Tr. 1166, 1169-70)

636. To the extent some patients may take one of the four classes of antidepressants listed in Claim 1 before taking one of Defendants' ANDA Products, the majority of any such patients still will not infringe Claims 4, 5, and 7 because they will not satisfy key step 2, which requires that the first "medication is ceased or reduced or has to ceased or reduced due to sexually related adverse events." (PTX-17 at 20:38-39; Rothschild Tr. 1657-59)

637. As even Plaintiffs' expert, Dr. Clayton, admitted, if a person switches from an antidepressant in one of the four listed categories to vortioxetine because the listed antidepressant was not efficacious, the patient would not infringe Claim 1 of the '096 patent. (Clayton Tr. 1169-70)

638. The most common reason for stopping a first antidepressant and switching to another, including switching to vortioxetine, is lack of efficacy of the first antidepressant. (Rothschild Tr. 1658; *see also* Clayton Tr. 1170)

639. Ashton, a source cited by Plaintiffs, states that "[t]he most frequently cited reason for discontinuation [of an antidepressant] was lack of efficacy (92 patients [44%])." (PTX-124 at 5; Clayton Tr. 1171) "Lost interest in sex" ranked third with 23%. (*Id.*)

640. Not all sexual dysfunction is TESD. (Clayton Tr. 1163) Sexual dysfunction is often caused by MDD. (DTX-1935 at 1-2) Sexual dysfunction that occurs as a symptom of MDD is not TESD. (Clayton Tr. 1163-64)

641. Not all studies that report on sexual dysfunction in depressed patients distinguish between sexual dysfunction that is caused by the MDD itself versus TESD that is caused by an antidepressant. For instance, Dr. Clayton's 2006 study relied on by Plaintiffs to quantify possible infringing use fails to make this distinction. (PTX-1399; Clayton Tr. 1164; Rothschild Tr. 1659)

642. The '096 Patent states that "[a]s much as 30-70% of patients on SSRIs report deficits in sexual function." (PTX-17 at 7:52-56; DTX-403 at 1; Dragheim Tr. 135-36) If 30-70% of patients taking SSRIs experience sexual dysfunction, the inverse is also true: the remaining 70-30% of patients taking SSRIs do not experience sexual dysfunction. (Dragheim

Tr. 136)

643. Further, compared to SSRIs, the reported incidence of sexual dysfunction is typically lower with the other classes of prior antidepressants listed in the claims (SNRIs, sNRIs, TCAs) – particularly sNRIs and TCAs. (Rothschild Tr. 1660-61; PTX-117 at 5; PTX-119 at 3)

K. Invalidity

1. The ’096 Patent Priority Date

644. The ’096 Patent purports to claim priority to four U.S. and Danish patent applications filed in 2007 (collectively, “2007 applications”). (PTX-17 at 1; Rothschild Tr. 1687-88)

645. The 2007 applications do not reasonably convey to a POSA that the named inventor of the ’096 Patent, Dr. Marianne Dragheim, possessed the subject matter of the TESD limitation of claim 1 at the time those applications were filed. The 2007 applications do not disclose each element of the TESD limitation. (PTX-17 at 26; Dragheim Tr. 129, 131-32; Rothschild Tr. 1688-89, 1693-94)

646. Two passages related to sexual dysfunction in the 2007 applications are identical to disclosures contained in the ’096 Patent. (*Compare* PTX-17 at 7:4-59, 7:64-8:4, 8:57-62 with PTX-8 at 19:1-20:14, 20:32-21:4; *see also* Clayton Tr. 1151-52) Neither of these disclosures mentions prior treatment with any other antidepressant medication in one of the four classes recited in the TESD limitation of Claim 1 of the ’096 Patent. (PTX-17 at 7:4-59, 7:64-8:4, 8:57- 62; PTX-8 at 19:1-20:14, 20:32-21:4; Dragheim Tr. 131-32; Rothschild Tr. 1688-89) Nor do these disclosures mention patients ceasing or reducing any prior antidepressant medication due to TESD. (PTX-17 at 20 7:4-59, 7:64-8:4, 8:57-62; PTX-8 at 19:1-20:14, 20:32-21:4; Dragheim Tr. 131-32; Rothschild Tr. 1688-89)

647. The only data in the 2007 applications related to sexual dysfunction is the same as that found at column 7, lines 4-59 of the '096 Patent (*compare* PTX-17 7:4-59 *with* PTX-8 19:1-20:8; Dragheim Tr. 129), which would not reasonably convey to a POSA that the inventor had possession of the claimed subject matter.

648. The earliest applications related to the '096 Patent which fully describe the subject matter of the TESD limitation were filed on September 17, 2008. (Rothschild Tr. 1687-88; DTX-398; DTX-412) Therefore, the priority date for the '096 Patent is September 17, 2008.

2. Prior Art Reference WO '005

649. WO 2007/144005, entitled 1- [2- (2, 4-dimethylphenylsulfanyl) -phenyl] piperazine as a compound with combined serotonin reuptake, 5-HT3 and 5-HT1A activity for the treatment of cognitive impairment ("WO '005"), published on December 21, 2007. (DTX-417; Rothschild Tr. 1688) WO '005 is § 102(a) prior art to the '096 Patent. (Rothschild Tr. 1687-88)

650. The USPTO considered WO '005 during examination of the application that issued as the '096 Patent. (PTX-17 at 1)

651. WO '005 expressly claims the compound "1-[2-(2,4-dimethylphenylsulfanyl) phenyl]piperazine," which is now known by the name vortioxetine, and is the same compound name recited in Claim 1 of the '096 Patent. (DTX-417 at 1 (Title & Abstract); DTX-417 at 3:18-19; Reider Tr. 160-61; Rothschild Tr. 1690) For example, Claim 5 of WO '005 is directed to "1-[2-(2,4-dimethylphenyl-sulfanyl)phenyl]piperazine hydrobromide salt in a crystalline form."

652. Through its recitation of the "hydrobromide salt," Claim 5 of WO '005 also expressly discloses the limitations of Claims 3 and 7 of the '096 Patent requiring the

"hydrobromic acid salt." (DTX-417 at 56; Rothschild Tr. 1690; DTX-417 at 5:3-6:22)

653. WO '005 also expressly discloses the crystalline form limitations of Claims 4 and 5 because Claims 6 and 7 of WO '005 contain the same limitations. (DTX-417 at 56:14-17; DTX-417 at 3:22-27, 5:16-22, 7:15-19, 56:3-5, 66, Figure 3; Rothschild Tr. 1690)

654. WO '005 discloses the dosage amount limitations of Asserted Claims 6 and 7, as WO '005 teaches that the "total daily dose is usually in the range of about 1 - 20 mg," which falls within the 1-50 mg range of Claim 6 and is identical to the range of "about 1 and 20 mg per day" of Claim 7. (DTX-417 at 6:10-13, 17:3-6, 17:11-14; Rothschild Tr. 1691)

655. WO '005 expressly discloses Claim 7's requirement that the compound be administered "orally," stating "[o]ral dosage forms" are preferred. (DTX-417 at 6:10-13; Rothschild Tr. 1691)

656. WO '005 expressly discloses Claim 1's "method for the treatment of a disease selected from the group consisting of depression," as it discloses and claims vortioxetine hydrobromide to treat depression. (DTX-417 at 9:30-10:4, 12:4-9, 57:27-58:7; Rothschild Tr. 1690) For example, WO '005 Claim 15 is directed to: "A method of treating a disease selected from affective disorders, depression . . ., the method comprising administering a therapeutically effective amount of a compound according to any of claims 1-8 to [a] patient in need thereof." (DTX-417 at 57:27-58:7)

657. However, WO '005 does not disclose key information that a POSA would need to interpret it, including which "compounds of the present invention" its subjects were exposed to, the dosage or number of dosages to which subjects were exposed, subject attributes, or anything about the study design, such as whether there was a placebo and/or active control. (Rothschild

Tr. 1738-39)

658. Defendants' expert, Dr. Rothschild, testified that he was not offering an opinion that WO '005 would allow a POSA to make and use the invention claimed in the '096 Patent. (Rothschild Tr. 1738) Rather, in his opinion, WO '005 "would motivate a POSA to pursue" the invention claimed in the '096 Patent. (Rothschild Tr. 1737)

659. A POSA in November 2007 and September 2008 would have understood that vortioxetine is a serotonergic antidepressant. (Clayton Tr. 1160-61; Rothschild Tr. 1697, 1710; DTX-696 at 26) WO '005 describes the compounds of the present invention as "potent inhibitors of the human serotonin transporter, i.e. they inhibit serotonin reuptake." (DTX-417 at 10) It would not have been obvious to a POSA that treatment with a Serotonin reuptake inhibitor would benefit, and a POSA would not have had a reasonable expectation of success in using an SRI to treat, patients with depression who fall within the TESD limitation. (*See* Dragheim Tr. 117, 130; Clayton Tr. 1160-61; Rothschild Tr. 1697, 1710; DTX-696 at 3, 26; PTX-1046 at 1; PTX-1400 at 1)

660. WO '005 does not inherently disclose the TESD limitation of Claim 1 of the '096 Patent.

661. WO '005 summarizes clinical study data, which it states "suggest[s] that clinical intervention using compounds of the present invention is associated with surprisingly few deficits in sexual functioning." (DTX-417 at 13:25-14:2)

662. WO '005's clinical study summary suggests that the vortioxetine may be used to reduce sexually related adverse events. (Rothschild Tr. 1691-93) Still, the few sentences in WO '005 about 114 subjects exposed to unidentified compounds would have been insufficient to sway a POSA from the deeply-rooted expectation that SRIs are linked to TESD.

663. Furthermore, as the Court has found above (*see supra* FF ¶ 619), a POSA would prescribe vortioxetine as a first-line treatment in a not insubstantial number of instances. That reasoning similarly leads the Court to find that a POSA reviewing WO '005 would also read it to teach only that a POSA could prescribe vortioxetine as a first-line treatment. It would not have been obvious to a POSA from WO '005 to switch an MDD patient who had previously taken one of the four types of antidepressants to vortioxetine in order to avoid TESD.

664. Defendants' anticipation and obviousness contentions based on the WO '005 Patent are entirely intertwined with Plaintiffs' theory of infringement of the '096 Patent. For example, Defendants propose that "***if*** either of Plaintiffs' infringement positions with respect to the '096 patent are credited, ***then*** WO '005's disclosure of vortioxetine for treating depression inherently discloses the TESD limitations of claim 1 of the '096 patent." (D.I. 1053 ¶ 173 (emphasis added); *see also* Rothschild Tr. 1691-92)

665. As Plaintiffs' infringement positions are not being credited, neither are Defendants' invalidity contentions based on WO '005.

3. Prior Art Reference WO '232

666. International Publication No. WO 2003/029232 ("WO '232"), entitled "Phenyl-Piperazine Derivatives as Serotonin Reuptake Inhibitors," was published in 2003 and is prior art to the '096 Patent. (SF ¶ 293; DTX-696; Rothschild Tr. 1672-73)

667. The USPTO considered WO '232 and U.S. 7,144,884, which claims priority to WO '232, during examination of the application that issued as the '096 Patent. (PTX-17 at 1)

668. During prosecution of the '096 Patent, the Examiner repeatedly rejected application claim 28 (which issued as Claim 1) for obviousness based on U.S. Pat. Pub. No. 2005/0014740 ("Ruhland"), which is the U.S. publication of WO '232. (DTX-88 at 1247-48, 1300-04, 2526-28)

669. In overcoming these rejections Plaintiffs argued, "The Examiner asserts that Ruhland teaches Compound I is useful in the treatment of depression. The general treatment of depression, however, is not the invention claimed in claim 28." (DTX-88 at 1276, 2561)

670. Defendants have provided no motivation or reason for a POSA to combine the HBr salt with 1-[2-(2,4-DMPS)P]P, out of all of the possible compound-salt combinations in the disclosure. Nor have they provided evidence of a reasonable expectation of success in doing so.

671. It would not have been obvious to a POSA that treatment with an SRI would benefit patients with depression who fall within the TESD limitation of the '096 Patent. (*See* Dragheim Tr. 117, 130; Clayton Tr. 1160-61; Rothschild Tr. 1697, 1710; DTX-696 at 3, 26; PTX-1046 at 1; PTX-1400 at 1) Nor would a POSA have had a reasonable expectation of success in doing so. A POSA would have been discouraged from treating the claimed patient population with the compounds disclosed in WO '232. A POSA looking for an antidepressant to treat such patients would have looked to antidepressants without a direct effect on serotonin, drawing from the example of bupropion, which is an inhibitor of norepinephrine and dopamine reuptake. (PTX-1055 at 1)

672. WO '232 does not specifically disclose or identify VHBr. Instead, WO '232 describes broad chemical genera encompassing millions of compounds, 24 preferred compounds, and a list of dozens of non-limiting exemplary acid addition salts that may or may not be combined with the disclosed compounds. (DTX-696 at 9-10; Rothschild Tr. 1727-28) Six of these "exemplary" salts are inorganic. (DTX-696 at 9-10)

673. WO '232 does not point to any particular salt form of 1-[2-(2,4-DMPS)P]P. (DTX-696 at 9-10) Dr. Rothschild did not explain how a POSA would understand the separate mentions of 1-[2-(2,4-DMPS)P]P and HBr salt in WO '232 to constitute a disclosure of VHBr as

claimed. (Rothschild Tr. 1672-75)

674. WO ’232 does not discuss any of the disclosed compounds’ effects on sexual functioning in patients with depression or patients who have previously been treated with another antidepressant. (DTX-696)

675. WO ’232 expressly discloses claim 1’s “method for the treatment of a disease selected from the group consisting of depression . . . .” because it discloses vortioxetine hydrobromide for the treatment of major depressive disorder. (Rothschild Tr. 1672; DTX-696 at 2, 6, 7, 9, 10, 22, 29)

676. WO ’232 states that the disclosed compounds “are administered in unit dosage form containing . . . most preferably about 0.1 to 50 mg of the active compound of the invention,” which is nearly the same as claim 6’s range of “1-50 mg.” (DTX-696 at 11:25-28; PTX-17 at 26, 20:54-56; Rothschild Tr. 1684) This does not disclose Claim 7’s specific dosage range of “about 1 and 20 mg per day” that can be used to treat the patients specified in the TESD limitation. (PTX-17 at 26, 20:57-59)

677. The ’096 Patent states it will be understood that deriving the appropriate therapeutically effective amount for patients “may be achieved using routine experimentation . . . .” (PTX-17 at 21, 9:47-59; Rothschild Tr. 1684)

678. WO ’232 also expressly discloses claim 7’s requirement that the claimed compound be administered “orally” because it states that the compounds disclosed “may be administered by any suitable route, for example orally . . . .” (PTX-696 at 11:18-20; Rothschild Tr. 1684)

679. WO ’232 does not disclose the ’096 Patent’s limitation requiring that vortioxetine be prescribed to MDD patients who have previously taken one of four specified classes of other

antidepressants and are now being prescribed vortioxetine due to TESD associated with the prior antidepressant.

680. Instead, at most WO ’232 states that SSRIs were the “first choice therapeutics in the treatment of depression” in the prior art, from which it follows that in the population of patients who had previously been treated for depression, many would have been treated with SSRIs as a first-line treatment. (DTX-696 at 2:9-12; *see also* Clayton Tr. 1127; PTX-1377 at 3; Rothschild Tr. 1685-1686)

681. As of November 2007, at least some patients who previously took an SSRI would have experienced sexually related adverse events. (PTX-17.20, 7:52-56; Clayton Tr. 1089:3-1093:19; Rothschild Tr. 1713:2-12) Because in November 2007 and September 2008 vortioxetine was considered a serotonergic antidepressant (Clayton Tr. 1160-61; Rothschild Tr. 1697, 1710; DTX-696 at 26), it would not have been obvious to a POSA that treatment with an SRI would benefit – and a POSA would not have had a reasonable expectation of success in using an SRI on – patients with depression who fall within the TESD limitation. (*See* Dragheim Tr. 117, 130; Clayton Tr. 1160-61; Rothschild Tr. 1697, 1710; DTX-696 at 3, 26; PTX-1046 at 1; PTX-1400 at 1)

682. Furthermore, as the Court has found above (*see supra* FF ¶ 619), a POSA would prescribe vortioxetine as a first-line treatment in a not insubstantial number of instances. That reasoning similarly leads the Court to find that a POSA reviewing WO ’232 would read it to teach only that a POSA could prescribe vortioxetine as a first-line treatment. It would not have been obvious to a POSA from WO ’232 to switch an MDD patient who had previously taken one of the four types of antidepressants to vortioxetine in order to avoid TESD.

683. While Defendants are correct that Plaintiffs’ induced and contributory

infringement positions for the ’096 Patent are both premised on Plaintiffs’ position that Defendants’ Proposed ANDA Products – which would be indicated for MDD generally – will be used by patients consistent with the TESD limitations (*see, e.g.*, Clayton Tr. 1119-20), the Court has rejected Plaintiffs’ infringement position. (*See supra* ¶¶ 608, 613-17)

684. Defendants’ invalidity contentions based on WO ’232 rely on a view that, if the Court is persuaded by Plaintiffs’ infringement theory, WO ’232 inherently discloses the TESD limitation of Claim 1 of the ’096 Patent. (Rothschild Tr. 1685) As the Court has not been persuaded by Plaintiffs’ infringement theory, the Court likewise rejects Defendants’ contingent inherent anticipation theory of invalidity.

685. The Court has rejected Plaintiffs’ infringement position. Accordingly, it also rejects Defendants’ invalidity positions based on WO ’232, which the Court views as dependent on acceptance of Plaintiffs’ infringement position.

4. Objective Indicia Of Non-Obviousness

a. Nexus

686. Objective indicia support the non-obviousness of Claims 4, 5, and 7 of the ’096 Patent.

687. Trintellix embodies the claimed inventions. (Clayton Tr. 1148)

688. Trintellix is prescribed and used in a way that meets all limitations of Claim 7 of the ’096 Patent. (Clayton Tr. 1147)

689. The use of Trintellix in accordance with the method of Claim 7 of the ’096 Patent falls within the FDA-approved use for Trintellix. (Clayton Tr. 1147-48)

690. Trintellix meets the crystalline form limitations of Claims 4 and 5 of the ’096 Patent and embodies Claims 4 and 5. (Clayton Tr. 1148)

691. There is a nexus between certain objective indicia of non-obviousness and Claims

4, 5, and 7 of the ’096 Patent. (Clayton Tr. 1147-48)

692. Whether compared to the disclosure of WO ’232, the disclosure of WO ’005, or other available antidepressant drugs, several objective indicia support non-obviousness.

b. Long-felt but unmet need

693. Prior to Trintellix, there was a long-felt need for efficacious and tolerable treatment options for MDD patients who fall within the TESD limitation. (Clayton Tr. 1154; Mattingly Tr. 858; PTX-132 at 11; PTX-135 at 12)

694. While bupropion (Wellbutrin®), mirtazapine (Remeron®), and nefazodone (Serzone®) are associated with relatively low incidences of TESD, they did not meet the needs of all patients. (Clayton Tr. 1156-58)

695. While bupropion and mirtazapine have been endorsed by the APA as “optimal agents” for treating depression (Rothschild Tr. 1656-57; PTX-125 at 7; PTX-126 at 11), both – as well as nefazodone – have unfavorable side-effect profiles.

