IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA AB, Plaintiff, v. AUROBINDO PHARMA LTD., et al. Defendants.	C.A. No. 14-664-GMS (CONSOLIDATED)

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiff AstraZeneca alleges that pharmaceutical products proposed by defendants Aurobindo Pharma Ltd., Aurobindo Pharma U.S.A., Wockhardt Bio AG, Wochardt USA LLC, Amneal Pharmaceuticals LLC, Sun Pharmaceutical Industries Ltd., Sun Pharmaceutical Industries Ltd., Sun Pharma Global FZE, Mylan Pharmaceuticals Inc., Watson Laboratories, Inc., and Actavis Laboratories FL, Inc. (collectively "Aurobindo") infringe the asserted claims of U.S. Reissue Patent No. RE44,186 ("RE'186 patent" or "the patent-in-suit").[1] The court held a three-day bench trial on September 19, 2016 through September 21, 2016. (D.I. 369-371.) Presently before the court are the parties' proposed finding of fact and conclusions of law concerning the validity of the RE'186 patent, specifically whether the asserted claims are invalid as obvious under 35 U.S.C. § 103. (D.I. 373, 374, 375.)

[1] AstraZeneca asserts claims 25 and 26 of the RE'186 patent. Two additional patents were originally at issue: U.S. Patent No.7,951,400 ("'400 patent") and U.S. Patent No. 8,628,799 ("'799 patent"). Following stipulations dismissing all claims concerning the '400 patent and '799 patent, the court dismissed these cases from the consolidated action: Civil Action Nos. 14-cv-665, 14-cv-666, 14-cv-695, 14-cv-698, and 14-cv-845.

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that the asserted claims of the RE'186 patent are not invalid due to obviousness. These findings of fact and conclusions of law are set forth in further detail below.

II. Findings of Fact[2]

A. The Parties

1. Plaintiff AstraZeneca is a company operating and existing under the laws of Sweden, with its principal place of business at S-151 85 Södertälje, Sweden.

2. Plaintiff's subsidiary, AstraZeneca Pharmaceuticals LP, is a limited partnership operating and existing under the laws of Delaware, with its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803.

3. Wockhardt Bio AG. is a corporation organized and existing under the laws of Switzerland, having a principal place of business at Grafenauweg 6, 6300 Zug, Switzerland.

4. Wockhardt USA LLC is a limited liability company, existing under the laws of the State of Delaware and having a principal place of business at 20 Waterview Boulevard, Parsippany, New Jersey 07054.

5. Wockhardt USA LLC is an indirect subsidiary of Wockhardt Bio AG.

6. Aurobindo Pharma Ltd. is a corporation organized and existing under the laws of India, having a principal place of business of Plot #2, Maitri Vihar, Ameerpet, Hyderabad – 500038, Andhra Pradesh, India.

7. Aurobindo Pharma U.S.A., Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 6 Wheeling Road, Dayton, New Jersey 08810.

8. Aurobindo Pharma U.S.A., Inc. is a wholly owned subsidiary of Aurobindo Pharma Ltd.

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[2] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 338, Ex. A) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional. The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion and Conclusions of Law section of this opinion, preceded by the phrase "the court finds" or "the court concludes."

9. Amneal Pharmaceuticals LLC is a limited liability company, existing under the laws of the State of Delaware and having a principal place of business at 400 Crossing Boulevard, Third Floor, Bridgewater, New Jersey 08807.

10. Sun Pharmaceutical industries Ltd. is a company organized and existing under the laws of India, having a principal place of business at Acme Plaza, Andheri-Kurla Rd., Andheri (E), Mumbai – 400 059, India.

11. Sun Pharma Global FZE is a company organized and existing under the laws of the United Arab Emirates, having a principal place of business at Executive Suite #43, Block Y, SAIF Zone, P.O. Box 122304, Sharjah, United Arab Emirates.