696. Bupropion is associated with adverse side effects other than TESD, such as sleep disturbance, irritability, headache, agitation, and anxiety that many patients find intolerable. (Clayton Tr. 1157) As observed in Ashton, insomnia and agitation are among the adverse events that patients reported to be “extremely difficult to live with.” (PTX-124 at 7) Bupropion is also associated with an increased incidence of seizures, as reflected in the Wellbutrin Prescribing Information. (PTX-1029 at 5; *see also* Mattingly Tr. 841; Clayton Tr. 1157)

697. Mirtazapine is associated with side effects like weight gain and sedation that many patients find intolerable. (Clayton Tr. 1157-58; Mattingly Tr. 841; PTX-1377 at 3; PTX-1031 at 15) As reported by Ashton, weight gain was the second most common reason for noncompliance and was the top adverse effect that patients reported as “extremely difficult to live with.” (PTX-124 at 6-7)

698. Nefazodone is associated with life-threatening hepatic failure. (Clayton Tr. 1158-59; PTX-1033 at 3) In 2002, a black box warning was added to the nefazodone Prescribing Information warning of life-threatening hepatic failure. (PTX-1033 at 3; Mattingly Tr. 841; Clayton Tr. 1159) Serzone (branded nefazodone) was withdrawn from the U.S. market by 2004 (Clayton Tr. 1159), and regulatory authorities in Canada, Europe, and Australia also removed nefazodone's approval (Rothschild Tr. 1717). Since 2013, nefazodone prescriptions have not exceeded 0.1% of prescriptions for MDD in the U.S. (Clayton Tr. 1159; Rothschild 1717-18; PTX-457)

699. Scientific literature recognized a need for a drug like Trintellix even after bupropion, mirtazapine, and nefazodone were available in the U.S. (*Compare* PTX-132 (2007), PTX-134 (2004), PTX-135 (2007) *with* PTX-125 (2000) at 8)

700. In 2004, Cassano & Fava observed: "Long-lasting side effects of antidepressants, such as . . . sexual dysfunction, can significantly impair a patient's ability to function in professional, familial, and social capacities" and that "these long-term treatment side effects are likely to have a dramatic impact on patient outcome and treatment adherence." (PTX-134 at 1-2; Clayton Tr. 1154-55)

701. In 2007, Rosenzweig-Lipson stated: "The high incidence of sexual dysfunction associated with antidepressants makes this a key area for improvement in the next generation of antidepressants. Novel mechanisms that demonstrate antidepressant efficacy equivalent to or better than existing antidepressants will also need to be associated with minimal effects on sexual function." (PTX-132 at 11; Clayton Tr. 1155)

702. Clayton 2007 stated: "The high incidence of antidepressant-associated sexual dysfunction and weight gain emphasizes that, despite the variety of antidepressants available,

there is still an unmet need for efficacious and well-tolerated therapeutic agents." (PTX-135 at 12; Clayton Tr. 1155-56)

703. The FDA also recognized the need for an antidepressant like Trintellix. (Dragheim Tr. 119; PTX-2958 at 4-5) Indeed, in 2012, at a regulatory science forum, the FDA and industry experts agreed that "sexual dysfunction associated with antidepressants is an important entity that should be adequately assessed during clinical trials with the use of available instruments and described in product labels." (PTX-71 at 1; PTX-72; Clayton Tr. 1101)

704. Trintellix satisfied the long-felt but unmet need for an efficacious and tolerable treatment option for MDD patients who fall within the TESD limitation of the '096 Patent. (Clayton Tr. 1154-56, 1159-60)

705. The USPTO considered evidence demonstrating vortioxetine's better overall tolerability than other antidepressants, specifically venlafaxine and duloxetine, during prosecution of the '096 Patent. (Dragheim Tr. 137-38)

706. The FDA concluded that a 2-3 point change on the CSFQ brought on by use of vortioxetine is clinically meaningful. (PTX-4475 at 26)

c. Unexpected results

707. The ability to use Trintellix in accordance with the TESD limitation of the '096 Patent was a surprising and unexpected benefit, particularly given that vortioxetine is an SRI agent. (*See* Clayton Tr. 1160-61, 1086, 1089; Dragheim Tr. 117, 130)

d. Praise and recognition

708. The FDA rigorously reviews superiority studies and imposes a high bar for studies to be added to prescribing information. (Dragheim Tr. 126, 128; Peck Tr. 1305) The FDA readily approved the 318 and 4001 Superiority Studies. (Dragheim Tr. 128; Clayton Tr. 1161-62)

709. The FDA's decision to allow Plaintiffs to add the clinical study information related to TESD to Section 14 of the Trintellix® prescribing information is not praise of a type that makes it less likely the challenged claims were obvious. (Rheinstein Tr. 2108-10)

710. The FDA's Citizen Petition decision criticizes Plaintiffs for overstating the benefits of vortioxetine in reducing TESD based on the data in Section 14, observing that "numerous patients in the vortioxetine group reported worsening on their CSFQ-14 total scores during the study" (DTX-514 at 16), "the protected information [Section 14] does not describe a benefit at the 20 mg/day dose" (DTX-514 at 16), and "approximately 48% of patients [taking vortioxetine] continued to experience sexual dysfunction . . . ." (DTX-514 at 17)

5. Lack Of Written Description Challenge To Claims 4, 5, And 7

711. The content added to the 2007 applications by the September 17, 2008 applications related to sexual dysfunction is located in Claim 1 itself; in column 7 lines 59-63; and in column 8 lines 10-22. (DTX-398 at 12:3-6, 17-26; DTX-412 at 18:3-6, 17-26; PTX-17 at 7:59-63, 8:10-22)

712. The first two sexual dysfunction-related additions made in 2008 consist of either the claim language or paraphrasing of it in the specification. (Rothschild Tr. 1670, 1688-89, 1693-94; DTX-398 at 12:3-6; DTX-412 at 18:3-6)

713. In addition, the '096 Patent contains the following additional disclosure, which directly mirrors the claim language and further supports the claims' written description:

> [T]he compounds used in the present invention may also be useful as second line treatment for patients who cannot use other drugs, such as other antidepressants, [including SSRIs, NRIs, SNRIs, or TCAs] due to sleep or [SRAEs]. In this embodiment, the patient has received another medication (or is still receiving it), which medication was ceased or reduced (or has to be ceased or reduced) due to sleep or [SRAEs].

(PTX-17 at 8)

XII. Facts Related To Disputes Concerning The Cognitive Impairment Patent

A. Background

714. There are four domains of cognition – executive function, learning and memory, attention, and processing speed – all of which may be adversely affected in adults with depression. (McIntyre Tr. 1226-28)

715. Cognitive impairment is very common in MDD patients and is often independent of the mood symptoms of MDD. (McIntyre Tr. 1229)

716. Conradi explained that 94% of patients exhibited cognitive impairment during a major depressive episode ("MDE"); after resolution of depressive symptoms, 44% of patients continued to experience cognitive impairment. (McIntyre Tr. 1229; PTX-373 at 1)

717. Historically, antidepressants have not demonstrated an ability to alleviate/mitigate cognitive impairment in adults with depression. (McIntyre Tr. 1230-31; PTX-373 at 4; PTX-4593 at 7; PTX-134 at 2, 7)

718. Vortioxetine is the only antidepressant approved in the U.S. for MDD that has been shown to improve cognitive impairment in patients with MDD in replicated, randomized, double-blind, placebo-controlled trials with cognition as the primary endpoint. (McIntyre Tr. 1233-34; PTX-1193 at 6)

719. Vortioxetine's ability to alleviate cognitive impairment in MDD patients has been demonstrated in two studies (FOCUS and CONNECT) using the Digit Symbol Substitution Test ("DSST") as a primary end point. (McIntyre Tr. 1235; PTX-388 at 3; PTX-392 at 3) The DSST is a widely-used and well-established psychometric tool. The DSST is most associated with processing speed, but measures all four domains of cognition. (McIntyre Tr. 1236-3; PTX-393 at 2)

720. The FOCUS Study found that patients receiving 10 mg of vortioxetine exhibited a

statistically significantly greater improvement on the DSST compared to patients receiving placebo. (McIntyre Tr. 1234-35; PTX-392 at 4)

721. The CONNECT Study found that patients receiving 10 and 20 mg of vortioxetine exhibited a statistically significantly greater improvement on the DSST compared to patients receiving placebo. (McIntyre Tr. 1234-35; PTX-388 at 4)

722. Path analyses performed in the FOCUS and CONNECT studies demonstrated that vortioxetine's ability to alleviate cognitive impairment is attributable not only to vortioxetine's improvement of the mood symptoms of MDD, but also to the drug's additional effect on cognitive impairment in MDD specifically. (McIntyre Tr. 1237-38; PTX-388 at 5; PTX-392 at 6-7) Path analysis is a statistical approach used to determine the magnitude of an effect that is directly attributable to the intervention. Path analysis is accepted by academics, the scientific community, and regulators. (McIntyre Tr. 1238)

723. The path analysis in the CONNECT Study found that 75.7% of the effect of vortioxetine on cognitive functioning could be directly attributed to improvement in cognitive functioning and was not mediated by improvements in mood. (PTX-388 at 5; McIntyre Tr. 1238)

724. The path analysis in the FOCUS Study found that one-half to two-thirds of the effect of vortioxetine on cognitive functioning could be directly attributed to improvement in cognitive functioning and was not mediated by improvements in mood or depressive symptoms. (PTX-392 at 6-7; McIntyre Tr. 1238)

725. Study No. 12541 ("the Elderly Study"), which investigated the drug's effect on cognition through use of cognitive measures as secondary end points, supports vortioxetine's ability to alleviate cognitive impairment in MDD patients. The Elderly Study found that patients

receiving 5 mg of vortioxetine showed a statistically significantly greater improvement on the DSST compared to patients receiving placebo. (PTX-393 at 6) The path analysis in the Elderly Study found that improvement in DSST performance was attributable to vortioxetine's direct and independent effect on cognitive functioning. (PTX-393 at 6)

726. The CONNECT, FOCUS, and Elderly studies are available in the published scientific literature. (McIntyre Tr. 1237; PTX-388; PTX-392; PTX-393)

727. Vortioxetine's ability to alleviate/mitigate cognitive impairment in patients with MDD is well-known to clinicians. (Mattingly Tr. 844-45; Clayton Tr. 1177; McIntyre Tr. 1247; PTX-388; PTX-392; PTX-4593; PTX-393)

728. Baune conducted a network meta-analysis comparing the effects of various antidepressants on cognition using the DSST. (McIntyre Tr. 1239; PTX-4593 at 2) The Baune meta-analysis included SSRIs (sertraline, citalopram, fluoxetine, escitalopram), SNRIs (duloxetine), TCAs (desipramine, nortriptyline), MAOIs (phenelzine), and vortioxetine. (McIntyre Tr. 1239-40; PTX-4593 at 7) Baune found that the only antidepressant that showed a statistically significant improvement on cognitive function as measured by performance on the DSST was vortioxetine. (McIntyre Tr. 1239; PTX-4593 at 6-7) SSRIs, MAOIs, and TCAs had an adverse effect on (i.e., they worsened) cognitive functioning. (McIntyre Tr. 1239-40; PTX-4593 at 6-7)

729. The '910 Patent issued September 8, 2015. (PTX-16)

730. The '910 Patent was submitted for inclusion in the Orange Book in May 2018. (*See* Peck Tr. 1338-39; D.I. 225 at 1)

731. The '910 Patent is listed in the FDA Orange Book for Trintellix® with Patent Use Code U-2309, "use in the treatment of major depressive disorder to improve processing speed, an

aspect of cognitive function." (SF ¶ 181)

732. The Trintellix Prescribing Information describes the results of the FOCUS and CONNECT studies in detail. Specifically, it states:

Digit Symbol Substitution Test in Major Depressive Disorder

Two, eight week, randomized, double-blind, placebo-controlled studies were conducted to evaluate the effect of TRINTELLIX on the Digit Symbol Substitution Test (DSST) during the treatment of acute MDD. The DSST is a neuropsychological test that most specifically measures processing speed, an aspect of cognitive function that may be impaired in MDD. Patients are asked to match nine symbols with their corresponding number (1 to 9) according to a key; the score is the correct number of matches achieved in 90 seconds. For reference, the mean score for healthy 45 to 54 year-old subjects is 50 (SD=15).

Study 7 randomized adult patients meeting the diagnostic criteria for recurrent MDD to receive TRINTELLIX 10 mg, TRINTELLIX 20 mg, or placebo once daily. Study 8 randomized adult patients meeting the diagnostic criteria for recurrent MDD and reporting subjective difficulty concentrating or slow thinking to receive a flexible dose of TRINTELLIX (10 or 20 mg) or placebo once daily. Neither study included patients whose MDD was in remission yet who continued to experience difficulty concentrating or slow thinking. Patients' mean age was 46 (SD=12) and 45 (SD=12) in Study 7 and 8, respectively. In both studies, patients in the TRINTELLIX group had a statistically significantly greater improvement in number of correct responses on the DSST (*Table 6*); depressed mood as assessed by change from baseline in MADRS total score also improved in both studies.

Table 6. Effect of TRINTELLIX on the Digit Symbol Substitution Test (DSST)

Study No.	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[1] (95% CI)
Study 7	TRINTELLIX (10 mg/day)[2]	193	42.0 (12.6)	9.0 (0.6)	4.2 (2.5, 5.9)
	TRINTELLIX (20 mg/day)[2]	204	41.6 (12.7)	9.1 (0.6)	4.3 (2.6, 5.9)
	Placebo	194	42.4 (13.8)	4.8 (0.6)	--
Study 8	TRINTELLIX (10/20 mg/day)[2]	175	42.1 (11.9)	4.6 (0.5)	1.8 (0.3, 3.2)
	Placebo	167	43.0 (12.3)	2.9 (0.5)	--

SD: standard deviation, SE: standard error, LS Mean: least-squares mean, CI: unadjusted confidence interval.
[1] Difference (drug minus placebo) in least-squares mean change from baseline.
[2] Doses are statistically significantly superior to placebo.

The effects observed on DSST may reflect improvement in depression. Comparative studies have not been conducted to demonstrate a therapeutic advantage over other antidepressants on the DSST.

(PTX-4475 at 23-24; McIntyre Tr. 1240)

733. There is no other antidepressant available in the U.S. that has clinical trial data in its prescribing information using a measure of cognitive functioning as a primary end point or demonstrating the drug's ability alleviate/mitigate one or more domains of cognitive function. (McIntyre Tr. 1241; Mattingly Tr. 845)

734. In approving the inclusion of the FOCUS and CONNECT studies in the Trintellix Prescribing Information, the FDA concluded that the changes in DSST are "clinical[ly] meaningful[]" and "reflect[] an improvement in an important aspect of cognitive dysfunction in depression, speed of processing." (PTX-85 at 17)

B. The Method Of Claim 6 Of The '910 Patent Is An Approved Use Of Vortioxetine

735. Use of vortioxetine to treat cognitive impairment in a patient diagnosed with depression is an approved use of Trintellix and will be an approved use of Defendants' ANDA Products, if approved. (Peck Tr. 1302-03)

736. If the FDA did not approve the use of vortioxetine in patients with MDD to

alleviate cognitive impairment, it would have required a limitation of use in the Indications and Usage section of Defendants' labels. (Peck Tr. 1312-13; PTX-60 at 13-17) The absence of such a limitation reflects that the FDA approved Trintellix and Defendants' ANDA Products for the treatment of cognitive impairment in patients diagnosed with depression. (Peck Tr. 1306, 1312-13)

737. The FDA approved the inclusion of the FOCUS and CONNECT studies in the Trintellix Prescribing Information because the studies relate to an approved use. The FDA would not have approved the inclusion of the cognition studies in the Trintellix Prescribing Information if such studies implied effectiveness for an unapproved use. (PTX-58 at 6; Peck Tr. 1307-08)

738. Takeda's promotional activity further confirms that the method of Claim 6 of the '910 Patent is within the approved use of vortioxetine. Takeda promotional materials encourage physicians to "fight the fog of depression with Trintellix" and report the data from the FOCUS and CONNECT studies. (PTX-1704 at 1-2; *see also* McIntyre Tr. 1249-50) The FDA has not instituted an enforcement action against Takeda's promotion of vortioxetine's ability to alleviate cognitive impairment. (Peck Tr. 1314)

C. Additional Facts Related To Infringement

739. Plaintiffs assert that all Defendants (other than Sandoz) will contribute to infringement of Claim 6 of the '910 Cognitive Impairment Patent. (D.I. 987 Ex. 4A (Alembic) ¶¶ 3-6; *id.* Ex. 4C (Lupin) ¶¶ 3-6; *id.* Ex. 4D (Macleods) ¶¶ 3-6; *id.* Ex. 4G (Sigmapharm) ¶¶ 3-6; *id.* Ex. 4J (Zydus) ¶¶ 3-5)

740. If approved, Defendants' ANDA Products will have the same cognitive effects as Trintellix. (McIntyre Tr. 1246-47)

741. There will be direct infringement of Claim 6 of the '910 Patent because clinicians

will sometimes prescribe Defendants' ANDA Products for a use that infringes Claim 6. (McIntyre Tr. 1244, 1252)

742. Defendants have not contested that they have knowledge of the '910 Patent. (D.I. 985, Ex. 1C (Lupin) ¶ 101; Ex. 1D (Macleods) ¶ 66; McIntyre Tr. 1252)

743. Defendants' ANDA Products are a material part of the method of treatment described in Claim 6 of the '910 Patent because Defendants' ANDA Products are integral to the performance of the claimed method. The method of Claim 6 cannot be practiced without a vortioxetine dosage form. (PTX-16 at 45; McIntyre Tr. 1253)

744. The doses of vortioxetine Defendants seek approval for are therapeutically effective amounts for treating cognitive impairment in patients with MDD. (McIntyre Tr. 1253-54)

745. Clinicians are aware from the Trintellix Prescribing Information (specifically, Section 14) that vortioxetine alleviates cognitive impairment in patients with MDD. (McIntyre Tr. 1247; PTX-4475 at 23-24; PTX-1419 at 22-23)

746. Clinicians are aware from the scientific literature that vortioxetine alleviates cognitive impairment. (McIntyre Tr. 1247-49) McIntyre 2014 reported the results of the FOCUS study. (*See* PTX-392) Mahableshwarkar 2015 reported the results of the CONNECT study. (*See* PTX-388) McIntyre 2016 describes a meta-analysis of three vortioxetine clinical trials which found that vortioxetine, but not duloxetine, significantly improved cognition. (PTX-393 at 1; *see also* PTX 1193 at 6) Baune found that vortioxetine was the only antidepressant that improved performance on the DSST versus placebo and vortioxetine was linked to statistically significantly greater improvements on the DSST compared to other antidepressants. (PTX-4593 at 1)

747. Clinicians are aware of vortioxetine's ability to alleviate cognitive impairment from marketing materials, academic and professional conferences, and their own clinical experience. (McIntyre Tr. 1237, 1247-50; *see also* PTX-388; PTX-392; PTX-393)

748. Clinicians will sometimes prescribe vortioxetine to treat cognitive impairment in patients with MDD even if Defendants' Prescribing Information omits the CONNECT and FOCUS data because clinicians are aware of vortioxetine's ability to alleviate cognitive impairment from numerous other sources. (*See* McIntyre Tr. 1250-51, Mattingly Tr. 845-46)

749. Each Defendant's proposed prescribing information contains only one indication, which is "the treatment of major depressive disorder (MDD) in adults." (SF ¶ 232; PTX-4363 at 3 (Sigmapharm); PTX-4565 at 2 (Lupin); PTX-4566 at 4 (Macleods); PTX-4567 at 5 (Alembic); DTX-1169 at 2 (Sandoz); DTX-1933 at 4 (Zydus); Rothschild Tr. 1646-47)

750. The remaining Defendants (other than Sandoz) have each filed "carve-outs" pursuant to 21 U.S.C. § 505(j)(2)(A)(viii) to Patent Use Code U-2309 to exclude reference to studies using the DSST during the treatment of acute MDD. (McIntyre Tr. 1285-86; Rheinstein Tr. 2113-14)

751. Zydus' proposed prescribing information (DTX-1933) is representative of Defendants' proposed prescribing information related to Plaintiffs' allegations of infringement. (*See* Peck Tr. 1341; Rothschild Tr. 1649; Rheinstein Tr. 2115; 21 C.F.R. § 314.105(d); 21 C.F.R. § 314.127(a)(7))

752. Zydus' proposed prescribing information carves out two sets of information in Sections 6.1 and 14. (*Compare* PTX-4475 at 9, 23-24, 26-28 *with* DTX-1933 at 11, 25-30; DTX-507 at 22-23; DTX-514 at 1-2) Those two sets of carve outs relate to: (1) cognitive impairment information in Section 14; and (2) TESD comparative information in Sections 6.1

and 14 (discussed above).

753. With the exception of Sandoz, those same two sets of carve outs are also made in all other Defendants' proposed prescribing information. (SF ¶ 232; Rheinstein Tr. 2115; *compare* PTX-1196 at 21-22, 47-51, *with* PTX-4363 at 10, 27-28 (Sigmapharm); PTX-4565 at 8, 23-24 (Lupin); PTX-4566 at 9, 21 (Macleods); PTX-4567 at 12, 28-29 (Alembic); DTX-1169 at 8, 20-21 (Sandoz); DTX-1933 at 11, 29-30 (Zydus))

754. DSST results from the FOCUS and CONNECT trials are included in the Trintellix® Label, but not Defendants' labels. (Rothschild Tr. 1664-65; McIntyre Tr. 1286; Rheinstein Tr. 2113-14; *compare* PTX-4475 at 23-24 *with* DTX-1933)

755. A physician would not change her prescribing habits or reach conclusions about vortioxetine's purported effect on cognitive impairment based on the DSST results included in the Trintellix® Label and not included in Defendants' Proposed ANDA Products' labels. (Reus Tr. 1991-94, 1994-96; Rothschild Tr. 1708-09)

756. Consistent with the proposed indication in Defendants' proposed Prescribing Information, Defendants' Proposed ANDA Products will often be prescribed for the purpose of treating MDD, not for the purpose of treating cognitive impairment. (Rothschild Tr. 1645, 1666-67; Rheinstein Tr. 2108-11; DTX-1933 at 4)

757. Dr. Rothschild persuasively opined that there will be substantial non-infringing uses of Defendants' ANDA Products, specifically, that (1) vortioxetine will be prescribed to some patients who do not have cognitive symptoms and (2) vortioxetine will be prescribed for the treatment of MDD for purposes unrelated to cognition. (Rothschild Tr. 1666-67)

758. It will not be unusual or occasional for patients to be prescribed Defendants' ANDA Products for reasons that do not include combating cognitive impairment.