12. Sun Pharma Global FZE is a wholly-owned subsidiary of Sun Pharma Global Inc., a corporation organized and existing under the laws of the British Virgin Islands, which in turn is a wholly-owned subsidiary of Sun Pharmaceutical Industries Ltd.

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

14. Watson Laboratories, Inc. is a corporation organized and existing under the laws of Nevada, having a principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey 07054.

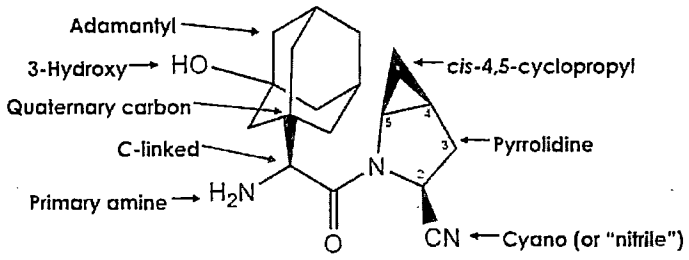
15. Actavis Laboratories FL, Inc. (f/k/a Watson Laboratories, Inc. – Florida) is a corporation organized and existing under the laws of Florida, having a principal place of business at 4955 Orange Drive, Davie, Florida 33314.

16. The court has subject matter jurisdiction and personal jurisdiction over all parties.

B. Background

1. These consolidated actions arise out of Defendants' submission of several Abbreviated New Drug Applications ("ANDAs") under § 505(j) of the Federal Food, Drug and Cosmetic Act to the United States Food and Drug Administration ("FDA"), seeking approval to market and sell generic saxagliptin pharmaceutical drug products prior to the expiration of AstraZeneca's RE'186 patent.

2. Saxagliptin is chemical compound that is an FDA-approved DPP4 inhibitor that has been used to treat type 2 diabetes. Saxagliptin has the following chemical structure:



3. Saxagliptin's structure includes a *cis*-4,5-cyclopropyl group fused to a cyanopyrrolidine ring. The resulting *cis*-4,5-cyclopropyl-cyanopyrrolidine moiety represents the P1 group. Saxagliptin also contains a 3-hydroxyadamantyl group that is *C*-linked through a quarternary carbon (a carbon with four non-hydrogen groups attached to it) to the peptide backbone, resulting in primary amine. The *C*-linked 3-hydroxyadamantyl glycine moiety represents the P2 group.

4. AstraZeneca is the holder of New Drug Application ("NDA") No. 022350, by which the FDA granted approval for the marketing and sale of 2.5 mg and 5 mg strength saxagliptin hydrochloride tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

5. AstraZeneca markets 2.5 mg and 5 mg strength saxagliptin hydrochloride tablets in the United States, through its Delaware subsidiary AstraZeneca Pharmaceuticals LP, under the trade name "Onglyza®."

6. Pursuant to 21 U.S.C. § 355 and attendant FDA regulations, the RE'186 patent is listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") with respect to Onglyza®.

7. The Orange Book includes 2.5 mg and 5 mg strength Onglyza® together with the RE'186 patent.

8. AstraZeneca is the holder of NDA No. 200678, by which the FDA granted approval for the marketing and sale of 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg strength saxagliptin hydrochloride and metformin hydrochloride extended release tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

9. AstraZeneca markets 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg strength saxagliptin hydrochloride and metformin hydrochloride extended release tablets in the United States, through its Delaware subsidiary AstraZeneca Pharmaceuticals LP, under the trade name "KombiglyzeTM XR."

10. Pursuant to 21 U.S.C. § 355 and attendant FDA regulations, the RE'186 patent is listed in the Orange Book with respect to Kombiglyze TM XR.

11. The Orange Book includes 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg strength KombiglyzeTM XR together with the RE'186 patent.

C. The Patent-in-Suit

1. U.S. Reissue Patent Number RE44, 186 ("the RE'186 patent"), issued on April 30, 2013, and is entitled "Cyclopropyl-fused pyrrodlidine-based inhibitors of dipeptidyl peptidase IV and method." The RE'186 patent names Jeffrey A. Robl, Richard B. Slusky, David J. Augeri, David R. Magnin, Lawrence G. Hamann, and David A. Betebenner as inventors.