759. In approving the addition of DSST data to the Trintellix label, the FDA noted:

> There is no expectation that there would be disadvantages of including DSST information in labeling *unless* the DSST results are perceived as demonstrating a greater effect on cognitive dysfunction relative to other antidepressant drugs. This could lead to physicians to use vortioxetine instead of other therapies, as the "only" drug with cognitive dysfunction benefit, despite no evidence of superior benefit to standard antidepressant treatments, and evidence of benefit on an endpoint, DSST, that measures only an aspect of cognitive dysfunction. My assessment, however, is that this risk can be mitigated by clear labeling (as the division in prior meeting minutes had already informed the applicant) stating that the improvements were seen in *speed of processing* and that these improvements have not been demonstrated to be either a direct benefit (i.e., separate from and beyond the benefits on depression) or a distinct effect of the vortioxetine relative to other standard antidepressant agents…

(PTX-85 at 17; *see also* Peck Tr. 1355)

760. Consistent with the FDA's statement, the Trintellix label states: "The effects observed on DSST may reflect improvement in depression. Comparative studies have not been conducted to demonstrate a therapeutic advantage [of vortioxetine] over other antidepressants on the DSST." (PTX-4475 at 24)

761. Defendants do not seek approval of their Proposed ANDA Products for treating cognitive impairment. Defendants' Proposed ANDA Products will not be indicated for treating cognitive impairment. (Peck Tr. 1340-41; Rothschild Tr. 1664-65; Rheinstein Tr. 2108-11)

762. Plaintiffs' own expert, Dr. Clayton, testified that she does not "specifically prescribe vortioxetine for cognitive impairment." (Clayton Tr. 1177; *see also* Rothschild Tr. 1667-68)

763. Plaintiffs' expert, Dr. McIntyre, admits that Conradi (PTX-373), which he cites, demonstrates that the majority of patients do not experience cognitive symptoms after a major depressive episode ("MDE"). (McIntyre Tr. 1271) Outside of MDEs, Conradi reports that cognitive problems were present in 44% patients with MDD, i.e., less than half of patients. (PTX-373 at 7, Table 4)

764. Prescribing vortioxetine for the purpose of treating MDD is a substantial non-infringing use. (Rothschild Tr. 1665-67)

765. To clinicians, treatment of any symptoms of cognitive impairment with vortioxetine would, in an insubstantial number of instances, be incidental to the purpose of the physician prescribing the drug, which is to treat the MDD, as indicated in the Defendants' proposed Prescribing Information. (Rothschild Tr. 1665-67, 1680-81)

766. To clinicians treating MDD in patients with vortioxetine whose MDD has not responded adequately to other antidepressant medications, amelioration of any cognitive impairment is incidental to the treatment of MDD. (Rothschild Tr. 1665-67, 1680-81)

767. The '910 patent itself recognizes that "[c]ognitive disorders may to some extent be secondary to depression in the sense that an improvement in the depressive state will also lead to an improvement of the cognitive impairment." (PTX-16 at 29, 7:39-42)

768. Defendants will not contributorily infringe Claim 6 of the '910 Patent. Instead, Defendants' Proposed ANDA Products are suitable for substantial non-infringing uses.

D. Invalidity

769. Defendants contend that Claim 6 of the '910 Patent is invalid due to inherent anticipation by WO '232 and due to obviousness, also based on WO '232. (Rothschild Tr. 1666-67, 1669, 1678-80)

770. WO '232 was considered by the USPTO during examination of the application that issued as the '910 Patent. (PTX-16 at 1)

771. Claim 6, incorporating Claims 1 and 3, and considering the relevant claim construction, requires:

- A method of treating cognitive impairment involving decline in speed of processing, executive function, attention, or verbal learning and memory

- In a patient diagnosed with major depressive disorder, the method comprising
- Administering a therapeutically effective amount of
- The hydrobromide salt of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine
- For the purpose of combating cognitive impairment involving decline in speed of processing, executive function, attention, or verbal learning and memory
- And the method alleviates a symptom or complication of the cognitive impairment or delays the progression of the cognitive impairment

(PTX-16 at 39:31-40:25; McIntyre Tr. 1277-78; SF ¶ 189-92; D.I. 358; D.I. 683)

772. The ’910 Patent specification states that “[c]ognitive impairment is among the classic features of depression, such as e.g. [MDD]. Cognitive disorders may to some extent be secondary to depression in the sense that an improvement in the depressive state will also lead to an improvement of the cognitive impairment.” (SF ¶ 194; PTX-16 at 7:38-41)

773. WO ’232 does not specifically disclose or identify VHBr. Instead, WO ’232 describes broad chemical genera encompassing millions of compounds, 24 preferred compounds, and a list of dozens of non-limiting exemplary acid addition salts that may or may not be combined with the disclosed compounds. (DTX 696 at 9 10; Rothschild Tr. 1727 28) Six of these “exemplary” salts are inorganic. (DTX 696 at 9 10)

774. Treatment of MDD in a population of patients necessarily includes treating cognitive impairment, because treating a patient’s MDD would also alleviate that patient’s symptoms, including cognitive impairment in at least some patients in that population. (Rothschild Tr. 1666-67, 1678-79; McIntyre Tr. 1256)

775. The ’910 Patent itself does not require that a specific therapeutically effective amount be identified, noting instead that “determining an appropriate dosage may be achieved using routine experimentation” and is “within the ordinary skills of a trained physician.” (PTX-

16 at 30 (9:35-47))

776. WO ’232 does not teach, disclose, or suggest that 1-[2-(2,4-DMPS)P]P can be used to treat cognitive impairment involving decline in speed of processing, executive function, attention, or verbal learning and memory; in fact, the words “cognition” and “cognitive” are nowhere found in WO ’232. (DTX-696; Rothschild Tr. 1728)

777. Treating a patient diagnosed with depression does not necessarily mean treating cognitive impairment or treating a patient with MDD for the purpose of combating cognitive impairment. (*See* Rothschild Tr. 1666)

778. While many patients with depression suffer from cognitive deficits, not all do. (Rothschild Tr. 1666; McIntyre Tr. 1229, 1268-69; PTX-373 at 1, 6; PTX-383 at 7; PTX-358 at 65; *see also* Mattingly Tr. 845-46)

779. WO ’232 does not disclose – either expressly or inherently – that 1-[2-(2,4-DMPS)P]P would actually “alleviate[] a symptom or complication of the cognitive impairment or delay[] the progression of the cognitive impairment.” (*See* DTX-696; Rothschild Tr. 1728) There is no mention of 1-[2-(2,4-DMPS)P]P’s effect on cognition or cognitive impairment. (*Id.*)

780. WO ’232 states that its compounds can be administered in a broad range of doses, but does not specify which dosages apply to any of the millions of compounds disclosed in the reference for the purpose of treating the disclosed disorders. (DTX-696 at 11:25-28; Rothschild Tr. 1684)

781. WO ’232 would not have provided the requisite motivation nor given a POSA a reasonable expectation of success in achieving improvement in cognitive impairment with vortioxetine. It contains no suggestion that a POSA could expect an MDD patient’s cognitive impairment to improve by administering any of the disclosed compounds. (DTX-696;

Rothschild Tr. 1728) It describes its disclosed compounds as SRIs. (DTX-696 at 3) There was no teaching in the art that any SRI could be used to treat cognitive impairment in patients with MDD. The teaching at the time of invention was that many SRIs impaired cognition. (Mattingly Tr. 840, 861, 864; PTX-4593 at 7)

782. WO '232 discloses only that the disclosed compounds are SRIs. (DTX-696 at 3) Defendants have not identified any other information about 1-[2-(2,4-DMPS)P]P that would have been available to a POSA prior to the priority date of the '910 Patent.

783. Defendants' experts have failed to persuasively explain why a POSA would have had a reasonable expectation of success of achieving the method of treatment claimed in the '910 Patent based on the disclosures of WO '232 alone or in combination with Oxman (DTX-363). Nor have they explained why a POSA would have been motivated to modify WO '232 to arrive at the invention of Claim 6 or to combine it with Oxman.

784. Oxman does not teach or suggest that all SSRIs have the same effect on cognition; nor does it connect procognitive effects to SRI activity. Rather, Oxman specifically teaches that different antidepressants have different effects on cognitive function, which are influenced by complex and unpredictable interactions between neurotransmitters, and neurotransmitter receptors, including 5-HT receptor subtypes. (DTX-363 at 4, 5)

E. Objective Indicia Of Non-Obviousness

1. Nexus

785. Trintellix embodies Claim 6 of the '910 Patent. (McIntyre Tr. 1256)

786. There is a nexus between the objective indicia of non-obviousness and Claim 6 of the '910 Patent. (McIntyre Tr. 1256)

787. Whether compared to the disclosure of WO '232 or other available antidepressant drugs, objective indicia support non-obviousness.

2. Long-felt but unmet need

788. There was a long-felt, unmet need for drugs that addressed cognitive impairment frequently experienced by MDD patients. (PTX-383 at 1-2; PTX-324 at 4, 7; McIntyre Tr. 1260-61, Mattingly Tr. 858)

789. Before June 2006, clinicians and the scientific literature recognized that many MDD patients continued to experience functional disability due to persistent cognitive deficits, even after receiving treatment for mood symptoms. (PTX-358 at 20-21, 26-27, 64, 83) Cognitive impairment can be debilitating and impair patients' ability to work and function. (PTX-383 at 1; PTX-358 at 88-89) This need persisted until approval of Trintellix.

790. Oxman, published in 1996, recognized this need: "Development of drugs with both antidepressant and clinically significant cognitive-enhancing effects would be a major advance for older patients and should be pursued." (DTX-363 at 5)

791. Common antidepressants available before Trintellix – including SSRIs, SNRIs, NRIs, and TCAs – were known to worsen cognitive function. (Mattingly Tr. 840, 861, 864; PTX-4593 at 7)

792. In a study examining outcomes for patients who had been hospitalized for an MDE, Jaeger found: "Nearly 60% of our sample remained significantly disabled or worse at the time of follow up, supporting other reports of high rates of persisting functional disability in this population." (PTX-383 at 7; PTX-359 at 31-35; McIntyre Tr. 1261) Moreover, "measures of attention continue to show deficits even with full remission and after correction for residual mood symptoms." (PTX-383 at 2; *see also* PTX-358 at 78, 81, 88-89)

793. The '910 Patent observes "studies have shown persistent cognitive impairment upon recovery from depression." (PTX-16 at 29)

794. This need was not met by other medications, such as sertraline, and duloxetine.

As reflected in Baune, duloxetine (an SNRI) and sertraline (an SSRI) showed a modest benefit relative to placebo, but the benefits were not statistically significant and they were of questionable clinical significance, given that the benefits were smaller than the average magnitude of cognitive deficits in MDD. (PTX-4593 at 7, 9; *see also* PTX-359 at 38)

795. While Baune was published in 2018, it was a meta-analysis of 12 studies, a third of which were published before the '910 Patent's priority date. (PTX-4593 at 6)

796. While duloxetine has shown improvement (which was not statistically significant) on one domain, vortioxetine is the only antidepressant shown to be effective for treating cognitive impairment across all four domains of cognition. (PTX-1193 at 5-8)

3. Unexpected results

797. Trintellix's ability to alleviate cognition in patients with MDD was unexpected. (McIntyre Tr. 1259)

798. Historically, antidepressants have not demonstrated an ability to alleviate cognitive impairment in adults with depression; some further impaired cognition. (McIntyre Tr. 1230-31; PTX-373 at 4; PTX-4593 at 7; PTX-134 at 2, 7)

799. A POSA would not have expected compounds with SRI effects to alleviate cognitive impairment. (McIntyre Tr. 1230-31)

800. FOCUS and CONNECT demonstrate that vortioxetine has a clinically relevant effect on cognitive impairment in MDD. (PTX-85 at 17)

801. FOCUS and CONNECT are placebo-controlled studies. (McIntyre Tr. 1234-35; PTX-392 at 4; PTX-388 at 4)

802. With the DSST data (measuring processing speed), the FDA required the statement that "[t]he effects observed on DSST may reflect improvement in depression." (PTX-4475 at 24; McIntyre Tr. 1285-86; Reus Tr. 1976, 1978; Rheinstein Tr. 2108-11; PTX-85)

803. The FDA specifically did not allow claims on other aspects of cognition, such as executive function, memory, attention, and concentration. (Reus Tr. 1976, 1978)

804. Unlike vortioxetine, duloxetine, which was used as an active-reference in the CONNECT and Elderly Studies, did not separate from placebo on the DSST. (PTX-388 at 4; PTX-359 at 44-45, 48; *see* PTX-358 at 67, 69; PTX-359 at 26, 29-30, 71)

4. Skepticism

805. After Plaintiffs filed an sNDA seeking to add the FOCUS and CONNECT studies to the Trintellix Prescribing Information, the FDA convened the Psychopharmacologic Drugs Advisory Committee ("PDAC") – comprised of experts in the field, the majority of whom were psychiatrists and, therefore, POSAs – to review the request. (McIntyre Tr. 1264; PTX-82 at 1; PTX-358) Although the PDAC recommended that the studies be included in the label, the FDA initially rejected the sNDA. (PTX-82 at 1; Peck Tr. 1309-10, McIntyre Tr. 1264) After a higher level of review following Plaintiffs' appeal (PTX-85 at 17; Peck Tr. 1310, McIntyre Tr. 1264), the FDA reversed its position, finding "sufficient support for the clinical meaningfulness of the changes in DSST, as reflecting an improvement in an important aspect of cognitive dysfunction in depression." (PTX-85 at 17; *see also* Peck Tr. 1310; McIntyre Tr. 1264)

806. The FDA's role as a public health agency is to be skeptical. (Rothschild Tr. 1695-96; Reus Tr. 1976, 1978; Rheinstein Tr. 2108-11; PTX-85)

807. Although the FDA treated Plaintiffs' request for inclusion of cognition data in the Trintellix Prescribing Information with a high degree of skepticism and was reluctant to approve the inclusion of such novel data, the FDA's responsibility is to be skeptical of all claims of efficacy. Its approval of inclusion of the FOCUS and CONNECT studies as part of the Trintellix Prescribing Information is not the type of skepticism that constitutes strong objective evidence of non-obviousness. (*See* Rothschild Tr. 1695-96; Reus Tr. 1976, 1978; Rheinstein Tr. 2108-11)

808. Plaintiffs have not identified skepticism from industry participants or skilled artisans, beyond the FDA.

5. Praise and recognition

809. The scientific literature (e.g., Baune) praised vortioxetine's ability to alleviate cognitive impairment in MDD patients. (McIntyre Tr. 1239-40, 1265; PTX-4593)

810. As a meta-analysis, Baune analyzed numerous studies investigating the cognitive effects of various drugs on cognition. (McIntyre Tr. 1239) Baune was published in a peer-reviewed medical journal. (McIntyre Tr. 1291)

811. Dr. McIntyre submitted written testimony to the PDAC which stated, "vortioxetine . . . has provided a tangible improvement in patients' cognitive symptoms . . . As a consequence, we are seeing a significant improvement in patient-reported quality of life, as well as patient-reported and objectively measured function." (PTX-403 at 1; *see also* McIntyre Tr. 1266)

812. There is direct evidence of doctors (POSAs) praising Trintellix's cognitive benefits. (*See* PTX-359 at 140-43 (Dr. James North testifying that vortioxetine made "a life-changing difference for [] patients."); PTX-359 at 127–30 (Dr. Mattingly testifying that vortioxetine improved cognitive impairment in three of his patients); PTX-402 at 1 (Dr. George Grossberg's written testimony describing Trintellix as "a real plus in this vulnerable population" that would "enable them to resume a fuller, more functional life"); *see also* PTX-359 at 60)

813. Patients have also praised Trintellix's effects on cognitive impairment. (PTX-359 at 135 (David Bartley testifying before the PDAC and praising Trintellix for providing a "cognitive juice, a bump in my ability to process information" and improving his ability to perform his job); PTX-4572 (Germaine Cabe written testimony that Trintellix's effects were "like a fog lifting from my brain, or the windshield wipers cleaning a rainy windshield"); PTX-

4571 at 1 (William Downs written testimony saying that on Trintellix, "[m]y mind is sharper, and I am less forgetful when it comes to dealing with the daily routines of life."); McIntyre Tr. 1267, 1288)

814. Actions by the FDA are not strong evidence of industry praise. (Rothschild Tr. 1695-96; Reus Tr. 1976, 1978)

815. There are millions of patients on antidepressants and tens of thousands of prescribers; testimonials from a handful of individual doctors and patients regarding their impression of the cognitive effects of Trintellix® are not evidence of industry praise of the subject matter of Claim 6 of the '910 patent. (Rothschild Tr. 1696-97; McIntyre Tr. 1288)

816. Plaintiffs have not identified praise or recognition from competitors.

LEGAL STANDARDS

I. Infringement

A. Burden Of Proof

A patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp*., 859 F.2d 878, 889 (Fed. Cir. 1988). This same burden of proof applies to both direct and indirect infringement. *See Manville Sales Corp. v. Paramount Sys., Inc*., 917 F.2d 544, 553 (Fed. Cir. 1990) (induced infringement); *SmithKline*, 859 F.2d at 889 (direct infringement).

B. Literal Infringement And Doctrine of Equivalents

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 27l(a). A patent owner may prove infringement under two theories: literal infringement or the doctrine of equivalents. Literal infringement occurs where "every limitation set forth in a claim" is "found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal JG Co.,* 54 F.3d

1570, 1575 (Fed. Cir. 1995).

Courts employ a two-step analysis in making an infringement determination. *See Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly-construed claims to the accused infringing product. *See id.*

If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.,* 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Id.* at 1552 n.9.

Infringement under the doctrine of equivalents occurs where the accused product embodies every element of a claim either literally or by an equivalent. *See Southwall,* 54 F.3d at 1575. This doctrine "allows the patentee to claim insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*., 535 U.S. 722, 733 (2002).

C. Indirect Infringement

In addition to direct infringement, a patentee may show that an accused infringer is liable for indirect infringement. One form of indirect infringement is induced infringement, which requires a showing of direct infringement as well as that "the alleged inducer knew of the patent, knowingly induced the infringing acts, and possessed a specific intent to encourage another's infringement of the patent." *Vita-Mix Corp. v. Basic Holding, Inc*., 581 F.3d 1317, 1328 (Fed. Cir. 2009). "[I]nduced infringement under § 271(b) requires knowledge that the induced acts constitute patent infringement." *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011).

Another form of indirect infringement is contributory infringement. To prove

contributory infringement, the patent owner must demonstrate: (1) an offer to sell, a sale, or an import; (2) of a component or material for use in a patented process constituting a material part of the invention; (3) knowledge by the defendant that the component is especially made or especially adapted for use in an infringement of such patents; and (4) the component is not a staple or article suitable for substantial non-infringing use. *See Fujitsu Ltd. v. Netgear Inc*., 620 F.3d 1321, 1326 (Fed. Cir. 2010) (citing 35 U.S.C. § 271(c)).

D. ANDA Infringement

In the specific context of a patent infringement action brought pursuant to 35 U.S.C. § 271(e)(2)(A) – the statutory provision under which Plaintiffs have sued defendants in the instant action – the infringement inquiry is "whether, if a particular drug were put on the market, it would infringe the relevant patent." *Acorda Therapeutics Inc. v. Mylan Pharm. Inc.,* 817 F.3d 755, 760 (Fed. Cir. 2016).

II. Invalidity

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 Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). 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. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original).

A defendant's burden to prove invalidity based on prior art (e.g., anticipation or obviousness) 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. Anticipation

A claim is anticipated under 35 U.S.C. § 102(a)(1) if "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention." For a patent claim to be invalid due to anticipation, each and every limitation must be found, either expressly or inherently, in a single prior art reference. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (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).

Mere disclosure of each and every limitation of a claim is not enough for anticipation. "An anticipating reference must enable that which it is asserted to anticipate." *Abbott Labs. v. Sandoz, Inc*., 544 F.3d 1341, 1345 (Fed. Cir. 2008). Furthermore, the anticipating single prior art reference must also disclose the limitations as arranged in the claim. *See Net Money IN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.").

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 non-obviousness. *See Graham v. John Deere Co. of Kansas City*, 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) (internal citation and quotation marks omitted); *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 in a determination that an invention would have been obvious, the Court is required to consider objective (or "secondary") considerations 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). Objective 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).

D. Written Description

To comply with the written description requirement, a patent's specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010) (internal alterations and quotation marks omitted). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. . . . [T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* Whether a specification satisfies the written description requirement is a question of fact. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc*., 744 F.3d 725, 729 (Fed. Cir. 2014).

"[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Id.* at 1352. However, "a description that merely renders the invention obvious does not satisfy the requirement." *Id.*

DISCUSSION

I. Defendants Have Failed To Prove That The Asserted Claims Of The Compound Patents Are Invalid

Defendants seeks to invalidate the asserted claims of the Compound Patents as obvious over ES '127 and Planas in view of Jílek, Kopicová, Pinder, and WO '678 and the knowledge of a POSA. (D.I. 1011 at 10) The Court concludes, for the reasons below, that Defendants have failed to prove obviousness by the required clear and convincing evidence.

A. Lead Compound Analysis

In determining the obviousness of a new chemical compound, the Federal Circuit applies

a "lead compound" analysis. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc*., 678 F.3d 1280, 1291 (Fed. Cir. 2012). In undertaking a lead compound analysis, to determine "whether a new chemical compound would have been prima facie obvious over particular prior art compounds," a court will ordinarily engage in a two-step inquiry, assessing: (1) "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development," and (2) "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." *Id.* at 1291-92.

A lead compound is a compound in the prior art that would be "most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). The analysis "focuses on those proposed lead compounds that the alleged infringer has attempted to prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art." *Otsuka*, 678 F.3d at 1292. A lead compound is a compound that is "a natural choice for further development efforts." *Altana Pharma AG v. Teva Pharm. USA, Inc*., 566 F.3d 999, 1008 (Fed. Cir. 2009). In any particular case, there may be more than one prior art compound that a chemist of ordinary skill would have considered for further development. *See id*.

In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties, such as activity, potency, toxicity, and other relevant characteristics. *See Otsuka*, 678 F.3d at 1292. "Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Id*.

Once a lead compound has been identified, a party seeking to invalidate a patent must then show the reason or motivation for all necessary modifications of the lead compound, which "may come from any number of sources and need not necessarily be explicit in the prior art." *Id.* The pertinent properties of the lead are relevant, for "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds." *Id.* at 1292-93 (internal quotation marks omitted). "[I]t is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship . . . to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (internal quotation marks omitted).

Plaintiffs first argue that Defendants' obviousness contention must be rejected because Defendants failed to conduct the required lead compound analysis. (D.I. 1059 at 9) Instead of beginning with a lead compound, Defendants' expert, Dr. Lepore, began his obviousness analysis with a "lead motif." Dr. Lepore discerns in six pieces of prior art – ES '127, Planas, Pinder, Kopicová, Jílek, and WO '678 – a common structure that, he asserts, would be the starting point for a POSA at the pertinent date seeking to develop an improved antidepressant. (*See, e.g.*, D.I. 1011 at 5-8)[17]

More particularly, Defendants contend a POSA in the early 2000s would have looked to

[17] Defendants' burden to prove invalidity based on prior art is "especially difficult when th[at] prior art was before the PTO examiner during prosecution." *Hewlett-Packard*, 909 F.2d at 1467. Several of the six pieces of prior art on which Defendants' predicate their obviousness theory were before the examiner during prosecution of one or both Compound Patents. (*See* FF ¶ 164 (citing evidence U.S. Patent No. 4,859,675, related to ES '127, was before examiner during prosecution of '279 Patent; *id.* ¶ 166 (Planas was identified on face of '279 (and '575) Patents as having been considered during prosecution; *id.* ¶ 174 (WO '678 is listed on face of '884, '279, and '575 Patents); *id.* ¶ 497 (GB '711 was identified on face of '884 and '575 Patents))

the development path a team at Wyeth took in the early 1990s to arrive at the multi-modal antidepressant Effexor (venlafaxine). (D.I. 1011 at 3) According to Defendants, the Wyeth team simplified the structure of ciramadol, an older compound known to have central nervous system activity, resulting in a motif of derivative compounds structurally similar to a known antidepressant, gamfexine. (*Id.*) Defendants contend this research strategy, dubbed the "venlafaxine path," would have been well known to a POSA. (*Id.* at 4) Defendants assert that a POSA in 2002, examining the prior art, would have found that three different research groups working independently to identify new antidepressants had all arrived at a common motif or scaffold, as depicted below:

Biarylether Piperazine Motif

(*Id.*) It is this biarylether piperazine Dr. Lepore uses as his "lead motif." (*Id.*)

The Court's rejection of Defendants' obviousness defense is not based on its rejection of Dr. Lepore's concept of a "lead motif." A "lead motif" analysis seems potentially compatible with the required lead compound analysis. Arguably, it may involve an analytically prior (and often unnecessary) part of a lead compound analysis. That is, a POSA's recognition of a lead motif ranging across multiple prior art references may inform her identification of a lead compound. The law requires the lead compound as the starting point, but it does not seem *per se* improper to identify a lead motif as part of the explanation for how a POSA would determine the lead compound. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) ("New compounds may be created from theoretical considerations rather than from attempts to

improve on prior art compounds.").

While the Court does not reject Defendants' analysis at the first step, the Court further – and dispositively – finds a lack of clear and convincing evidence for the numerous modifications a POSA would have been required to make to Dr. Lepore's lead motif or lead compound.

One reason Defendants have failed to persuade the Court is that Dr. Lepore did not adequately address the antidepressant landscape in 2001. (FF ¶ 157)[18] Beginning in the 1980s, the pharmaceutical industry focused on developing highly-selective molecules targeting SERT inhibition. (FF ¶ 158) A POSA at that time understood that greater selectivity translated into greater safety and tolerability. (FF ¶ 159; *see also* Reider Tr. 161 ("[W]e began to worship at the God of selectivity.")) By 2001, SSRIs had become the first choice for treatment of depression because they were understood to be effective, well-tolerated, and to have a vastly superior side effect profile compared to the older TCAs. (FF ¶ 160)

Defendants have not presented clear and convincing evidence for why a POSA in 2001 would have preferred the ten-year-old venlafaxine path over the then-current state of the art at the time of the invention: SSRIs and SNRIs with high-selectivity and a superior side-effect profile. Despite Wyeth's success with venlafaxine ten years earlier in the early 1990s, a POSA in 2001 would not have considered compounds with pharmacologic activity resembling TCAs or TeCAs as the most promising starting point for developing an improved antidepressant. (FF ¶ 160) Dr. Lepore does not identify any improvement in activity, potency, or toxicity reasonably achievable from his proposed starting point.

Defendants point to Plaintiffs' expert, Dr. Reider, who was working on developing of a

[18] Throughout the Discussion section of this Opinion, the Court highlights certain of its Findings of Fact. All of the Findings of Fact set out earlier in this Opinion remain the findings of fact of the Court and all of them support the Court's conclusions, as explained in the Discussion.

non-SSRI antidepressant around the same time. (Reider Tr. 179-80) Dr. Reider's work, however, was done closer in time to the venlafaxine path – in the mid-1990s – and his work led to a failed antidepressant. (*Id.*) In the Court's view, the evidence establishes that a POSA in early 2000s would have been motivated to pursue the state-of-the-art SSRIs and SNRIs at the time, rather than pursue the venlafaxine path based on older technology. (FF ¶ 160) Dr. Reider's failed non-SSRI antidepressant activity would only have further motivated a POSA in the SSRI direction.

Even if, somehow – and for reasons Defendants failed to prove – a POSA would have pursued the venlafaxine path, Defendants do not present clear and convincing evidence that a POSA would have selected the specific compounds from the six references which Defendants contend would form the lead motif. Defendants have not proven by clear and convincing evidence that prior art compounds exhibit the pertinent properties "such as activity and potency, adverse effects such as toxicity, and other relevant characteristics in evidence." *Otsuka*, 678 F.3d at 1292. Accordingly, a POSA at the time of the invention would not have been motivated to select the specific prior art compounds that contribute to Dr. Lepore's lead motif. *See generally id.* ("Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and [claimed compound] does not inform the lead compound selection.")

ES '127 does not disclose any biological activity for any disclosed compounds, including the compounds of Examples 6 and 7 chosen by Dr. Lepore. (FF ¶¶ 162-63) Planas describes sifaprazine as structurally related to the open ring TeCA, mianserin, and pharmacologically similar to TCAs. (FF ¶ 165) Consequently, neither ES '127 nor Planas "disclose the antidepressant utility of the biarylether piperazine lead motif." (FF ¶ 168)

Kopicová describes the preparation of 28 compounds which are either phenylthiobenzyl-piperazines or benzylbenzyl-piperazine, but are not the biarylether piperazines of the lead motif. (FF ¶ 170) Defendants focus on Compound V, which displays protracted slight depressions of blood pressure (*id.*); Dr. Reider explained, however, the "most you can take out of that is the compound affects blood pressure." (Reider Tr. 2050)

Jílek discloses 29 compounds. (FF ¶¶ 171-72) Compound VI was identified as a "promising potential antidepressant" while Compounds XI and XXV were merely described as "interesting compounds" (DTX-257 at 6), yet Dr. Lepore, for unconvincing reasons, somehow selects Compound XI and not Compound VI. (D.I. 1011 at 7) Dr. Lepore does not have persuasive reasons for why a POSA would not have selected Compound XXV or any other of Jilek's compounds. Neither compound VI nor XXV contains the piperazine moiety found in 1-[2-(2,4-DMPS)P]P of the asserted claims. (FF ¶ 173) The open ring analogs of Jilek, including compound V selected by Dr. Lepore, "did not show any psychotropic activity." (DTX-257 at 1)

WO '678 describes several broad genera of preferred embodiments of formula I, including 69 "most preferred embodiments." (FF ¶ 175) WO '678's disclosure of formula III is limited to its synthesis or the synthesis of formula I compounds. (FF ¶ 176) WO '678 does not disclose biological activity, pharmacological effects, or clinical efficacy for compounds of formula III or any other intermediate. (FF ¶¶ 176-77) WO '678 does not disclose or suggest that the intermediate of formula III has any utility apart from preparing compounds of formula I. (*Id.*)

Without disclosures of relevant biological, pharmacological, or clinical properties of the compounds that compose its lead motif, a POSA would not have selected these compounds as the basis of its antidepressant lead motif with any reasonable expectation of success. (FF ¶ 178) The dearth of relevant biological data on Dr. Lepore's lead motif establishes that a POSA would

not have selected these compounds as the basis for her lead motif.

Even if all of this were not the case – that is, even if Defendants had proven (though they did not) that a POSA would have found it obvious to select and start with their lead motif, and even had they proven (though they did not) a POSA would have had a motivation and reasonable expectation of success had she pursued the development path proposed by Dr. Lepore – Defendants' obviousness challenge would still fail for the additional reason that the many necessary modifications to move from Dr. Lepore's lead motif to arrive at vortioxetine would not have been obvious to a POSA. (FF ¶ 179)

Far more modifications are necessary to move from the lead motif to vortioxetine than Defendants suggest. Defendants reason that a POSA would modify the lead motif to improve resistance to metabolic degradation, while preserving antidepressant activity. (D.I. 1011 at 15) Defendants contend a POSA would know of two strategies to accomplish this metabolic stability: (1) protect the distal phenyl group of the lead motif from oxidation; and (2) select a thioether group (X = S) as the bridge group of the final optimized compound. (*Id.*) Following such strategies yields four compounds, only one of which is vortioxetine.[19]

However, as Dr. Reider far more persuasively explained, many more decisions are required to move from Dr. Lepore's lead motif (and to develop the motivation to modify it) to the resulting four compounds. (Reider Tr. 2050-53) Dr. Reider visually depicted these many decisions in the diagram reproduced above as Finding of Fact ¶ 180, which the Court finds highly persuasive. Dr. Reider additionally described, again with great credibility, that in 2001 a

[19] Defendants claim ES '127 and WO '678 teach that a methyl or chloro group can be added to the ortho and para positions of the distal phenyl group of the lead motif to serve as blocking groups to prevent aryl oxidation. (D.I. 1011 at 16) Defendants do not cite any prior art or documentary evidence that the distal phenyl groups of the lead motif are susceptible to oxidation. (D.I. 1053 ¶ 28)

POSA would not have been motivated to make all of these modifications; nor would a POSA would have had a reasonable expectation of success in doing so. (FF ¶ 181) For example, even assuming a POSA would have been motivated to add methyl groups to the distal phenyl group, a POSA would have considered making substitutions (1) at locations other than in the para position and (2) using substituents other than a single methyl group (e.g., halogens, hydroxy, aryl, and acyl groups, or alkyl, alkenyl, and alkynyl groups of various lengths). (FF ¶¶ 186-87) Likewise, Defendants do not demonstrate by clear and convincing evidence that a POSA would have been motivated to replace the methylene bridge of mianserin, the compounds of ES '127, and Planas with a thioether, instead of, for example, the more obvious choice of an ether. (FF ¶¶ 182-85)

There are other problems with Defendants' obviousness theory, but the Court will limit its discussion to just one more. Yardley, a publication cited by Defendants which describes the development of venlafaxine, acknowledges that "minor structural alterations can frequently induce profound changes in the profile of central nervous system drugs." (DTX-270 at 1) A POSA would not ignore the possible effects of structural differences on biological activity. *See Takeda Pharm. Co. Ltd. v. Torrent Pharm. Ltd.*, 2021 WL 560763, at *3 (Fed. Cir. Feb. 16, 2021); *Mylan Pharm., Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366, 1376 (Fed. Cir. 2019) ("The Board also was entitled to reject bioisosterism as a basis for a motivation to modify compound 3l.").

For at least all of these reasons, Defendants failed to prove, by the required clear and convincing evidence, that the Asserted Claims of the Compound Patents are invalid due to obviousness.

B. Objective Indicia of Nonobviousness

Objective evidence "can be the most probative evidence of non-obviousness in the

record, and enabl[e] the court to avert the trap of hindsight." *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013). Such evidence "must be considered before reaching an obviousness conclusion." *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1355 (Fed. Cir. 2013). In connection with the Compound Patents, the Court has considered the objective indicia of nonobviousness and finds that they provide further support for its conclusion that Defendants have failed to meet their burden to invalidate the asserted claims.[20]

1. Long-Felt But Unmet Need

"Evidence of a long-felt but unresolved need can weigh in favor of . . . non-obviousness of an invention because it is reasonable to infer [that] the need would not have persisted had the solution been obvious." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016). Plaintiffs have proven, by a preponderance of evidence, that at the time of the invention of the Compound Patents, there was a long-felt but unmet need for an antidepressant that could offer a better side effect profile without sacrificing efficacy. (FF ¶¶ 191-94)

Vortioxetine's efficacy and tolerability over other antidepressants has been repeatedly shown in clinical and head-to-head studies. (FF ¶ 193) As measured in the largest meta-analysis of antidepressant studies, Cipriani, vortioxetine is among the antidepressants with the highest efficacy and tolerability (i.e., least adverse side effects). (*Id.*)

Defendants critique Cipriani as unreliable because its head-to-head studies had large confidence intervals and the evidence has been described as low quality or very low quality. (D.I. 1053 ¶ 72) Defendants contend that the placebo-controlled studies of Cipriani place

[20] Dr. Lepore opined that the closest prior art was the compounds of Formula III in WO '678 and Examples 6 and 7 of ES '127. (D.I. 1052 at 8-9) The Court has found, however, that the closest prior art at the time of the invention was the dominant selectivity antidepressants such as SSRIs and SNRIs. (FF ¶ 160) Thus, the Court's objective indicia analysis compares vortioxetine to SSRIs and SNRIs.

vortioxetine in the middle of all antidepressants for efficacy and acceptability, and point to peer-reviewed publications which criticize Cipriani for being too optimistic and not objective. (*Id.* at ¶¶ 73-76) However, Cipriani itself states that it focused on head-to-head studies to make its results "as relevant and robust as possible." (PTX-4594 at 7)

2. Failure of Others

The "failure of others to find a solution to the problem which the patent[s] . . . purport[] to solve" may be probative of non-obviousness because it suggests "the presence of a significant defect [in the prior art], while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *Symbol Techs., Inc. v. Opticon, Inc*., 935 F.2d 1569, 1578-79 (Fed. Cir. 1991) (internal quotation marks omitted; brackets in original).

Plaintiffs purport to point to evidence that other sophisticated companies and researchers tried but failed to develop an antidepressant with reduced adverse side effects. (D.I. 1059 at 22) But the record is devoid of such evidence. Plaintiffs have not proven this objective factor.

3. Unexpected results

Evidence that a "claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" may suggest that an invention is non-obvious. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "[E]vidence of unexpected results may be [considered] . . . even if that evidence was obtained after the patent's filing or issue date." *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011); *see also Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

Vortioxetine is a multi-modal antidepressant demonstrating activity as a serotonin transporter inhibitor, 5-HT1D, 5-HT3, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist. (FF ¶ 190) Its clinical effects result from the combination

of a direct effect on receptor activity and SERT inhibition. (FF ¶ 195) The fact that vortioxetine exhibited multimodal activity that produced a safe, well-tolerated, and effective drug was a surprising and unexpected result, as "there is really no way to design something that has this multitude of activities." (Reider Tr. 159; *see also* FF ¶ 196)

Vortioxetine's multi-modal modes of action paired with its side effect profile would have been surprising to a POSA, when comparing vortioxetine to the prevalent SSRI antidepressants at the time of invention. (FF ¶¶ 197-98) This is an objective indicator that the Asserted Claims of the Compound Patents were not obvious.

4. Industry Praise

"Evidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious. Industry participants, especially competitors, are not likely to praise an obvious advance over the known art." *Apple*, 839 F.3d at 1053.

Plaintiffs' evidence of purported industry praise consists of literature investigating vortioxetine's efficacy, adverse effects, and procognitive effects; expert testimony; customer testimonials; and the FDA approval of information for the Trintellix Prescribing Information, including the low incidence of TESD, cognitive benefits, weight neutrality, and absence of discontinuation syndrome. (*See* D.I. 1058 ¶ 79) This is not persuasive evidence of industry praise. The literature consists of scientific investigation of antidepressant activity, not lauding of any particular compound. (*See* PTX-4594; PTX-4593) Literature in the record also criticizes vortioxetine. (*See* DTX-581; DTX-1218) FDA approval of prescribing information, unlike praise from competitors, does not equate to industry praise. (*See* Rothschild Tr. 1695-96; Reus Tr. 1976, 1978; Rheinstein Tr. 2108-11; *see also generally Power-One, Inc. v. Artesyn Techs., Inc*., 599 F.3d 1343, 1352 (Fed. Cir. 2010) (noting that industry praise, especially from

competitor, tends to indicate that invention would not have been obvious))

5. Commercial Acquiescence

Commercial acquiescence, especially when an entire industry takes licenses to patented technology, may be evidence that the technology of the licensed patent was not obvious. *See Bosch Auto. Serv. Sols., LLC v. Matal*, 878 F.3d 1027, 1038 (Fed. Cir. 2017), *amended* (Mar. 15, 2018) ("[L]icensing, without more, is generally not a strong indication of nonobviousness if it cannot also be shown that the licensees did so out of respect for the patent rather than to avoid litigation expense"); *see also Iron Grip Barbell Co. v. USA Sports, Inc*., 392 F.3d 1317, 1324 (Fed. Cir. 2004) ("Our cases specifically require affirmative evidence of nexus where the evidence of commercial success presented is a license, because it is often cheaper to take licenses than to defend infringement suits.") (internal quotation omitted). Here, there are no licenses in the record; moreover, there is no evidence that generic manufacturers submitted Paragraph III certifications to the FDA for the '884 and '279 Patents out of respect for the patents rather than a desire to avoid litigation expense. Plaintiffs have not established this factor.

C. Conclusion

In sum, Defendants have not proven that the Compound Patents are invalid due to obviousness, for at least two reasons. First, Defendants failed to meet their burden to prove that the lead motif would have been an obvious lead compound to develop as an antidepressant in 2001 with a reasonable expectation of success. Second, even if the lead motif were a lead compound, Defendants failed to meet their burden to show a POSA would have been motivated to modify the lead motif with a methyl or chloro group in the ortho and para positions of the distal phenyl group of the lead motif, and a thioester in the methylene "X" position, with any reasonable likelihood of success. Plaintiffs' evidence of objective indicia of nonobviousness, though not nearly as strong as Plaintiffs seem to believe, further supports the Court's conclusion.

II. Plaintiffs Have Failed To Prove That Any Defendant Infringes The Asserted Claims Of The Crystalline Form Patents

A. Several Overarching Deficiencies Greatly Undermine The Persuasive Force Of Plaintiffs' Contentions

As explained throughout the Findings of Fact, and further below, there are specific failings in Plaintiffs' efforts to prove infringement of the Crystalline Form Patents against each Defendant.[21] There are several other deficiencies that apply to Plaintiffs' infringement case against multiple Defendants. While none of these failings is dispositive, individually and collectively they do much to undermine the persuasive force of Plaintiffs' efforts.

First, Plaintiffs' theory of infringement against Alembic and Zydus depends on the presence of, at most, just a single one of the multiple characteristic peaks the Crystalline Form Patents disclose as being required to establish the presence of the claimed crystalline form in these Defendants' internal documents. (D.I. 1057 at 21-22, 33, 59) Plaintiffs insist that while, in some XRPD tests in the record, only a single characteristic peak is detected, a POSA would conclude – based on all the evidence – that all of the required characteristic peaks are actually present. (*Id.* at 58-61) On this point, the Court was not persuaded by the testimony of Dr. Myerson, who cited no literature to support his opinion that use of a single peak is a scientifically valid method of identifying a particular crystalline form. (FF ¶ 210) Instead, Dr. Kahr persuasively explained that the absence of even one (and all the more so the absence of two or three) peaks characteristic of a particular crystalline form is strong evidence that that form is not present. (FF ¶ 211)

A single peak may provide a sufficient basis on which to ground a finding that

[21] The Crystalline Form Patents are asserted against all defendants other than Sandoz. Hence, in discussing the Crystalline Form Patents, "Defendants" refers to Alembic, Lupin, Macleods, Sigmapharm, and Zydus, collectively.

crystallization is present (as opposed to having an amorphous compound). *See Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc*., 477 F. Supp. 3d 306, 348 (D. Del. 2020). A single peak may also be indicative of the presence of a particular crystalline form so long as the weight of the XRPD images does not rule out the likely presence of other characteristic peaks of that form. Where, as here, however, the overwhelming abundance of careful XRPD images developed expressly for purposes of determining infringement detects no more than one of the multiple characteristic peaks – effectively ruling out the remaining peaks characteristic of the particular form – and particularly where the claims identify the particular crystalline form by the presence of multiple characteristic peaks, evidence of the presence of just a single (even discriminatory) peak is not sufficient to amount to proof by a preponderance of the evidence. *See generally Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562 (Fed. Cir. 1997) (affirming district court finding that "diagnostic" peak in IR spectrum was "insufficient to differentiate" between two forms, and describing analysis based on single peak as "meaningless"); *Cephalon, Inc. v. Sun Pharms., Ltd*., 2012 WL 12904999 (D.N.J. Dec. 20, 2012) (rejecting infringement premised on single XRPD "diagnostic" peak that could not differentiate between multiple polymorphic forms); *Roche Palo Alto LLC v. Ranbaxy Lab'ys Ltd*., 2009 WL 3261252, at * 23 (D.N.J. Sept. 30, 2009) (rejecting sufficiency of single peak as basis to differentiate between the crystalline form and other possible forms in XRD analysis).