2. AstraZeneca is the assignee of the RE'186 patent.

3. AstraZeneca is the owner by assignment of the RE'186 patent. AstraZeneca has standing to bring suit on the RE'186 patent.

4. U.S. Application No. 13/308,658 ("the '658 Application"), which issued as the RE'186 patent, was filed with the United States Patent and Trademark Office ("PTO") on December 1, 2011.

5. The RE'186 patent is a reissue of U.S. Patent No. 6,395,767 ("the '767 patent"), which originally issued on May 28, 2002.

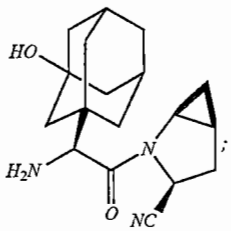
6. The '767 patent was filed on February 16, 2001 and claims priority to provisional application 60/188,155 ("the '155 application) filed on March 10, 2000.

1) The Asserted Claims

7. AstraZeneca has asserted infringement of claims 25 and 26 of the RE'186 patent against each defendant.

i. RE'186 Patent, Claim 25

8. Claim 25 of the RE'186 patent reads: A compound that is



or a pharmaceutically acceptable salt thereof.

ii. RE'186 Patent, Claim 26

9. Claim 26 of the RE'186 patent reads: The compound as defined in claim 25, wherein the pharmaceutically acceptable salt is the hydrochloride salt.

10. Claim 26 is directed to the single compound saxagliptin hydrochloride salt.

D. Procedural History

1. On May 23, 2014, AstraZeneca filed suit against Aurobindo asserting infringement of the RE'186 patent. (Civil Action No. 1:14-cv-1469-GMS (D.I. 1).)

2. In a Complaint dated May 23, 2014, AstraZeneca filed suit against Wockhardt asserting infringement of the RE'186 patent and the '400 patent. (Civil Action No. 1:14-cv-667-GMS (D.I. 1).

3. In a Complaint dated August 15, 2014, AstraZeneca filed suits against Watson, Actavis, Inc., and Actavis LLC asserting infringement of the RE'186 patent and the '400 patent. (Civil Action No. 1:14-cv-1051-GMS (D.I. 1).)

4. In a Complaint dated June 2, 2014, AstraZeneca filed suit against Sun Pharma asserting infringement of the RE'186 patent and the '400 patent. (Civil Action No. 1:14-cv-694-GMS (D.I. 1).)

5. In a Complaint dated June 2, 2014, AstraZeneca filed suit against Mylan asserting infringement of the RE'186 patent and the '400 patent. (Civil Action No. 1:14-cv-696-GMS (D.I. 1).)

6. In a Complaint dated June 2, 2014, AstraZeneca filed suit against Amneal asserting infringement of the RE'186 patent and the '400 patent. (Civil Action No. 1:14-cv-697-GMS (D.I. 1).)

7. In a Complaint dated October 31, 2014, AstraZeneca filed suit against Actavis Laboratories FL, Inc., Actavis, Inc., and Actavis LLC asserting infringement of RE'186 patent and the '799 patent. (Civil Action No. 1:14-cv-1356-GMS (D.I. 1).)

8. The Plaintiff's patent infringement claims against Aurobindo, Amneal, Wockhardt, Sun Pharma, Mylan, Watson, and Actavis were consolidated under Civil Action No. 14-664 on October 8, 2014.

9. On October 8, 2014, the court consolidated Civil Action Nos. 14-cv-664, 14-cv-665, 14-cv-666, 14-cv-667, 14-cv-694, 14-cv-695, 14-cv-696, 14-cv-697, 14-cv-698, 14-cv-845, and 14-cv-1051.[3] (Civil Action No. 1:14-cv-664-GMS (D.I. 23).)

10. On November 17, 2014, AstraZeneca, Actavis Laboratories FL, Inc., Watson, Actavis, Inc. and Actavis LLC jointly filed a Stipulated Order to Consolidate Civil Action No. 14-cv-1356 with

[3] The consolidated action originally involved the RE'186 patent, U.S. Patent No. 7,951,400 ("'400 patent"), and/or U.S. Patent No. 8,628,799 ("'799 patent"). Following stipulations dismissing all claims concerning the '400 and '799 patents (formulation patents), Civil Action Nos. 14-cv-665, 14-cv-666, 14-cv-695, 14-cv-698, and 14-cv-845 were dismissed from the consolidated action.

Consolidated Civil Action No. 14-cv-664, (Civil Action No. 1:14-cv-1356-GMS (D.I. 7)), which the court granted on November 19, 2014. (D.I. 8.)

11. On January 23, 2015, AstraZeneca and Aurobindo jointly filed a Stipulated Order to Consolidate Civil Action No. 14-cv-1469 with Consolidated Civil Action No. 14-cv-664 (Civil Action No. 1:14-cv-1469-GMS, D.I. 12), which the court granted on January 27, 2015. (D.I. 13.)

12. On January 27, 2015, AstraZeneca, Watson, Actavis, Inc., and Actavis LLC jointly filed a Stipulated Order of Dismissal to dismiss Watson Laboratories Inc., Actavis, Inc., and Actavis LLC without prejudice from Civil Action No. 1:14-cv-1051. The court granted the Stipulation on January 27, 2015. (D.I. 19.)

13. On January 27, 2015, AstraZeneca, Actavis Laboratories FL, Inc., Watson, Actavis, Inc., and Actavis LLC jointly filed a Stipulated Order of Dismissal to dismiss Watson Laboratories Inc., Actavis, Inc., and Actavis LLC without prejudice from Civil Action No. 1:14-cv-1356. The court granted the Stipulation on January 27, 2015. (D.I. 10.)

14. The court held a three-day bench trial in this matter on September 19 through September 21, 2016. (D.I. 369-371.) Aurobindo stipulated to infringement of all asserted claims. Thus, the sole issue is Aurobindo's obviousness defense with respect to the RE'186 patent.

III. Discussion and Conclusions of Law

These consolidated cases arise under the patent laws of the United States, 35 U.S.C. §§ 1331, 1338, 2201, and 2202. Venue is proper in this court under 28 U.S.C. 1391(b) and (c), and 1400(b). The defendants challenge the validity of the RE'186 patent as obvious in light of the prior art. After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that the defendants have failed to establish by clear and convincing evidence that the asserted claims of the RE'186 patent would have been obvious to a person of ordinary skill in the art as of the February 16, 2001 filing date. The asserted claims of the RE'186 patent are valid under 35 U.S.C. § 103. Aurobindo's Rule 52(c) motion is denied and AstraZeneca's Rule 52(c) motion is granted. The court's reasoning follows.

A. Obviousness

1) The Legal Standard

A patent may not be obtained "if the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art" ("POSA"). 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson–Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"A patent shall be presumed valid." 35 U.S.C. § 282(a). A party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence[4] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit teaching, suggestion, or motivation in the prior art, the "TSM test," in order to find

[4] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp. v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

obviousness. *See id.* at 415. The *KSR* Court acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 200).

2) Level of Ordinary Skill in the Art

The court must first determine the level of ordinary skill in the art at the time of the filing of the RE'186 patent. The parties agree that a person of ordinary skill in the art relevant to the RE'186 patent is a medicinal chemist with (1) a Ph.D. in chemistry and several years of practical experience working with pharmaceutical chemical compounds for potential and eventual clinical use in patients; or (2) a Bachelor's or Master's degree in chemistry with significantly more experience.[5] The court concludes that the parties' definitions of ordinary skill in the art do not differ in a meaningful way.[6]

[5] The defendants' description of a person of ordinary skill in the art is derived from Dr. Powers' testimony. (Tr. 88:2-10 (Powers).) The plaintiff's identification of a person of ordinary skill in the art is derived from Dr. Weber's testimony. (Tr. 203:19-204:9 (Weber).)