Second, Plaintiffs' efforts to persuade the Court that Defendants' ANDA Products that are manufactured using amorphous API will, in time, convert to crystalline forms, were generally unavailing. Frequently, Plaintiffs' evidence involved testing that occurred under conditions – in terms of variables such as time, temperature, and pressure – that are unrealistic and/or that are well outside of what will be permitted with proper handling of the ANDA Products. (FF ¶¶ 219-

23)

Third, Plaintiffs' infringement case against Defendants Alembic, Macleods, and Zydus depends to a great extent on internal testing Defendants did themselves. (D.I. 1057 at 21-35) However, without exception, this testing was performed on less sensitive XRPD instruments than the testing performed by the experts for this case, and in no instance were Defendants' pre-suit tests done for the purpose of determining infringement. Plaintiffs identify no internal documents that compare any of the Asserted Claims to the proposed ANDA Products. (FF ¶ 212) For many of the internal tests, much is also unknown, including who performed the tests, their skills and experience, and the conditions under which the tests were conducted. (FF ¶¶ 213-14)

Fourth, with respect to Lupin and Zydus, part of Plaintiffs' infringement case is based on Defendant internal testing of development batches. (D.I. 1057 at 33-35, 44-45) There was no persuasive evidence that development batches are representative of the ANDA Product Lupin or Zydus seeks approval to sell. (FF ¶¶ 224-26)

Finally, Plaintiffs' handling of the samples of Defendants' ANDA Products further undermines the Court's confidence that the relatively paltry evidence of infringement they did produce adds up to proof by a preponderance of the evidence. In several instances, Defendants timely provided unexpired samples of their proposed products and Plaintiffs then waited to ask their experts to test those samples until after they expired. (FF ¶¶ 231-33, 235-36, 241-42) Plaintiffs candidly admit that the record is devoid of any explanation for this approach. (FF ¶ 237) That candor, while welcome, does not make their weak evidence any stronger. The validity of Plaintiffs' testing evidence is further called into question by the manner in which Plaintiffs and their experts handled and transported the samples.[22] (FF ¶¶ 227-44)

[22] Defendants contend that a mixture of their metastable crystalline or amorphous drug substance

B. Alembic

Plaintiffs allege that Alembic's ANDA Product contains the beta form of vortioxetine hydrobromide, which, according to the asserted claims, must have XRPD peaks at 6.89, 9.73, 13.78 and 14.62 ± 0.10º 2θ and/or must be characterized by the XRPD pattern of FIG. 3. (D.I. 1057 at 21) It is undisputed that Alembic's ANDA Product has "Form C" vortioxetine as its API – which is not claimed by either of the Crystalline Form Patents (and is, in fact, claimed by an Alembic patent). (FF ¶¶ 245-48) Plaintiffs have not proven by a preponderance of evidence that Alembic's Form C will convert to crystalline beta form. Plaintiffs performed no experiments to determine whether Form C converts to the beta form upon manufacturing, and their expert, Dr. Myerson, admits that at least some Form C remains in the ANDA Product. (FF ¶¶ 254-56) Alembic conducted 24-month and 36-month stability studies, based on which it reported to the FDA that its product does not convert to beta form. (FF ¶¶ 253-55)

Dr. Myerson agreed that if Alembic's ANDA Product was undergoing conversion to the beta form, he would expect to see the peaks at 6.89° 2θ, 9.73° 2θ, 13.78° 2θ, and 14.62° 2θ to become more intense or grow in size over time. (Myerson Tr. 748-49) There is not, however, any such evidence. (*See* FF ¶ 260)

In pre-suit internal testing, Alembic selected a single XRPD peak at approximately 6.8° 2θ to determine the possible presence of the beta form of vortioxetine HBr in Alembic's ANDA Product. (FF ¶¶ 262-64) In that process, Alembic conducted XRPD testing on exhibit batches of its ANDA Product (5 mg, 10 mg, 15 mg, and 20 mg) for "polymorphic screening of beta form,"

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and one or more infringing crystalline forms does not satisfy the Court's construction of "mixtures thereof," which is "mixtures of only the foregoing listed forms." (D.I. 1047 at 60; D.I. 358) Because the Court has already found that Plaintiffs failed to prove that any Defendant will infringe any claim of the '630 Patent, the Court need not address this alternative non-infringement argument.

recording both regular XRPD scans from 0° to 40° 2θ and slow XRPD scans from approximately 6.65° to 7.18° 2θ. (FF ¶ 262) In some of these tests, under accelerated and long-term stability conditions, Alembic identified a 6.8° 2θ peak. (FF ¶¶ 268-69) These test results, and detection of just a single characteristic peak, is, at best, weak evidence of the presence of the beta form in Alembic's ANDA Product.

Dr. Kahr compared diffractograms of exhibit batches of Alembic's ANDA Product to FIG. 3 of the '684 Patent and concluded that Alembic's ANDA Product has many peaks that FIG. 3 does not, and vice versa. (FF ¶ 274) There is not a single diffractogram of Alembic's ANDA Product that shows all four claimed XRPD peaks of the beta form. (FF ¶ 275) That is, Alembic never identified XRPD peaks at all of 6.89, 9.73, 13.78, and 14.62 ± 0.10º 2θ in any sample of its ANDA Product. (*Id.*) As Plaintiffs' expert, Dr. Myerson, admitted, all eight of the XRPD diffractograms of exhibit batches at 36 months are missing at least two claimed characteristic peaks of the beta form. (FF ¶ 282)

It is striking that Plaintiffs disclosed no test results conducted by their experts (if any were) on Alembic's ANDA Product. (FF ¶¶ 290-93) Alembic is the only one of the five Defendants accused of infringing the Crystalline Form Patents for which Plaintiffs did not disclose any testing results. (FF ¶ 294) While not dispositive, the Court agrees with Alembic that it is reasonable to infer that Plaintiffs likely tested Alembic's product and found no evidence that it contains the beta form.

For all of these reasons, and the additional reasons supported by the Court's findings of fact, Plaintiffs have failed to prove that Alembic's proposed ANDA Product infringes the claims of the Crystalline Form Patents.

C. Lupin

The vortioxetine HBr API in Lupin's ANDA Product is intended to be amorphous, not

crystalline. (FF ¶ 296) Plaintiffs contend that Lupin's amorphous API converts to the alpha and beta crystalline forms. (*Id.*) Plaintiffs have failed to prove that Lupin's ANDA Product infringes the Crystalline Form Patents.

In the course of Lupin's manufacturing process, the API is dissolved and becomes amorphous and is no longer in crystalline form. (FF ¶ 299) Plaintiffs' expert, Dr. Myerson, agreed that the dissolution step should remove any crystalline vortioxetine hydrobromide. (*Id.*) Dr. Cockcroft testified that once the vortioxetine hydrobromide is dissolved, it remains in the amorphous form throughout the remainder of the process. (FF ¶ 301) At the FDA's request, Lupin prepared and submitted a Polymorphic Evaluation Report, which demonstrates that after the vortioxetine hydrobromide is converted to amorphous form in Lupin's manufacturing process, it remains in the amorphous form at each subsequent stage of the process throughout its 24-month shelf life. (FF ¶¶ 301-04; *see also* Myerson Tr. 978-79)

Plaintiffs' argument that, notwithstanding this evidence, conversion does occur is predicated, first, on Lupin's internal testing of a development batch. (FF ¶ 309) Lupin's testing of a development batch after one month of storage at 40°C/75% RH detected crystalline XRPD peaks that were not present in the corresponding placebo and which corresponded to the alpha form of vortioxetine hydrobromide. (FF ¶ 308) The development batch, however, differs from Lupin's proposed ANDA Product, in terms of both its formulation and manufacturing process, and is not representative of Lupin's ANDA Product. (FF ¶¶ 309-10) Moreover, the diffraction pattern for the development batch was missing major peaks attributable to the alpha form, as admitted by Dr. Myerson. (FF ¶ 311)

Lupin tested its exhibit batches as part of its Polymorphic Evaluation Report, which are representative of its ANDA Product, and the results of these tests support the conclusion that

Lupin's ANDA Product does not contain crystalline vortioxetine HBr. (FF ¶ 304; DTX-927 at 4) Plaintiffs fault Lupin's testing for not having an established limit of detection. (D.I. 1054 at 31) At best, this argument detracts from the weight of evidence ***against*** infringement but it does nothing to help Plaintiffs meet their affirmative burden to prove that Lupin's ANDA Product does contain crystalline vortioxetine.

Testing conducted by Plaintiffs' expert, Dr. Morin, on four untreated Lupin samples also found an absence of the alpha and beta forms of vortioxetine HBr. (FF ¶¶ 314-16; *see also* Cockcroft Tr. at 1769-72) So Plaintiffs attempt to show conversion through S-XRPD tests on samples of Lupin's ANDA Product that were exposed to 75% RH at 40 °C.[23] (D.I. 1057 at 45-46) These conditions, however, are "extreme," as Dr. Cockcroft explained. (FF ¶ 319) Lupin controls environmental conditions during manufacturing of its ANDA Product to not more than 25° C and not more than 45% relative humidity. (*Id.*) Lupin's proposed prescribing information requires storage at 25° C, with a permitted range of 15° to 30° C – but not including 40° C. (*Id.*) Therefore, Plaintiffs did not prove that Lupin's ANDA Product will encounter such conditions either during manufacturing or when stored in a manner consistent with Lupin's label and industry practice.

For all of these reasons, and the additional reasons supported by the Court's findings of fact, Plaintiffs have failed to prove that Lupin's proposed ANDA Product infringes the claims of the Crystalline Form Patents.

[23] At trial, Plaintiffs' experts were permitted to offer opinions on the presence of alpha and beta forms in Lupin's ANDA Product in samples treated at 40° C and 75% relative humidity, but not opinions with respect to samples tested under other conditions. (Morin Tr. 558-63; Myerson Tr. 732-34, 1009-11) This is because, in response to Defendants' objection, Plaintiffs failed to show that any other pertinent opinions were properly and timely disclosed. (*See* Tr. at 558-63)

D. Macleods

The vortioxetine HBr API in Macleods' ANDA Product is intended to be amorphous, not crystalline. (FF ¶ 327) Plaintiffs contend that, after conversion, Macleods' ANDA Product contains the alpha form of vortioxetine hydrobromide characterized by an XRPD pattern shown in Figure 2 of the Crystalline Form Patents. (D.I. 1057 at 25) Plaintiffs base their contention on Macleods' internal testing and Dr. Morin's confirmatory analysis. (FF ¶¶ 333-40, 345, 347, 351-55, 357) Plaintiffs failed to prove infringement.

Macleods conducted XRPD tests on its drug product stored under long-term stability conditions for 24 months in 30-tablet bottles, 90-tablet bottles, and blister packages. (FF ¶ 335) All accelerated and long-term stability testing done by Macleods on its tablets – both initially and during all stability testing, when the tablets were packaged in 30 and 90 count bottles – confirmed the tablets to be within specification, which requires an amorphous form. (FF ¶ 342; PTX-4563 at 13) Plaintiffs critique Macleods' testing method because it will not detect the alpha form in its drug substance if it is present at less than 1%. (FF ¶ 332) As Dr. Myerson acknowledged, below a limit of detection, "[y]ou just don't know if it's there or not." (Myerson Tr. 814) As with Lupin, this argument has merit, and it helps Plaintiffs, but it is not sufficient – in light of all the evidence presented – to prove by a preponderance of the evidence that Macleods' ANDA Product contains crystalline vortioxetine.

The FDA asked Macleods to conduct a stress test of its premix, in which the premix was removed from its ANDA packaging, and exposed to various heat and moisture conditions outside of what the ANDA specifications allow. (FF ¶ 344) Though Macleods detected varying amounts of XRPD peaks consistent with the alpha form at different testing conditions, including 40° C / 75% RH and 25° C / 80% RH, the premix maintained its amorphous form for 28 days when stored at conditions specified by the ANDA. (FF ¶¶ 345-46)

Plaintiffs' reliance on conversion it identified in batches of Macleods' ANDA Product that were contained in blister packs (FF ¶¶ 333, 336-40), instead of stored in the bottles for which Macleods is seeking FDA approval (FF ¶ 343), is unpersuasive. Macleods does not seek to sell its product in blister packs (FF ¶ 341), and Plaintiffs have failed to show that conversion (evidently due to moisture) experienced in blister packs is at all representative of what will occur in the very different packaging Macleods will actually use for its product. (Suryanarayanan Tr. 1816-19)

Plaintiffs also rely on 6-month stability testing conducted on drug substance used in exhibit batches. (FF ¶ 347) While this substance is representative of what Macleods will use in its ANDA Product, Macleods conducted follow-up testing and determined the sample had been improperly handled. The out-of-specification alert was determined not to be due to the quality of the product. (FF ¶ 348)

Testing conducted by Plaintiffs' expert, Dr. Morin, did not detect any crystalline peaks in the two untreated samples of Macleods drug substance. (FF ¶¶ 349-50) Dr. Morin detected peaks consistent with the alpha form in the Macleods drug substance samples treated at 22° C / 75% RH, 40° C / 30% RH, and 40° C / 75% RH. (FF ¶¶ 351-52) Dr. Morin also detected peaks consistent with the alpha form in an untreated sample of Macleods drug product. (FF ¶ 355) However, the alpha peak at 17.49° 2θ was not seen in the diffractogram (FF ¶¶ 354), and Dr. Morin did not detect vortioxetine HBr alpha peaks in two other untreated drug product samples (FF ¶ 356). Further, all of the testing conducted by Dr. Morin on Macleods' ANDA Product was performed on expired samples that were not handled or stored as required by the Macleods ANDA specifications. (FF ¶¶ 359-60, 363)

For all of these reasons, and the additional reasons set out in the Court's findings of fact,

Plaintiffs have failed to prove that Macleods' proposed ANDA Product infringes the claims of the Crystalline Form Patents.

E. Sigmapharm

The vortioxetine HBr API in Sigmapharm's ANDA Product is intended to be amorphous; its premix is an amorphous solid dispersion. (FF ¶¶ 364-66) Plaintiffs allege that Sigmapharm's ANDA Product contains the alpha and beta forms of crystalline vortioxetine. (D.I. 1057 at 37) Plaintiffs have failed to prove that Sigmapharm's ANDA Product infringes any claim of the Crystalline Form Patents.

Dr. Morin tested untreated samples of Sigmapharm's drug product intermediate (also referred to as Sigmapharm's drug substance) as well as samples exposed to (1) room temperature 22° C / 75% RH; (2) 40° C / 30% RH; and (3) 40° C / 75% RH. (FF ¶¶ 376-77) Dr. Morin did not detect any crystalline peaks in the untreated samples of Sigmapharm's drug product intermediate. (FF ¶ 378-79) It was not until after treatment for days at the conditions listed above that Dr. Morin observed XRPD peaks associated with the alpha and beta forms in Sigmapharm's drug product intermediate. (FF ¶¶ 380-82) Moreover, all of the samples of intermediate tested by Dr. Morin were expired. (FF ¶ 398)

Similarly, Dr. Morin tested untreated samples of Sigmapharm's drug product as well as samples exposed to (1) 22° C / 50% RH; (2) 22° C / 75% RH; (3) 30° C / 60% RH; (4) 30° C / 75% RH; (5) 40° C / 60% RH; and (6) 40° C / 75% RH. (FF ¶¶ 383-84) Again, in the untreated samples, Dr. Morin did not observe a single peak associated with crystalline vortioxetine HBr. (FF ¶¶ 385, 389) It was not until after treatment of samples of Sigmapharm's ANDA Product that Dr. Morin observed the appearance of peaks that correspond to the alpha and beta forms of vortioxetine HBr, with two different exhibit batches yielding consistent results. (FF ¶¶ 386-88)

Plaintiffs insist that Sigmapharm's ANDA Product quickly absorbs large amounts of

water, leading the drug substance and tablet to become "cakey" after only a single day of exposure to normal conditions. (D.I. 1057 at 41) In the opinion of Dr. Morin, the Sigmapharm tablets are so highly hygroscopic that the tablet coating is ineffective in preventing the absorption of water into the tablet, leading to crystallinity. (Morin Tr. 448; *see also* D.I. 1057 at 41) Sigmapharm responds, persuasively, that it is the stress tests conducted by Dr. Morin – which intentionally destroy samples and cause "caking" – making these results unrepresentative. (D.I. 1047 at 47) As Plaintiffs admit, "there's no evidence that any defendant will try to sell a cakey or sticky tablet." (FF ¶ 392)

As Plaintiffs further acknowledge, and as detailed above, "Dr. Morin did not detect any crystalline forms of vortioxetine HBr in untreated samples of . . . Sigmapharm's drug products." (FF ¶¶ 385, 389) Even in the samples of Sigmapharm's 20 mg tablets that produced caking and stickiness at 50% relative humidity, Dr. Morin did not observe any of the four characteristic peaks of the alpha or beta forms. (FF ¶ 391) Sigmapharm's expert, Dr. Hollingsworth, conducted synchrotron testing of unexpired samples of Sigmapharm's ANDA Product and found no signs of the presence of alpha or beta crystalline vortioxetine HBr. (FF ¶¶ 407-08) Sigmapharm has also performed proper long-term and accelerated stability studies of its ANDA Product and Drug Product Intermediate in connection with its ANDA submissions, which showed no evidence of claimed crystalline vortioxetine HBr. (FF ¶ 405)

Plaintiffs argue Sigmapharm's label encourages adulteration of its tablets, by, for example, allowing its product to absorb up to 6% water content, which Plaintiffs note is more than twice the water content of tablets tested by Dr. Morin. (D.I. 1054 at 28) Plaintiffs also remark that over time, as the tablets are stored under the storage conditions permitted by the label, the tablets absorb water, which may cause crystallization. (*Id.*) While these theoretical

possibilities cannot be entirely ruled out, the more pertinent evidence is the actual testing conducted by both sides, which on the whole shows no crystallization, even in the expired (older than 24 months) samples tested by Dr. Morin.

For all of these reasons, and the additional reasons set out in the Court's findings of fact, Plaintiffs have failed to prove that Sigmapharm's proposed ANDA Product infringes the claims of the Crystalline Form Patents.

F. Zydus

The vortioxetine hydrobromide in Zydus' proposed ANDA Product is an amorphous solid dispersion. (FF ¶ 411) Plaintiffs contend that Zydus' ANDA Product contains the gamma form of vortioxetine hydrobromide. (D.I. 1057 at 32) They base this contention on Zydus' internal XRPD testing and Dr. Morin's SXRPD testing. (*Id.* at 33-35)

The development batch results Plaintiffs turn to as indicative of infringement (FF ¶ 418) are not relevant to the infringement analysis because they are not representative of the product Zydus will sell. The development batches contain different amorphous solid dispersions of vortioxetine than the API contained in Zydus' proposed ANDA Product and different excipients, in a different polymer, from those contained in Zydus' proposed ANDA Product. (FF ¶ 419)

Plaintiffs argue that an exhibit batch exposed to accelerated stability conditions (40 °C / 75% RH) for three months demonstrated a peak at 11.82 ± 0.1° 2θ. (FF ¶ 420) Plaintiffs also contend that Dr. Morin detected the gamma form in all tested samples of Zydus' drug product, including three untreated samples. (D.I. 1057 at 36)

The Court agrees with Zydus that the single peak identified in the exhibit batch is not sufficient to prove the presence of the gamma form, especially because even that peak is not present in other exhibit batches. (*See* D.I. 1047 at 61-68) Plaintiffs point to a polymorphic study conducted by Zydus in which it determined that a crystalline peak at 11.82° 2θ is "indicative and

discriminatory" of the gamma form of vortioxetine HBr. (FF ¶ 420) As Zydus' expert, Dr. Sacchetti, testified, Zydus did not identify a peak at 11.82° 2θ in its polymorphic study to find the gamma form, but instead was simply looking for the presence of any crystalline material. (FF ¶ 423) Zydus' XRPD software detected a peak at 11.82° 2θ in exhibit batch EE70021 that was subjected to accelerated stability conditions of 40 °C / 75% RH for three months. (FF ¶ 421) Exhibit Batch No. EE70021 was made the same way Zydus' ANDA Product will be made if it is approved and sold. (FF ¶ 422)

In the Court's view, Dr. Myerson placed undue weight on a single feature present in a single diffractogram. As Dr. Sacchetti testified, a scientist, looking for repetition and reproducibility, would not conclude from noise in a single diffractogram that Zydus' product contains crystalline material. (FF ¶ 424) More probative is Zydus' internal testing showing that its proposed ANDA Product remains amorphous throughout its two-year expiry period even under accelerated conditions. (FF ¶¶ 425-26)

Dr. Morin tested untreated samples of Zydus' drug substance and samples exposed to: (1) 22° C/ 75% RH; (2) 40° C/ 30% RH; and (3) 40° C/ 75% RH. (FF ¶ 427) Dr. Morin did not detect any crystalline forms in the untreated samples of Zydus' drug substance. (FF ¶ 429) Dr. Morin detected peaks consistent with the gamma form in drug substance samples that were exposed to 40° C / 75% RH and 22° C / 75% RH after one day of treatment. (FF ¶ 430)

Dr. Morin tested untreated samples of batch nos. EE70060 and EE70054 of Zydus's drug product and samples exposed to: (1) 22° C / 50% RH; (2) 22° C / 60% RH; (3) 22° C / 75% RH; (4) 30° C / 60% RH; (5) 40° C / 60% RH; and (6) 22° C / 60% RH. (FF ¶ 431) Dr. Morin detected the gamma form of vortioxetine HBr – including four XRPD Peaks at 11.82, 16.01, 17.22, and 18.84 ±0.1° 2θ – in all the treated and untreated samples of Zydus' drug product he

tested. (FF ¶ 432)

All Zydus samples Plaintiffs tested were expired and subjected to storage, shipping, and handling conditions that would violate the storage and handling conditions set forth in Zydus' ANDA. (FF ¶¶ 434, 436-38) Dr. Sacchetti explained that Dr. Morin's sample preparation methods were likely to induce crystallization because his freezing process produced supersaturated relative humidity. (FF ¶ 435) In sum, the record does not establish by a preponderance of the evidence the presence of a claimed crystalline form in Zydus' ANDA Product.