[6] Dr. Weber disagreed with Dr. Powers' definition of a POSA, because he omitted the "fundamental" qualification captured in the last sentence of her definition: familiarity with the spectrum of properties needed for a

3) The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

The court will consider whether Aurobindo has established a *prima facie* case of obviousness in light of the evidence adduced at trial. To establish a *prima facie* case of obviousness in cases involving new chemical compounds, the accused infringer must identify a known "lead" compound, a reason for selecting that compound, and "some reason that would have led a chemist to modify a known compound" in a way that leads to the claimed invention. *Bristol–Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). Aurobindo argues that the asserted claims were obvious for three reasons: (1) a person of ordinary skill in the art would have been motivated to select vildagliptin[7] as a lead compound; (2) a person of ordinary skill in the art would have been motivated to move the hydroxyadmantyl group; and (3) a person of ordinary skill in the art would have added a cyclopropyl ring. The court addresses each of these arguments in turn.

i. Selection of Vildagliptin as a Lead Compound

To establish a *prima facie* case of obviousness, Aurobindo must first establish that the POSA would have selected a given lead compound. *See Takeda*, 492 F.3d 1350, 1360 (Fed. Cir. 2007); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1379 (Fed Cir. 2006). Aurobindo argues that a POSA would have been motivated to select vildagliptin as a lead compound. (D.I. 374 at 10-12.) Aurobindo relies on the testimony of Dr. Powers and contends that vildagliptin was a likely lead compound because it demonstrated good potency, a favorable class history, and efficacy in biological data. (*Id.* at 11.) Aurobindo maintains, given the literature

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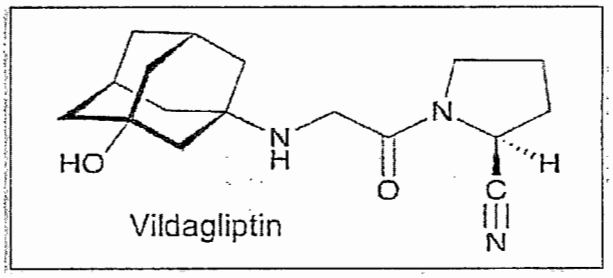
successful drug, the potential difficulties in obtaining them, and potential effects of pharmaceutics in the body. Dr. Weber underscored that Dr. Powers has no relevant experience in the field of reversible DPP-4 inhibitors, has not published in the field, and has no experience with human clinical trials. AstraZeneca contends that Dr. Power is not a POSA. At trial, the court recognized Dr. Powers as a POSA.

[7] AstraZeneca refers to this compound by Villhauer-063 Ex. 1, but the court will refer to it as "vildagliptin" for convenience, unless it is necessary to distinguish among prior art Villhauer compounds.

on potent and stable DPP4 inhibitors, a POSA would have recognized that vildagliptin structurally met the criteria of a lead compound. (*Id.*) Aurobindo contends *in vitro* tests showed good potency in human plasma. (*Id.*) Particularly, Aurobindo notes that of the three compounds with reported potency data as of the priority date, vildagliptin showed at least two-fold greater potency. (*Id.* at 11-12.)



In contrast, AstraZeneca argues that there is no reason, absent the use of hindsight, that the POSA would have selected vildagliptin as a lead compound. (D.I. 373 at 10 Tr. 199:7-18, 209:6-20, 225:5-24 (Weber).) AstraZeneca relies on Dr. Weber's testimony noting that vildagliptin was not the natural choice for further development in light of data on two more advanced compounds that had already entered the clinic: Probiodrug's compound P32/98 and Novartis' compound NVP-DPP728. (Tr. 199:7-18, 209:6-20, 225:5-24 (Weber).) According to Dr. Weber, P32/98 and NVP-DPP728 were the only two compounds that had advanced into the clinic. (Tr. 208:22-209:20 (Weber).) Dr. Weber further testified that *in vivo* data trumps *in vitro* data, but the ultimate data is human data. (Tr. 209:6-17 (Weber).) In addition, AstraZeneca argues there was no reason to choose vildagliptin (Villhauer-063 Ex. 1) over other prior art Villhauer compounds. (D.I. 373 at 10.)