For all of these reasons, and the additional reasons set forth in the Court's findings of fact, Plaintiffs have failed to prove that Zydus' proposed ANDA Product infringes the claims of the Crystalline Form Patents.

III. Zydus Has Not Proven The '575 Process Patent Is Invalid

Claim 3 of the '575 Patent is directed to a novel process for preparing vortioxetine by reacting 2,4-dimethylphenylthiol aniline (compound of formula IVa) with a bis(chloro or bromo)ethyl amine. (DTX-242 at 11) Zydus asserts that for the same reasons vortioxetine would have been obvious, Claim 3 of the '575 Patent would have been obvious over ES '127 and Planas in view of Jílek, Kopicová, Pinder, WO '678, and optionally further in view of GB '711, and the knowledge of a POSA. (D.I. 1011 at 22) The Court concludes, for the reasons below, that Zydus has failed to prove obviousness of the '575 Patent by the required clear and convincing evidence.

Dr. Lepore does not address why a POSA would have been motivated to combine the seven references he relied on to try to show obviousness of Claim 3 of the '575 Patent. (FF ¶ 494) Neither Planas nor Pinder discloses any synthetic methods. (FF ¶ 504) Jílek and Kopicová disclose methods that do not require a compound of formula IVa or a bis(chloro or

bromo)ethyl amine. (FF ¶ 505) Compounds of formula III of WO '678 can be prepared by either reacting an aniline with a bis(2-chloro)ethyl amine or a multistep synthesis. (FF ¶ 507)

GB '711 discloses the reaction of a biarylether aniline with a bis(halo)ethyl amine to form biarylether piperazines, which are encompassed by Dr. Lepore's biarylether piperazine motif. (FF ¶ 501) Zydus contends that ES '127 similarly discloses a method of making bioisosteric biarylmethylene piperazine compounds, including sifaprazine, Example 6, and Example 7, by reacting the relevant biaryl aniline with bis(halo)ethyl amines. (D.I. 1011 at 23) However neither reference discloses a compound of formula IVa, a phenylthiol aniline, or the specific 2,4-dimethylphenylthiol aniline of Claim 3 of the '575 Patent. (FF ¶ 506) The general reactions of GB '711 and ES '127 do not suggest the specific 2,4-dimethylphenylthiol aniline of Claim 3 of the '575 Patent. (*Id.*) A POSA also would not have been drawn to GB '711 when trying to synthesize an antidepressant because GB '711 discloses compounds useful for treatment of glucid and lipid metabolism disorders. (FF ¶¶ 498-99)

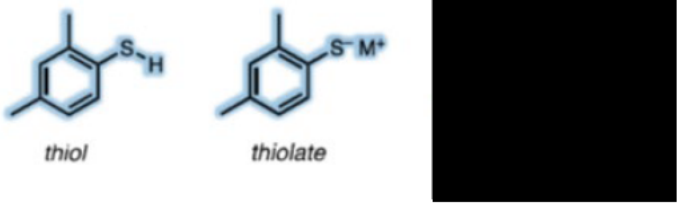
Zydus offers no reason why a POSA would choose to prepare a compound by a general method disclosed in only three of the seven references Dr. Lepore relies on, and Zydus ignores any method that does not utilize a bis(chloro or bromo)ethyl amine and an aniline. (FF ¶¶ 508-09) Dr. Lepore has not offered any explanation as to why a POSA would have a reasonable expectation to successfully formulate 1-[2-(2,4-DMPS)P]P according to Claim 3 of the '575 Patent, particularly when none of the seven references he relied on discloses 1-[2-(2,4-DMPS)P]P (FF ¶¶ 503, 510) Therefore, Zydus has not proven that Claim 3 of the '575 Process Patent is invalid due to obviousness.

IV. Plaintiffs Have Proven Lupin Will Infringe The '626 Process Patent

Lupin asserts that its manufacturing process to produce its ANDA Product does not infringe Claim 12 of the '626 Process Patent, either literally or under the doctrine of equivalents.

(FF ¶ 444) The '626 Patent is a process patent covering a specific palladium-catalyzed process for the making of vortioxetine (FF ¶ 445) Claim 12 is dependent upon Claim 11, which is dependent upon independent Claim 1. Claim 1 specifies "reacting" Compound II with Compound III and Compound IV. (FF ¶ 446) Compound II is either a thiol or thiolate. (FF ¶ 447)

One reason Lupin contends it does not infringe is because Lupin uses [redacted], which it calls "VRT-I," rather than the thiol or thiolate recited in Claim 1 as Compound II. (D.I. 1047 at 99) The thiol and thiolate of Compound II are highlighted in blue, and [redacted]



(*See* DDX-LUPIN-6 at 5)

Plaintiffs' expert, Dr. MacMillan, testified persuasively that [redacted] to compound II that is [redacted] in Stage I, Step B of Lupin's process. (FF ¶ 474) Lupin contends that because Compound IV in the same claim explicitly recites "R represents hydrogen or a protecting group," it follows that Compound II must not include a [redacted] group. (D.I. 1047 at 98-99) Although Compound II may not be explicitly drawn to include a protecting group, the process claim uses the open-ended "comprising," which is a "signal that additional steps may be performed in carrying out a claimed method." *Smith & Nephew, Inc. v. Ethicon, Inc.,* 276 F.3d 1304, 1311 (Fed. Cir. 2001). The Court is persuaded that the open-ended "comprising" allows for the additional step of the

[redacted] to become [redacted] to form Compound II.[24] (FF ¶ 486)

Lupin contends that when VRT-I is [redacted], it does not form Compound II. (D.I. 1047 at 108) Both Dr. MacMillan and Lupin's expert, Dr. Micalizio, agree that VRT-I must be [redacted] for the reaction to occur. (FF ¶¶ 472-73) While Dr. Micalizio does not agree that Compound II is formed upon the [redacted] of VRT-I, he also does not explain what is formed instead. (Micalizio Tr. 1851-52) Lupin's process for the manufacture of vortioxetine HBr occurs in three stages. (FF ¶ 461) Dr. MacMillan persuasively explained that during Stage I, Step B, VRT-I is exposed to the [redacted], which [redacted] of VRT-I and forms the [redacted] of Compound II. (FF ¶ 474)

Lupin faults Plaintiffs for not running any tests or citing batch records to verify Compound II in its final process. (D.I. 1047 at 108) This was unnecessary because the scientific literature and Lupin's internal documents both support that [redacted] to produce Compound II. (*See, e.g.*, FF ¶ 478) Dr. MacMillan testified that a Lupin internal study showed that treatment of [redacted] in Stage I, Step B process produces [redacted] (FF ¶ 475) The internal study further reported that [redacted] This is well-known reported reaction which is described in Literature." (*Id.*) Following [redacted] of VRT-I and generation of Compound II, Lupin's process for the preparation of vortioxetine HBr proceeds according to the reaction conditions described in Claim 12 of the '626

[24] Lupin cites to cases for the premise that "the transition term '[c]omprising' is not a weasel word with which to abrogate claim limitations, . . . or to impermissibly expand a claim's scope.'" (D.I. 1047 at 100) (citing *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1376 (Fed. Cir. 2005)) However, the additional step of [redacted], which both parties' experts agree must occur for the reaction to proceed (FF ¶ 473), does not negate the claim. It simply adds an additional step, as "comprising" is intended to do.

Patent. (FF ¶ 476)

Plaintiffs and Lupin also dispute the plain and ordinary meaning of "reacting" recited in Claim 1 of the '626 Patent. (FF ¶ 480) Plaintiffs contend the plain and ordinary meaning of "reacting" as used in Claim 1 of the '626 Patent is "the changing of a reactant(s) to product(s)." (D.I. 1057 at 10) Lupin contends "reacting" must be understood to mean "the specified chemicals are added to the reaction vessel at the beginning of the process as starting material." (FF ¶ 484) Both Dr. MacMillan and Dr. Micalizio agree that the term is "ubiquitous" in the field of chemistry. (FF ¶ 481) The Court agrees with Plaintiffs that a POSA would understand the plain and ordinary meaning of "reacting" to mean "the changing of a reactant(s) to product(s)." (FF ¶ 485)

Claim 1 requires "reacting" Compound II with Compounds III and IV. Lupin contends Plaintiffs' construction of "reacting" is wrong because "the changing of a reactant(s) to product(s)" is akin to forming or breaking chemical bonds, yet Compound II never forms bonds with either Compound III or Compound IV; rather they proceed through a palladium catalyst. (D.I. 1047 at 101) However, a POSA would understand that the two compounds react with the palladium catalyst to form different intermediates before yielding the final product. (FF ¶ 452)

Lupin asserts a POSA would immediately know that it is not scientifically possible for Compound II to "react" with Compounds III or IV in the sense of a bond formation. (D.I. 1047 at 102) This is further support that a POSA's understanding would be that the compounds react through a palladium catalyst. (FF ¶ 452)

The Court's construction, "the changing of a reactant(s) to product(s)," does not require that Compound II, Compound III, and Compound IV form and break bonds with one another. It also does not exclude Compound II, Compound III, and Compound IV from forming and breaking bonds with the palladium catalyst, as required by Claim 12. (FF ¶¶ 451, 457)

Lupin contends the inventors never referred to any of Compounds II, III, or IV as intermediates, despite repeatedly referring to other compounds as such. (D.I. 1047 at 103) But both Drs. MacMillan and Micalizio agree that a POSA would understand that when two compounds react through a palladium-catalyzed cross-coupling reaction, such as the one claimed by the '626 Patent, palladium-compound intermediates are formed. (FF ¶ 452) Therefore, a POSA would not misapprehend "reacting" to require direct interaction of Compound II and Compound III, in view of the well-understood formation of palladium-inserted intermediates. (FF ¶ 492)

The Court's construction of "reacting" is supported by the claims, the specification, the file history, and extrinsic evidence. The claims of the '626 Patent do not expressly recite "added," "reaction vessel," "beginning of the process," or "starting material," and they do not otherwise limit Claim 12 to a process in which "the specified chemicals are added to the reaction vessel at the beginning of the process as starting material." The inventors neither defined "reacting" nor expressly limited the scope of the term's ordinary meaning in the patent specification or prosecution history. (FF ¶¶ 482-83, 487) The 2004 Fifth Edition of the Oxford Dictionary of Chemistry defined "chemical reaction" as, *inter alia*, "the changing of a reactant(s) to product(s)." Dr. Laird, Lupin's invalidity expert (who was not called at trial), did not dispute the plain and ordinary meaning of "reacting." (FF ¶ 488)[25]

The '626 Patent claims specify two different types of reactions: a one-pot process, in which all reactants are together from the start of the process (Claim 3), and a two-pot process, comprising a series of reactions in which the initial reaction product later reacts with other compounds to yield the final product (Claim 2). (FF ¶ 453) Lupin's proposed construction would limit the process of Claim

[25] Plaintiffs are permitted to rely on Dr. Laird's testimony. *See* Fed. R. Civ. P. 32(a)(4); Fed. R. Evid. 703.

1 to the one-pot synthesis of Claim 3 (which requires Compounds II, III, and IV to be "mixed together at the start of the process"), thereby rendering Claim 3 superfluous and Claim 2 outside the scope of Claim 1. (FF ¶¶ 454, 486) This is among the many reasons the Court has adopted Plaintiffs' proposed construction.

It follows from the Court's adoption of Plaintiffs' proposed construction of reacting, along with the Court's findings of fact, that Lupin's process infringes. Lupin's process for manufacturing vortioxetine HBr comprises reacting [redacted] (at a temperature between 60° C and 130° C). (FF ¶¶ 457, 463-67; PTX-19 at Claims 1, 12) Therefore, Lupin's process for manufacturing vortioxetine HBr meets all of the limitations of Claim 12 of the '626 Patent and, hence, infringes that claim.

Because the Court has adopted Plaintiffs' construction of "reacting," the parties' disputes over infringement (literal and under the doctrine of equivalents) under Lupin's proposed construction are moot. Applying Plaintiffs' construction, for the reasons given above and those stated in the Court's Findings of Fact, the Court concludes that Plaintiffs have proven, by a preponderance of the evidence, that Lupin infringes Claim 12 of the '626 Patent.

V. Plaintiffs Have Failed To Prove That Defendants Will Indirectly Infringe Any Asserted Claim Of The '096 Sexual Dysfunction Patent

A. Crystalline Form Claims

Plaintiffs have asserted that Alembic, Lupin, and Sigmapharm infringe Claims 4 and 5 of the '096 Patent, which require the beta crystalline form of vortioxetine. (PTX-17 at claims 4, 5)

The ANDA Products of Alembic, Lupin, and Sigmapharm have not been proven to contain any crystalline forms of vortioxetine. (*See supra* at 192-96, 199-201) It follows, therefore, that not all limitations of Claims 4 or 5 are met and, thus, there is no infringement.

B. Induced Infringement

It is undisputed that Defendants' ANDA Products meet the compositional requirements of Claim 7 of the '096 Patent: the active ingredient in each is vortioxetine hydrobromide, and the ANDA Products will be offered in therapeutically effective amounts (5 mg, 10 mg, 15 mg, and/or 20 mg doses) and administered orally once daily. (FF ¶¶ 572, 575) Further, there is no dispute that the ANDA Products will be indicated for the treatment of MDD. (FF ¶ 574) Additionally, Defendants have represented to the FDA that their ANDA Products are bioequivalent to Trintellix. (FF ¶ 576)

The disputes regarding infringement of Claim 7 of the Sexual Dysfunction Patent focus on the claim limitation relating to the use of vortioxetine in a patient who has "previously received medication or is still receiving medication for the treatment of [depression], the medication is ceased or reduced or has to be ceased or reduced due to sexually related adverse events, and the medication is selected from the group consisting of selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors, noradrenaline/serotonin reuptake inhibitors, and tri-cyclics," which the Court will refer to hereinafter as the "TESD Limitation."

Direct infringement is a predicate for induced infringement. *See Vanda Pharm.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018); *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364-65 (Fed. Cir. 2017). Because a proposed ANDA product has not yet been marketed, a patentee can satisfy its burden to prove direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the patent. *See Vanda Pharm.*, 887 F.3d at 1130; *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003).

There is no real dispute that clinicians will be direct infringers of the claimed method on those occasions when clinicians prescribe vortioxetine to treat MDD patients who have ceased or reduced or have to cease or reduce an SSRI, SNRI, or TCA due to sexually related adverse events. (FF ¶¶ 532-34, 558) Such prescribing behavior satisfies the TESD limitation. Plaintiffs have proven that clinicians do prescribe Trintellix in this way and that Defendants' ANDA Products will sometimes be prescribed in the same manner. (FF ¶ 558)[26]

Proving inducement requires more. Plaintiffs must further prove, by a preponderance of the evidence, that "the alleged inducer knew of the patent, knowingly induced the infringing acts, and possessed a specific intent to encourage another's infringement of the patent." *Vita-Mix*, 581 F.3d at 1328. While it is undisputed that Defendants knew of the '096 Patent at all times after it was issued (including now, prior to the launch of their proposed ANDA Products) (FF ¶ 610), Plaintiffs have failed to prove that Defendants will knowingly induce infringement of Claim 7 of the '096 Patent or that they possess a specific intent to encourage such infringement.

In undertaking the inducement inquiry, the Court must consider the proposed ANDA Products' labeling, as a whole, although certain portions may have heightened importance. *See Sanofi v. Watson Labs*., 875 F.3d 636, 645-46 (Fed. Cir. 2017)*; see also Vanda Pharm*., 887 F.3d at 1131. When "the label, taken in its entirety, fails to recommend or suggest to a physician that

[26] Defendants assert that use of their ANDA Products in accordance with the claimed method of the '096 Patent will be outside of the approved use. (D.I. 1047 at 89) The Court does not agree. As long as vortioxetine is prescribed to an adult diagnosed with MDD, the use is on-label. (FF ¶¶ 553-57) The asserted method claims all fall within the approved use for treating MDD. *See generally Braintree Lab'ys, Inc. v. Breckenridge Pharm., Inc.*, 688 F. App'x 905, 910 (Fed. Cir. 2017) (generic's position "would lead to the absurd result that a physician would understand [the] proposed product to be safe and effective for fully cleansing the colon, but not safe and effective at accomplishing a partial colon cleansing"). The Court's disagreement with this contention does not undermine any basis on which the Court has found that Plaintiffs failed to prove infringement.

[the drug] is safe and effective for inducing the claimed combination of effects in patients," intent to induce infringement is lacking. *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1324 (Fed. Cir. 2012). Therefore, the inducement analysis is guided by whether the proposed generic labeling, taken in its entirety, encourages, recommends, or promotes an infringing use. *See Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). "[P]ossible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." *Id.*; *see also Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003).

Defendants' labels, read as a whole – and also focusing on the portions Plaintiffs highlight – will not encourage, recommend, or promote an infringing use. Defendants have "carved out" the TESD comparative information from their proposed prescribing information. (FF ¶ 581) Due to Defendants' section VIII carve-outs, Defendants' labeling will not encourage, recommend, or promote the practice of switching MDD patients, who have previously experienced adverse sexual side effects while taking one of the four classes of antidepressants, to vortioxetine. That is, the labels do not encourage, recommend, or promote practice of the TESD Limitation.

As a result of the carve-outs, the only information related to TESD in Defendants' proposed Prescribing Information appears in the "Adverse Reactions" Section 6.1 of Defendants' proposed labels. (FF ¶¶ 578-79, 582-84) This information uses ASEX data to report the incidence of TESD that developed in patients without sexual dysfunction at baseline using vortioxetine at 5, 10, 15, and 20 mg doses compared with a placebo. (FF ¶¶ 582-84)

Plaintiffs have failed to persuade the Court that clinicians would understand from the data in Section 6.1, which appear under the heading "Voluntarily Reported Adverse Reactions of

Sexual Dysfunction," that vortioxetine has placebo-like levels of sexually related adverse events and would, therefore, be encouraged to prescribe vortioxetine for use according to the claimed method. (D.I. 1057 at 74-76; FF ¶ 592) Instead, as Defendants correctly state, "Defendants' skinny labels leave nothing that 'encourage[s], recommend[s], or promote[s]' claim 1's three key steps: (1) the patient must take a first antidepressant in one of the four recited classes; (2) the patient must cease or reduce or have to cease or reduce that antidepressant 'due to' TESD; and (3) the patient must then take vortioxetine." (D.I. 1047 at 81; FF ¶¶ 585-89)

Plaintiffs contend that clinicians are aware that other antidepressants, particularly SSRIs, SNRIs, and TCAs, have high rates of TESD, so they would understand that the reported rates of TESDs connected with vortioxetine – 2-15% placebo-adjusted rate – are low, making the drug particularly useful in treating patients who have ceased or reduced or have to cease or reduce an SSRI, SNRI, or TCA due to sexually related adverse events. (D.I. 1057 at 76-77) The Court agrees with Defendants that the possibility that some prescribers might undertake a "scholarly scavenger hunt" is insufficient to show that Defendants, as manufacturers of generic drugs, are encouraging an infringing use. (D.I. 1047 at 82) (citing *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, at *19 (D.N.J. Aug. 29, 2014); *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017) ("'[V]ague' instructions that require one to 'look outside the label to understand the alleged implicit encouragement' do not, without more, induce infringement.")) Defendants' Prescribing Information contains no reference in Section 6.1 to any other antidepressant, let alone a comparison between the rates of TESD for vortioxetine and other drugs. (FF ¶¶ 585-89) In fact, Defendants' label expressly instructs against making such comparisons. (FF ¶ 593) Defendants are instructing clinicians not to directly compare adverse reaction rates in the clinical trials of one drug to the rates in the clinical

studies of another drug. (*Id.*) That prescribers may do so anyway does not make Defendants liable for inducing infringement. *See Takeda Pharms.*, 785 F.3d at 631; *see also Warner-Lambert Co.*, 316 F.3d at 1364 ("[M]ere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven."). Furthermore, experts for both sides testified at trial it is improper to draw comparisons between vortioxetine's rate of TESD, as reported in Section 6.1, and other antidepressants' rates, as measured in separate studies. (FF ¶ 594)

The cases Plaintiffs rely on for the view that clinicians will read Defendants' prescribing information with the knowledge they already possess, and this combination may amount to encouragement by Defendants to prescribe vortioxetine to patients meeting the TESD limitation, do not support their position. In *Vanda*, 887 F.3d at 1131, "experts for both parties testified that the referred to 'laboratory tests' are genotyping tests." Thus, the district court did not err when it determined that a label instructing that laboratory (genotyping) tests are available resulted in induced infringement of the asserted claims. *Id.* In *Vanda*, instructions were given by the Defendants' proposed label, and outside knowledge was only needed to understand that laboratory tests were genotyping tests. Here, the required outside knowledge Plaintiffs' theory relies on is far greater. (FF ¶ 531) All that Defendants provide is a warning as to adverse effects for the prescribed drug, with no instruction as to how the adverse effects for vortioxetine compare with the adverse effects for other drugs. (FF ¶¶ 578-79, 583-84)

In *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010), the Federal Circuit found induced infringement where the defendant had carved out of its label some, but not all, of the information encouraging the patented use. The defendant's label included an instruction that "[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma

stability is achieved" and "[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose." *Id.* at 1057. The court found that this instruction, along with a letter from the FDA putting the defendant on notice, might cause a user to infringe the claim limitation of once daily dosing. *See id.* at 1057-58. Again, what is missing from Defendants' label here, and which (under Plaintiffs' theory of infringement) must be supplied by clinicians themselves, is far greater. (FF ¶ 531)

In *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1330 (Fed. Cir. 2021), the Federal Circuit held "[t]he combination of Teva's partial label, Dr. McCullough's element-by-element testimony that the partial label explicitly instructs administering carvedilol for the claimed use of decreasing mortality caused by CHF, and Dr. Zusman's admission that the post-MI LVD indication falls within the definition of congestive heart failure is substantial evidence that supports the jury's finding" of induced infringement. In addition to Teva's partial label and extensive expert testimony, the court further pointed to "Teva's product catalogs, Teva's advertising and promotional activities, Teva's Monthly Prescribing References for doctors, and testimony from Teva's own company witnesses, all of which the jury could have relied on to find Teva intended to encourage, recommend, or promote infringement." *Id.* at 1333. Here, by contrast, all Plaintiffs point to is Defendants' label – which, for the reasons explained above, the Court believes will not encourage infringement of the TESD Limitation – and clinicians' supposed background knowledge. (FF ¶ 607) The court, as factfinder, is not persuaded by a preponderance of the evidence that this will encourage, recommend, or promote infringement.