The court agrees that Aurobindo fails to demonstrate that a POSA would have selected vildagliptin as a lead compound. Lead compound analysis "requires the challenger to demonstrate . . . that one of ordinary skill in the art would have had a reason to select a proposed lead compound

or compounds over other compounds in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd,* 619 F.3d 1346, 1354 (Fed. Cir. 2010). In the court's view, Aurobindo's lead compound analysis is flawed because their expert narrowly focused on potency. The plaintiff's expert Dr. Weber testified that a POSA would have considered other pharmacokinetic and pharmacodynamics properties involved in what determines the final dose of a compound, not simply potency. (Tr. 214:8-215:8 (Weber).)

Furthermore, the court finds that a POSA would not have ignored the human clinical data of compound P32/98 and compound NVP-DPP728 in favor of limited *in vivo* rat data. This specific error reveals the taint of hindsight bias in Dr. Powers' analysis of the prior art. Dr. Powers admitted that NVP-DPP728 was a "perfectly reasonable lead compound", Tr. 97:6- 16 (Powers), and that, in forming his opinion, he did not consider that NVP-DPP728 had actually been shown to be effective in humans. (Tr. 143:6-10 (Powers); Tr. 339:4-11 (Weber).) The experts agree that instability due to a cyclization was a serious problem for DPP4 inhibitors in 2000. (Tr. 112:14 - 113:7 (Powers); Tr. 212:17-22 (Weber).) Because a POSA would have recognized that P32/98 did not suffer from the chemical instability problem in the art, Tr. 211:13-21 (Weber), the court finds that P32/98 would have also been a natural lead.

The court also considers it important that prior art references included later Novartis compounds that were just as potent and that also incorporated Ashworth II's "optimum" P1 group. (Tr. 141:11-142:4 (Powers); PTX-2066 at 3; JTX-126 at 2-3.) Aurobindo has not shown why one skilled in the art would have ignored the more recent advances of the compound in making a lead compound selection. The court is not persuaded by the biological data—insulin response in an animal model— because several compounds in the Villhauer patents had better insulin response in the *in vivo* rat assay than Villhauer-063 Ex. 1. (JTX-49 at 4, PDX-223.)

Dr. Powers' approach to the lead compound analysis fatally undermines his credibility. Dr. Powers did not perform an analysis of the art as a whole. (D.I. 373 at 7.) Instead, Dr. Powers initially looked at the chemical structure of saxagliptin. Then, with that structure in mind, Dr. Powers looked to a selection of prior art ***handpicked*** by Aurobindo's counsel in order to select the compound for his obviousness analysis. (Tr. 122:9-123:6 (Powers).) This is evidence of classic hindsight bias. Based on the Dr. Weber's testimony, the court concludes that a POSA would have considered P32/98 and NVP-DPP728 in addition to several other lead compounds.

ii. First Modification of Vildagliptin

Even accepting Aurobindo's selection as lead compound, the court finds that Aurobindo has not established by clear and convincing evidence that modifying the lead to yield saxagliptin would have been obvious to a POSA. *See Daiichi* at1352 ("Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old.").

Aurobindo argues the POSA would have moved the hydroxyadamantyl group from the nitrogen of the glycine to the *alpha*-carbon of the glycine in order to improve potency. Dr. Powers testified that a person of ordinary skill would have been motivated to do so because the prior art taught that DPP4 preferred bulky groups, with a free amino group, at its P_2-substrate binding pocket. (Tr. 79:13-14 (Powers).) According to Aurobindo, a POSA would have been motivated to make this modification for three reasons directed to increasing the potency of the molecule: (1) primary amines more closely resemble the natural substrates for DPP4, (2) beta-branching was known to increase potency, and (3) primary amines were generally more potent than secondary

amines. (D.I. 374 at 14.) Specifically, Aurobindo relies on the teachings of Mentlein (JTX-57) and Ashworth I (JTX-50). Mentlein disclosed that natural substrates of DPP4 enzymes are peptides with primary amines at N-terminus. (JTX-57 at 5.) Ashworth I taught that the most potent, reversible DPP4 inhibitors were primary amines. (JTX-53 at 4-5.)