In *Amarin Pharma Inc. v. Hikma Pharms. USA*, 449 F. Supp. 3d 967, 1001 (D. Nev. 2020), the court found plaintiff's expert testimony that severe hypertriglyceridemia is generally a chronic condition requiring long-term treatment to mean that the defendant's ANDA product

would be prescribed for more than 12 weeks, meeting a 12-week claim limitation. The court wrote: "Prescribing doctors would bring that understanding to bear when they read Defendants' proposed labelling lacking an explicit duration of treatment – and most of them would prescribe Defendants' proposed ANDA Products for more than 12 weeks." *Id.* Here, even if prescribing doctors bring to bear their knowledge of the adverse sexual effects of SSRIs, SNRIs, NRIs, or TCAs when reading the proposed label, the label's reporting on the sexually adverse effects of vortioxetine does not constitute encouraging use comparative to the other drugs' side effects. The other drugs and their side effects are not mentioned in comparison in the label. (FF ¶¶ 585-89)

Plaintiffs' own actions provide further support for the Court's conclusions. FDA regulations require that an NDA holder submit for listing in the Orange Book any patent that covers a method of using the drug that is the subject of the NDA "within 30 days of the date of issuance of the patent." 21 C.F.R. §§ 314.53(c)(2)(ii), (d)(3). Plaintiffs did not, however, submit the '096 Patent within 30 days. Instead, Plaintiffs listed the '096 Patent as covering Trintellix® in October 2018, only after the FDA approved a supplement to the NDA that added the TESD comparative information to the Trintellix® Prescribing Information. (FF ¶¶ 539-42) This comports with an understanding that the '096 Patent does not cover products sold without the TESD comparative information. (*Id.*)

While Plaintiffs' case most prominently relies on Section 6.1 of Defendants' labels, Plaintiffs also point to Sections 2.5, 5.2, and 7.1, which, they assert, would cause clinicians to understand that vortioxetine can be administered after or concomitantly with SSRIs, SNRIs, or TCAs. (D.I. 1057 at 77) None of these sections, however, even mentions sexual dysfunction. (FF ¶ 598) Instead, as Dr. Rothschild put it, they relate to the "bad things that can happen when

you mix vortioxetine with other medications, particularly serotonergic medications" like SSRIs or SNRIs. (FF ¶ 599) A clinician would not read any or all of these sections of Defendants' proposed labels as encouraging, recommending, or promoting co-administration of vortioxetine and another antidepressant.

Accordingly, Plaintiffs have failed to prove induced infringement.

C. Contributory Infringement

To establish contributory infringement under 35 U.S.C. § 271(c), a plaintiff must show by a preponderance of the evidence that (1) there is direct infringement; (2) the accused infringer will import, sell or offer to sell its ANDA Products in the United States; (3) the accused infringer is aware of the patent and knows that its product is especially made for use that infringes the patent; and (4) the product is a material part of the invention and not a staple commodity or article suitable for a substantial noninfringing use. *See Fujitsu Ltd.*, 620 F.3d at 1326.

"Non-infringing uses are substantial when they are not unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp.*, 581 F.3d at 1327. Determination of whether a noninfringing use is substantial takes into account "not only the use's frequency, but also the use's practicality, the invention's intended purpose, and the intended market." *i4i Ltd. P'ship*, 598 F.3d 831, 851 (Fed. Cir. 2010). The burden of showing the absence of a substantial noninfringing use is on the party asserting patent infringement. *See Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006). However, "[o]nce a patentee has made out a prima facie showing that a product is not 'suitable for substantial non-infringing use', the burden then shifts to the accused infringer to demonstrate otherwise." *In re Depomed Patent Litig.*, 2016 WL 7163647, at *25 (D.N.J. Sept. 30, 2016) (quoting *Golden Blount, Inc.*, 438 F.3d at 1363).

Plaintiffs have proven there will be direct infringement when a clinician prescribes one of

Defendants' ANDA Products to a patient with MDD, who has ceased or reduced or has to cease or reduce treatment with an SSRI, SNRI, or TCA due to sexually related adverse events. This will happen at least some of the time. (FF ¶ 558) Further, Defendants do not contest that (1) they will import, sell, or offer to sell their ANDA Products in the United States; and (2) they have knowledge of the '096 Patent. (FF ¶¶ 573, 610) Nor do Defendants seem to dispute their ANDA Products are a material part of the method of treatment claimed in the '096 Patent. (*See* D.I. 1047 at 73-79; FF ¶ 611)

The parties' principal dispute is whether there are substantial non-infringing uses for Defendants' ANDA Products. (*See* D.I. 1057 at 85-91; D.I. 1047 at 73-79; D.I. 1054 at 49-53) Defendants identify three noninfringing uses: (1) where there is no prior treatment with an antidepressant (i.e., first-line use of vortioxetine); (2) where there was prior treatment with an antidepressant other than an SSRI, SNRI, or TCA; and (3) where the prior antidepressant was not ceased or reduced due to sexually related adverse events. (D.I. 1047 at 73-79; FF ¶ 615) Defendants have proven that all three of these are substantial non-infringing uses. (FF ¶ 617)

1. Use of Defendants' ANDA Products as First-Line Treatment

Defendants contend their ANDA Products will be first-line treatment. (D.I. 1047 at 74) Plaintiffs counter that any such use will be merely unusual or occasional. The Court agrees with Defendants.

Defendants' expert, Dr. Rothschild, has prescribed vortioxetine as a first-line treatment three times – even though no generic version is available. (FF ¶ 620) Plaintiffs' expert, Dr. Clayton, agreed that "[i]n an ideal world" – suggesting one in which insurance companies were willing to pay for first-line treatment of MDD with vortioxetine – she would consider prescribing vortioxetine as a first-line treatment. (Clayton Tr. 1165-66) In a pre-litigation video, Dr. Clayton stated that for MDD patients who "don't want to experience sexual dysfunction, you

start with a medication that's less likely to do that," suggesting again that she (and clinicians who might listen to her) would consider vortioxetine as a first-line treatment. (Clayton Tr. 1165-66; FF ¶ 621)

The Court is persuaded not only that use of Trintellix as a first-line treatment of MDD is currently a substantial non-infringing use but, more importantly, that in a genericized market Defendants' ANDA Products will be prescribed as a first-line treatment in a not-insubstantial number of cases. (FF ¶¶ 623, 625) Accordingly, Plaintiffs have failed to prove contributory infringement.

2. Use of Defendants' ANDA Products After Only Taking an Antidepressant Not Covered by the Asserted Claims

The record also establishes that even for those MDD patients for whom vortioxetine is not their first antidepressant, a not-insubstantial number of them will have only used other ADs that do not fall into the categories required for meeting the TESD Limitation. (FF ¶¶ 627-28)

For instance, bupropion and mirtazapine are not SSRIs, SNRIs, NRIs, or TCAs. According to 2010 APA Guidelines, however, both bupropion and mirtazapine were recommended among a list of "optimal" agents for treatment of depression and are now commonly used for treating MDD. (D.I. 1047 at 76; FF ¶ 630) Dr. Clayton acknowledged that patients to whom she prescribed vortioxetine had previously taken bupropion and mirtazapine. (FF ¶ 631) MAOIs and nefazodone are also antidepressants outside of the SSRIs, SNRIs, NRIs, or TCAs recited in Claim 1 of the '096 Patent. (FF ¶ 629) In clinical studies – relied on by Plaintiffs during prosecution of the '096 Patent – 75% of the patients involved had not taken SSRIs, SNRIs, NRIs, or TCAs in the past three months. (FF ¶¶ 632-34) Thus, the Court concludes that this is a substantial non-infringing use of Trintellix and, more importantly, will be a substantial non-infringing use of Defendants' ANDA Products.

3. Prescribing Defendants' ANDA Products After Ceasing or Reducing or Having to Cease or Reduce an SSRI, SNRI, or TCA Due to TESD

The record establishes that the most common reason for discontinuing an antidepressant is lack of efficacy. (*See, e.g.*, PTX-124; FF ¶ 639) Switching from an SSRI, SNRI, NRI, or TCA due to lack of efficacy, however, does not meet the TESD Limitation. (FF ¶ 635) That is, switching from one of the identified classes of antidepressants to vortioxetine because the earlier antidepressant was ineffective is a non-infringing use. (FF ¶ 636) Switching to vortioxetine because of sexual dysfunction caused by depression itself, and not TESD, is also not covered by claim 1. (FF ¶¶ 640-41)

The Court concludes that this is a substantial non-infringing use of Trintellix and, more importantly, will be a substantial non-infringing use of Defendants' ANDA Products.

VI. Defendants Have Failed To Prove That The Asserted Claims Of The '096 Sexual Dysfunction Patent Are Invalid

Defendants seek to invalidate the asserted claims of the '096 Sexual Dysfunction Patent as lacking written description and for being anticipated by and obvious over WO '005 and WO '232. (D.I. 1011 at 32) The Court concludes, for the reasons below, that Defendants have failed to prove invalidity[27] by the required clear and convincing evidence.

A. The '096 Patent Is Not Entitled To An Effective Filing Date Based On The 2007 Applications, But It Has Adequate Written Description Based On The 2008 Applications

The asserted claims of the '096 Patent are not entitled to a priority date based on any of the four applications filed between November and December 2007 ("2007 applications") because

[27] As with the Compound Patents, Defendants' burden to prove invalidity of the claims of the Sexual Dysfunction Patent based on prior art is "especially difficult when th[at] prior art was before the PTO examiner during prosecution." *Hewlett-Packard*, 909 F.2d at 1467. During examination of the application that issued as the '096 Patent, the PTO considered WO '232 and U.S. Patent No. 7,144,884, which claims priority to WO '232 and WO '005. (FF ¶¶ 650, 667)

none of the 2007 applications "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). As a result, the earliest potential priority date for the '096 Patent is September 17, 2008 when Plaintiffs submitted to the PTO new applications with additional TESD-related content. (FF ¶ 648)

Plaintiffs assert that the 2007 applications disclose dosing vortioxetine between 1-20 mg, that the doses were therapeutic, that vortioxetine had placebo-like levels of sexually-related adverse effects ("SRAEs," also known as TESDs), and a POSA would have understood all therapeutic doses to have similarly low levels of SRAEs. (D.I. 1059 at 28) Plaintiffs further contend that the 2007 applications explain that prior antidepressants caused TESDs, citing SSRIs and TCAs as specific examples. (*Id.*) None of this, however, would convey to a POSA that vortioxetine would be beneficial for patients who ceased or reduced or have to cease or reduce treatment with an SSRI, SNRI, NRI, or TCA due to SRAEs. (*Id.* at 29-30)

Two passages in the 2007 applications describe sexual issues. The first documents spontaneous reports of sexual adverse effects and how other antidepressants are associated with sexual dysfunction. (PTX-8 at 19:1-20:14) The second posits that vortioxetine "is expected to be without sexual . . . related adverse effects." (*Id.* at 20:32-21:4) Neither passage makes any mention of administering vortioxetine to a patient who has been treated with another antidepressant in one of the four classes called out in the claims. (FF ¶ 646) Nor does either passage reference ceasing or reducing a first medication due to TESD before switching to vortioxetine. (*Id.*) Thus, there is nothing in these passages to suggest to a POSA that the inventors possessed a method that practices the TESD limitations, i.e., prior treatment with a first antidepressant in one of the four classes, ceasing or reducing that medication due to TESD, and

then administering vortioxetine. (FF ¶ 645; *see also generally PowerOasis, Inc. v. T-Mobile USA, Inc*., 522 F.3d 1299, 1310 (Fed. Cir. 2008) ("Obviousness simply is not enough; the subject matter must be disclosed to establish possession."))[28]

While Plaintiffs are not entitled to the 2007 priority date they seek, and this has implications for the prior art-based invalidity defenses discussed below, it does not doom the patent to invalidation for lack of written description. In connection with that defense, Plaintiffs have the benefit of the 2008 applications. The 2008 applications would reasonably convey to a POSA that the inventors had possession of the invention of the claims, including the TESD limitation. (*See* FF ¶ 648)

For these reasons, and the additional reasons supported by the Court's findings of fact, Defendants have failed to prove that the challenged claims of the '096 Patent lack adequate written description.

B. Claim 7 Of The '096 Patent Is Not Anticipated By WO '232 Or WO '005, And Claims 4, 5, And 7 Of The '096 Patent Are Not Anticipated By WO '005

WO '232 and WO '005 do not anticipate any of Claims 4, 5, and 7 of the '096 Patent.

As an initial matter, Defendants appear to concede that WO '232 and WO '005 may only be found to anticipate the claims of the '096 Patent if the Court accepts Plaintiffs' theory as to how Defendants' ANDA Products will infringe the '096 Patent. (*See* D.I. 1011 at 35-36) ("Although WO '232 does not expressly disclose the TESD limitations, if Plaintiffs' infringement positions are credited, then it follows that WO '232 inherently discloses the TESD limitations. . . . As with WO '232, to the extent either of Plaintiffs' infringement theories are credited, WO '005's general disclosure of vortioxetine to treat depression also inherently

[28] The Court need not determine if there are other deficiencies in Plaintiffs' effort to obtain the earlier priority date, as Defendants contend. (*See* D.I. 1011 at 34-35; D.I. 1059 at 30-31)

discloses the TESD limitations and WO '005 inherently anticipates claims 4, 5, and 7 of the '096 patent.") As explained in detail above, the Court has rejected Plaintiffs' attempt to prove Defendants' ANDA Products will infringe the '096 Patent. It follows that, on Defendants' own logic, Defendants' anticipation theory fails too.

Moreover, the disclosures in WO '232 do not disclose the limitations of Claim 7 of the '096 Patent as arranged in the claim. *See Net Money IN*, 545 F.3d at 1371 ("[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102."). WO '232 describes chemical genera encompassing millions of compounds, discloses vortioxetine among 24 preferred compounds, and provides a list of dozens of non-limiting, exemplary acid addition salts that may or may not be combined with the disclosed compounds. (FF ¶ 672) WO '232 does not disclose any particular salt form of vortioxetine. (FF ¶ 673) Dr. Rothschild did not persuasively explain how the separate mentions of vortioxetine and HBr salt in WO '232 would be understood by a POSA as a disclosure of vortioxetine HBr as claimed. (Rothschild Tr. 1672-75) Instead, he testified that in order to reach vortioxetine HBr from WO '232, a POSA could have worked with a chemist regarding salt selection and, in that manner, arrived at vortioxetine HBr. (Rothschild Tr. 1683) This is insufficient in light of the combined 36 organic and inorganic salts listed in WO '232, without disclosure of a preference for any particular one. (FF ¶¶ 672-73; PTX-696 at 9-10)

Also, WO '232 discloses a preferrable range of about 0.1 to 50 mg of the active compound. (FF ¶ 676) While Defendants contend that this is a dosage range that encompasses Claim 7's "about 1 and 20 mg per day" (D.I. 1011 at 35), the prior art disclosed a far broader

range; in the Court's view, it does not disclose the dosage limitation recited in Claim 7. Additionally, as Defendants admit, WO '232 says nothing about any of the disclosed compounds' effects on sexual functioning. (FF ¶ 679; D.I. 1011 at 35)

WO '005 expressly discloses vortioxetine, as the compound "1-[-2-[2,4-dimethylphenylsulfanyl)phenyl]piperazine" (FF ¶ 651); the "hydrobromic acid salt" (FF ¶ 652); a crystalline form with particular peaks and the XRPD at Figure 3 (FF ¶ 653); a dosage range that encompasses "about 1 and 20 mg per day" (FF ¶ 654); administration "orally" (FF ¶ 655); and use for treating depression (FF ¶ 656). As Defendants admit, however, WO '005 does not expressly disclose a method of treating patients with depression, anxiety, abuse, or chronic pain who ceased or reduced or have to cease or reduce treatment with an SSRI, SNRI, NRI, or TCA due to SRAEs. (D.I. 1017 at 32, 36; FF ¶ 660)

Nothing inherent to WO '232 or WO '005 embodies and therefore teaches the TESD limitation of the '096 patent. Because the Court does not credit Plaintiffs' infringement positions, Defendants' anticipation arguments cannot be credited. Defendants have not proven the '096 Patent is invalid for anticipation by WO '232 or WO '005.

C. Claim 7 Of The '096 Patent Is Not Rendered Obvious By WO '232

Defendants contend that even if the Court finds that WO '232 and WO '005 do not anticipate asserted Claims 4, 5, and 7 of the '096 Patent, Claim 7 of the '096 Patent is nevertheless obvious in view of WO '232. (D.I. 1011 at 36-37) As with their anticipation argument related to WO '232, Defendants contend WO '232 has all of the disclosures of Claim 7 of the '096 Patent except the TESD limitation. Defendants contend, nonetheless, that as of the 2008 priority date, a POSA would know that switching antidepressants – exactly what the TESD limitation requires – was one way to address TESD. (*Id.* at 37)

Defendants have not proven that a POSA would have been motivated to select

vortioxetine, or the vortioxetine hydrobromide salt, from the 24 preferred compounds and list of non-limiting exemplary acid addition salts in WO '232. (*See* FF ¶¶ 672-73; Rothschild Tr. 1672-75, 1683) The Court is not persuaded by Dr. Rothschild's testimony combining the 24 preferred compounds with just the six inorganic acid addition salts; Defendants have not proven a POSA would be motivated to limit the salt forms to just the inorganic salts disclosed in WO '232. (FF ¶¶ 672-73; Rothschild Tr. 1672-75, 1683) Even working with a chemist regarding salt selection, a POSA would not have had a reasonable expectation of success to arrive at vortioxetine HBr. (FF ¶¶ 672-73; Rothschild Tr. 1683) WO '232 did not present a small and finite number of predictable options to try. Nor did WO '232 give any direction as to which of the many possible combinations were likely to be successful. *See generally Sanofi-Synthelabo*, 470 F.3d at 1377-78 (stating that salt formation is "an unpredictable exercise").

Moreover, nothing in WO '232 suggests that any of the disclosed compounds would have a low incidence of TESD compared to SSRIs or any other antidepressants, or would have a particular benefit for patients who ceased or reduced or have to cease or reduce use of an SSRI, SNRI, NRI, or TCA due to SRAEs. (FF ¶ 674) Defendants contend that the background of the invention explains that "sexual dysfunction is a side effect common to all SSRIs" and that "[w]ithout addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen," and therefore, the newly-disclosed compounds, which include vortioxetine, suggests to a POSA that vortioxetine may provide a solution to TESD. (D.I. 1011 at 38; Rothschild Tr. 1685-86) Nothing in WO '232, however, discloses or even suggests that the preferred compounds would solve that problem. (FF ¶ 674) Nothing in WO '232 suggests that the preferred compounds should be used as a second-line treatment after the SSRI, SNRI, NRI, or TCA due to SRAEs, as opposed to the preferred compounds being used

as a first-line treatment instead of SNRI, NRI, or TCAs. (FF ¶¶ 680-82)

D. Claims 4, 5, And 7 Of The '096 Patent Are Not Rendered Obvious By WO '005

Defendants further contend that Claims 4, 5, and 7 of the '096 Patent are obvious in view of WO '005. (D.I. 1011 at 36-37) Plaintiffs counter that the disclosure of WO '005 is not limited to vortioxetine hydrobromide because WO '005 lists a free base (non-salt) form of vortioxetine, 29 specifically-named organic salts, the 8-halotheophylline salts, and 6 inorganic salt forms of vortioxetine, including the hydrobromide salt. (D.I. 1059 at 42) Claim 5 of WO '005, however, recites vortioxetine hydrobromide, suggesting (at least) it is a preferred compound. (FF ¶¶ 651-52)

Defendants contend that WO '005 further suggests the use of vortioxetine as a good treatment option to reduce TESD. (D.I. 1011 at 38) WO '005 states:

> It is well known that treatment with anti-depressants in general and SSRIs in particular may be associated with sexual dysfunction and which frequently leads to discontinuation of the treatment. As much as 30-70 % of patients on SSRIs report deficits in sexual function [*J.Clin.Psych.*, 66, 844-848, 2005], which deficits include decreased libido, delayed, reduced or absent orgasms, diminished arousal, and erectile dysfunction. A total of 114 subjects have been exposed to compounds of the present invention in clinical trials; of these 114 subjects, only one subject reported sexual dysfunction. These data suggest that clinical intervention using compounds of the present invention is associated with surprisingly few deficits in sexual functioning.

(DTX-417 at col. 13 line 25 to col. 14 line 2)

In the Court's view, this portion of WO '005 does not disclose key information that a POSA would need in order to understand it to disclose the TESD limitation, including which "compounds of the present invention" subjects were exposed to, the dosage or number of dosages to which subjects were exposed, subject attributes, and details of the study design (such as whether there was a placebo and/or active control). (FF ¶ 657) As Plaintiffs persuasively

argue, the "few sentences in WO '005 about 114 subjects exposed to unidentified compounds would have been insufficient to sway a POSA from the deeply rooted expectation that SRI is linked to TESD." (D.I. 1059 at 42; FF ¶ 662) A POSA in November 2007 and September 2008 would have understood that vortioxetine is a serotonergic antidepressant and would not have been motivated, nor had a reasonable expectation of success, in using it to practice the TESD limitation. (FF ¶ 659)

The clinical study disclosure in WO '005 would teach a POSA that she could prescribe vortioxetine as a first-line treatment. It would not have been obvious to a POSA from WO '005 to switch an MDD patient who had previously taken one of the four types of antidepressants to vortioxetine in order to avoid TESD. (FF ¶ 663)

For all of these reasons, and the additional reasons supported by the Court's findings of fact, Defendants have failed to prove Claims 4, 5, and 7 of the '096 Patent are obvious in view of WO '005.

E. Objective Indicia Of Nonobviousness

With respect to objective indicia of nonobviousness, Plaintiffs "must establish a nexus between the evidence and the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention."). Here, all of Plaintiffs' objective indicia of nonobviousness relate to vortioxetine's purportedly low incidence of TESD relative to other antidepressants. (D.I. 1059 at 43-45) As Plaintiffs admit, however, the claims do not require a reduced incidence of TESD. (*Id.*; s*ee also Kao*, 639 F.3d at 1068) Regardless, the objective indicia relate to the claimed subject matter of using vortioxetine as a second-line treatment for an MDD patient who had previously taken one of the four types of antidepressants in order to avoid TESD. (FF ¶¶

687-92) Thus, the Court concludes Plaintiffs have established a nexus. *See Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) ("Objective evidence of nonobviousness need only be reasonably commensurate with the scope of the claims.") (internal citations omitted)[29]

With respect to long-felt but unmet need, Defendants contend that prior to 2007 and 2008, other antidepressants – such as bupropion, nefazodone, or mirtazapine – alleviated symptoms of sexual dysfunction without compromising efficacy, and the side effects that occur with some of these medications may be beneficial to at least some MDD patients' particular symptoms. (D.I. 1011 at 40) The antidepressants Defendants contend were sufficient did not, however, meet the needs of all patients. (FF ¶¶ 693-94) These antidepressants had many unfavorable side-effect profiles. (FF ¶¶ 695-98) The FDA, as well as the scientific literature at the time, discussed the need for an antidepressant associated with low incidence of TESD. (FF ¶¶ 699-703) Thus, the Court concludes that prior to Trintellix, there was a long-felt need for efficacious and tolerable treatment options for MDD patients who fall within the TESD Limitation. (FF ¶ 704)

As for unexpected results, Plaintiffs assert that Trintellix was known to inhibit serotonin reuptake, and other serotonin-reuptake inhibitors were known to be associated with high rates of TESD; thus, Trintellix's low incidence of TESD was surprisingly beneficial (as demonstrated in clinical studies) for MDD patients who fall within the TESD Limitation. (D.I. 1059 at 45) The Court agrees with Plaintiffs that this was a surprising and unexpected result. (FF ¶ 707)

Regarding praise and recognition, Plaintiffs rely on the FDA's superiority studies in

[29] Defendants' obviousness defenses have been rejected for the reasons already stated. The objective indicia evidence, if established, only further undermines Defendants' showing; defeating Plaintiffs' attempt to prove objective indicia does not in any way strengthen Defendants' case. Hence, even if the Court is wrong about any or all of the objective indicia, the conclusion that the challenged claims are not invalid as obvious would not change.

relation to low incidence of SRAEs. (FF ¶ 708) But the FDA also made critical statements, including that "[n]umerous patients in the vortioxetine group reported worsening on their CSFQ-14 total scores during the study." (FF ¶ 710) The Court is not persuaded that FDA's approval of information equates to industry praise. (FF ¶ 709)

In sum, the objective indicia of nonobviousness support the Court's determination that asserted Claims 4, 5, and 7 of the '096 Patent are not obvious in view of WO '232 and/or WO '005.

VII. Plaintiffs Have Not Proven Infringement Of The Cognitive Impairment Patent

Plaintiffs have not met their burden of proof by a preponderance of the evidence that Defendants will contributorily infringe the '910 Patent.

Claim 6 of the '910 Patent is directed to a method of treating cognitive impairment in a patient diagnosed with MDD wherein the method is comprised of administering a therapeutically effective amount of the hydrobromide salt of vortioxetine and the method alleviates a symptom or complication of cognitive impairment or delays the progression of cognitive impairment. The parties have agreed "a method of treating cognitive impairment . . . in a patient diagnosed with depression" means "a method for the management and care of a patient diagnosed with depression for the purpose of combating cognitive impairment." (D.I. 459-1 at 2)

A substantial non-infringing use is that clinicians will prescribe vortioxetine separate from combating cognitive impairment. (FF ¶ 764) While the parties dispute how often clinicians intend to combat cognitive impairment when prescribing vortioxetine (D.I. 1047 at 93-95; D.I. 1057 at 97), the Court is persuaded by Defendants' evidence that this happens on less than a majority of occasions. (FF ¶¶ 756-58) For example, while Plaintiffs' expert, Dr. Mattingly, sometimes prescribes Trintellix for the purpose of alleviating cognitive impairment (Mattingly Tr. 245-56), and Dr. McIntyre recognized that "clinicians have been using

vortioxetine" for "this purpose" (McIntyre Tr. 1251), this testimony does not establish that a majority of clinicians prescribe vortioxetine for the purpose of alleviating cognitive impairment. The record does not establish that Drs. Mattingly and McIntyre's experiences are representative. (D.I. 1047 at 93; FF ¶ 762) As Dr. Rothschild explained, some – if not many or even most – patients will be prescribed Defendants' ANDA Products for the purpose of treating MDD, not for the purpose of treating cognitive impairment, for reasons including that at least some MDD patients will not even have cognitive symptoms. (FF ¶¶ 756, 763)

Plaintiffs' expert, Dr. Mattingly, testified that a patient may be prescribed vortioxetine for multiple reasons, including efficacy, treatment of cognitive impairment, and TESD experienced on an SSRI, SNRI, or TCA. (Mattingly Tr. 846-47) Whenever a patient is prescribed vortioxetine solely for the purpose of efficacy, or switched to vortioxetine solely due to TESD – which Plaintiffs argue occurs a substantial amount of the time – that patient's use does not infringe Claim 6 of the '910 Patent. (FF ¶ 758) These are substantial non-infringing uses.

Plaintiffs contend vortioxetine's proven reputation for alleviating cognitive impairment in MDD is a major driver of vortioxetine prescriptions, citing the FOCUS and CONNECT clinical trials and literature indicating that no other antidepressant has comparable data showing efficacy in alleviating cognitive impairment in MDD patients (D.I. 1057 at 94) However, the FDA noted Plaintiffs' studies have never established that vortioxetine has special utility for treating cognitive impairment independent of improving depression, or is any better than other antidepressants that improve cognitive function as a result of treating MDD as a whole. (FF ¶¶ 759-60)

Plaintiffs contend that even though "the FOCUS and CONNECT studies were not head-to-head designed to demonstrate superiority from a regulatory perspective," this "does not alter

the fact that they represent the best clinical trial data measuring cognitive function for any antidepressant on the market." (D.I. 1054 at 55) Even accepting this as true, the fact remains that there are substantial uses of Defendants' ANDA Products that will not infringe Claim 6 of the '910 Patent. These substantial uses include that (1) vortioxetine will be prescribed to some patients who do not have cognitive symptoms and (2) vortioxetine will be prescribed for the treatment of MDD for purposes unrelated to cognition. (FF ¶ 757)

Accordingly, Plaintiffs have failed to show that Defendants will contributorily infringe Claim 6 of the '910 Patent.

VIII. Defendants Have Not Proven Claim 6 Of The Cognitive Impairment Patent Is Invalid

A. Claim 6 Is Not Anticipated Nor Rendered Obvious By WO '232

Claim 6 of the '910 Patent recites a method of treatment for cognitive impairment, involving a decline in speed of processing, executive function, attention, or verbal learning and memory, in a patient with MDD. (FF ¶ 771) Defendants[30] contend that Claim 6 of the Cognitive Impairment Patent is anticipated or rendered obvious by WO '232. (D.I. 1011 at 25-26) The Court does not agree that Defendants have proved either invalidity defense by the required clear and convincing evidence.

Defendants essentially acknowledge that their anticipation theory only has merit if the Court is persuaded by Plaintiffs' infringement theory. (*See id.*) ("If Plaintiffs' infringement argument is correct that there is 'no substantial non-infringing use' of vortioxetine, then WO '232 already disclosed the claimed method of using vortioxetine 'for treating cognitive impairment.'") The Court has found, to the contrary, that Plaintiffs failed to prove

[30] As the '910 Patent is not asserted against Sandoz, "Defendants" in connection with any discussion of the Cognitive Impairment Patent refers to Alembic, Lupin, Macleods, Sigmapharm, and Zydus.

infringement. Therefore, WO '232 does not anticipate Claim 6 of the '910 patent.

Defendants' obviousness theory fares little better. WO '232 does not disclose a small and finite number of predictable options. (FF ¶ 773) Nor does it provide any direction as to which of the many possible combinations it discloses were likely to be successful to reach vortioxetine hydrobromide. (*Id*.) Dr. Rothschild did not identify how the separate mentions of vortioxetine and HBr salt in WO '232 would render obvious vortioxetine HBr as claimed. (Rothschild Tr. 1672-75) Dr. Rothschild stated that a POSA would have worked with a chemist on salt selection, but he offered no opinion on how a POSA would have been motivated to select the hydrobromide salt from among the many options disclosed in WO '232. (Rothschild Tr. 1683)

Defendants contend that a POSA also would have known that treating depression with an antidepressant would have treated every symptom of MDD, including any cognitive impairment. (D.I. 1011 at 27) There is nothing in WO '232 that points out why a POSA would have sought to administer vortioxetine hydrobromide for the purpose of combating cognitive impairment in a patient diagnosed with MDD, as opposed to just treating depression generally. (FF ¶¶ 776, 779) To the extent Defendants contend that a POSA's general knowledge or the scientific article Oxman would have provided this motivation, this is unavailing; Defendants rely on WO '232 as their lone obviousness prior art and do not offer a motivation for combining WO '232 with Oxman. (D.I. 1011 at 26)

Further, Dr. Rothschild's motivation and reasonable expectation of success testimony was conclusory and unpersuasive. He does not connect why a POSA would have used the disclosures in WO '232 to develop an antidepressant for the purpose of combating cognitive impairment in a patient diagnosed with MDD, as opposed to just treating depression. (FF ¶¶

781-83)

B. Objective Indicia Of Nonobviousness

As for the objective indicia of nonobviousness, Plaintiffs have demonstrated a sufficient nexus "reasonably commensurate with the scope of the claims." *Rambus Inc.*, 731 F.3d at 1257. Claim 6 requires treating cognitive impairment in a patient with MDD for the purpose of combating that cognitive impairment. The claim does not require improvement in cognition independent of any improvement that comes from improving MDD. Any improvement in cognition that results from improvement in a patient's MDD after administration of vortioxetine for the purpose of combating cognitive impairment is reasonably within the scope of the claim. (FF ¶¶ 785-87)[31]

1. Long-Felt But Unmet Need

Plaintiffs contend that prior to June 2006, clinicians, the FDA, and the scientific literature recognized that many MDD patients continued to experience functional disability due to persistent cognitive deficits even after receiving treatment, and some MDD treatments worsened cognitive functioning. (D.I. 1059 at 49) The Court finds Plaintiffs' evidence on this point to be persuasive. (FF ¶¶ 789-93) SSRIs, SNRIs, NRIs, and TCAs were known to worsen cognitive function (FF ¶ 791), and the need for drugs that addressed cognitive impairment in MDD patients was not met by other medications, such as sertraline, and duloxetine (FF ¶ 794). These earlier antidepressants did not have a statistically significant effect on cognitive deficits in MDD patients and were not effective in treating all four domains of cognition. (FF ¶¶ 794, 796)

[31] As with the other discussions of objective indicia elsewhere in this Opinion, the Court's conclusion that several objective indicia have been established only strengthens the Court's conclusion that the challenged claim has not been proven obvious. If the Court is wrong about the objective indicia evidence, this would in no way alter the Court's conclusion of non-obviousness.

2. Unexpected Results

Because historically antidepressants had not demonstrated an ability to alleviate cognitive impairment in adults with depression, and some worsened cognition, a POSA would not have expected vortioxetine, thought of as an SRI, to alleviate cognitive impairment. (FF ¶¶ 798-99) Placebo-controlled clinical studies on vortioxetine demonstrated a clinically relevant effect on cognitive impairment in MDD. (FF ¶¶ 800-01) This was unexpected, given that SSRIs, SNRIs, NRIs, and TCAs were known to worsen cognitive function. (FF ¶ 791)

3. Skepticism

"If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016). Plaintiffs point to the FDA's initial skepticism about vortioxetine's procognitive effects and how, later, FDA approved inclusion of clinical studies in the Trintellix Prescribing Information. (D.I. 1059 at 50) Eventually, the FDA concluded that these studies were "clinically meaningful" and reflected an improvement in "an important aspect of cognitive dysfunction in depression." (FF ¶ 805)

The Court does not agree, under the circumstances presented here, that the FDA's inclusion of the precognitive clinical studies is the type of skepticism that constitutes objective evidence of non-obviousness. (FF ¶ 807) The FDA's role as a public health agency is to be skeptical. (FF ¶ 806) Plaintiffs did not show skepticism from industry participants or skilled artisans.[32] (FF ¶ 808)

[32] *Neptune Generics, LLC v. Eli Lilly & Co*., 921 F.3d 1372, 1378 (Fed. Cir. 2019), does not compel a different outcome. In *Neptune*, the Federal Circuit affirmed a finding of skepticism based on third parties thinking the invention was impossible and the Patent Trial and Appeal Board ("PTAB") giving weight to skepticism from the FDA. (*Id.*) While this holding shows that FDA skepticism is not irrelevant, it does not require the Court to accord it sufficient weight as to find the objective indicia of skepticism, overall, supports Plaintiffs.

4. Praise and Recognition

Plaintiffs point to praise in scientific literature, from clinicians and patients, and the FDA's PDAC meeting. (FF ¶¶ 809-13) While this evidence is in the record, the Court is not persuaded that, under the circumstances here, it adds up to the type of praise and recognition indicative of non-obviousness. The Baune study was sponsored by Plaintiffs, and some testimonials were from paid consultants. (FF ¶¶ 809-12; McIntyre Tr. 1288-90) Such praise from clinicians compensated by Plaintiffs is not especially persuasive evidence. *See Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) ("[S]elf-referential commendation fall[s] well short of demonstrating true industry praise."). Further, there are millions of patients on antidepressants and tens of thousands of prescribers; testimonials from select individual doctors and patients regarding their impression of the cognitive effects of Trintellix® are also not particularly persuasive evidence of industry praise. (FF ¶ 815) Plaintiffs have not presented the kind of industry praise from competitors that this objective indication often turns on. (FF ¶ 816)

CONCLUSION

Regarding infringement, for the foregoing reasons, the Court concludes: (1) Plaintiffs failed to prove infringement of the Asserted Claims of Crystalline Form Patents by Alembic, Lupin, Macleods, Sigmapharm, and Zydus; (2) Plaintiffs proved infringement of Claim 12 of the '626 Process Patent by Lupin; (3) Plaintiffs failed to prove infringement of the Asserted Claims of the Sexual Dysfunction Patent by Alembic, Lupin, Macleods, Sandoz, Sigmapharm, and Zydus; and (4) Plaintiffs failed to prove infringement of the Asserted Claims of the Cognitive Impairment Patent by Alembic, Lupin, Macleods, Sigmapharm, and Zydus.

Regarding invalidity, for the foregoing reasons, the Court concludes: (1) Sigmapharm and Zydus failed to prove that the Asserted Claims of the Compound Patents are invalid;

(2) Zydus failed to prove that Claim 3 of the ’575 Process Patent is invalid as obvious; (3) Alembic, Lupin, Macleods, Sandoz, Sigmapharm, and Zydus failed to prove that the Asserted Claims of the Sexual Dysfunction Patent are invalid; and (4) Alembic, Lupin, Macleods, Sigmapharm, and Zydus failed to prove that Claim 6 of the ’910 Patent is invalid.

An appropriate order follows.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICTOF DELAWARE

H. LUNDBECK A/S, TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS INTERNATIONAL AG and TAKEDA PHARMACEUTICALS AMERICA, INC.,	
Plaintiffs,	C.A. No. 18-88-LPS (CONSOLIDATED)
v.	
LUPIN LIMITED, et al.,	
Defendants.	

ORDER

At Wilmington this **30th** day of **September, 2021**,

For the reasons stated in the 235-page sealed Opinion issued this same date,

IT IS HEREBY ORDERED:

1. Plaintiffs have not proven that Alembic's ANDA Product infringes claims 1-3 of U.S. Patent No. 8,722,684 ("the '684 Patent"), claims 5-7 of U.S. Patent No. 9,861,630 ("the '630 Patent"), claims 4, 5, and 7 of U.S. Patent No. 9,278,096 ("the '096 Patent"), and claim 6 of U.S. Patent No. 9,125,910 ("the '910 Patent").

2. Plaintiffs have not proven that Lupin's ANDA Product infringes claims 1-3 of the '684 Patent, claims 2-7 of the '630 Patent, claims 4, 5, and 7 of the '096 Patent, and claim 6 of the '910 Patent.

3. Plaintiffs have proven that Lupin's ANDA Product infringes claim 12 of U.S. Patent No. 9,101,626 ("the '626 Patent").

4. Plaintiffs have not proven that Macleods' ANDA Product infringes claim 1 of the '684 Patent, claims 2-4 of the '630 Patent, claim 7 of the '096 Patent, and claim 6 of the '910 Patent.

5. Plaintiffs have not proven that Sandoz's ANDA Product infringes claim 7 of the '096 Patent.

6. Plaintiffs have not proven that Sigmapharm's ANDA Product infringes claims 1-3 of the '684 Patent, claims 2-7 of the '630 Patent, claims 4, 5, and 7 of the '096 Patent, and claim 6 of the '910 Patent.

7. Plaintiffs have not proven that Zydus' ANDA Product infringes claim 1 of the '684 Patent, claims 8-10 of the '630 Patent, claim 7 of the '096 Patent, and claim 6 of the '910 Patent.

8. Sigmapharm and Zydus have not proven that any of claim 17 of U.S. Patent No. 7,144,884 ("the '884 Patent") and claims 5 and 15 of U.S. Patent No. 8,476,279 ("the '279 Patent") are invalid for obviousness.

9. Zydus has not proven that claim 3 of U.S. Patent No. 9,090,575 ("the '575 Patent") is invalid for obviousness.

10. Defendants have not proven that any of claims 4, 5, and 7 of the '096 Patent and claim 6 of the '910 Patent, are invalid for anticipation.

11. Defendants have not proven that any of claims 4, 5, and 7 the '096 Patent, and claim 6 of the '910 Patent, are invalid for obviousness.

12. Defendants have not proven that any of the claims of the '096 Patent are invalid for inadequate written description.

13. Because the Opinion was issued under seal, the parties shall meet and confer and,

no later than Monday, October 4, 2021 submit a proposed redacted version of it, accompanied by a memorandum setting out, with citations to applicable legal authorities, the basis for any proposed redactions. The Court will issue a public version of its Opinion thereafter.

14. The parties shall meet and confer and, no later than October 7, 2021, submit a joint status report, advising the Court of what, if anything, remains to be done in this case.

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT JUDGE