AstraZeneca responds that there was no such motivation and no reasonable expectation of success in making this modification. (D.I. 373 at 14-16.) Dr. Weber testified that the prior art taught away from eliminating *N*-linkage from vildagliptin because it would have been a step backwards to abandon what was perceived to be the stabilizing feature of the compound. (D.I. 373 at 35; Tr. 223:9-12, Tr. 262:5-12 (Weber).) Dr. Weber maintains that one skilled in the art would have been dissuaded from making Dr. Powers' proposed change, because it was recognized that the Novartis *N*-linked compounds already had good potency and stability. (Tr. 267:6-14 (Weber).)

The court finds that Dr. Powers failed to show a motivation to move the hydroxadamantyl group of his lead compound with any reasonable expectation of success. *See Medichem, S.A. v. Rolablo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (When prior art "suggest that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant the piece of prior art is said to 'teach away' from the claimed invention.). The limited structural information on moving from *N*-linkage to *C*-linkage, the existence of sufficiently potent compounds, and the inconsistency with an established solution to the stability problem in the field all demonstrate that Dr. Weber is the more credible of the experts on the proposition. Consequently, the court concludes this proposed modification would not have been obvious.

iii. Second Modification of Vildagliptin

Next, Aurobindo argues that a POSA would have expected to counteract the potential loss of stability that results from modifying vildagliptin to improve potency by creating a primary amine. (Tr. 110:117-111:18 (Powers); D.I. 374 at 16.) Aurobindo claims a POSA would have tried the simplest modification to cause rigidity and strain to the compound—adding a 4,5 cyclopropyl ring—in order to address the stability problem. (D.I. 374 at 16.) Aurobindo reasons that a POSA would have been aware of and used the known method of synthesis provided by the Hanessian 1998 reference in order to make the 4,5 cyclopropyl modification. (D.I. 374 at 17; JTX-51.) Aurobindo also argues that selection of the point of attachment for the cyclopropyl ring would have been straightforward for a POSA.

Aurobindo's analysis is flawed. First, Dr. Powers failed to explain why a POSA would introduce the problem of instability into a DPP4 inhibitor by moving from *N*-linkage to *C*-linkage and then adding a cyclopropyl group to solve the newly created stability problem. The combination of "several sequential modifications" is not obvious where there is no reason in the prior art to make the subsequent modification. *See Pfizer Inc., v. Mylan Pharm. Inc.*, 71 F. Supp. 3d 458, 473 (D. Del. 2014), *aff'd*, 628 F. App'x 764 (Fed. Cir. 2016). Because there was no reason to make the first modification, this second modification is nonobvious.

Second, Aurobindo has not shown a motivation to try cyclopropanation. The dearth of data as of the priority date is particularly troubling. AstraZeneca highlighted that there were no data available to show the effect of cyclopropanation on the stability of a DPP4 inhibitor, because no one other than the inventors proposed cycloproponation in the context of DPP4 inhibitors. (Tr. 228:2-8 (Weber); D.I. 373 at 16.) The court is not convinced that a POSA would look to the ACE inhibitor literature for guidance in designing a DPP4 inhibitor. AstraZeneca maintains that Dr.

Powers' proposed modification is contraindicated in the prior art, which clearly favored a five-membered ring at the P_1 position. (D.I. 373 at 16; JTX-51.) Dr. Weber testified that the prior art taught that increasing the ring size or adding a carbon to the ring was detrimental to potency. (Tr. 228:22-25, 236:7-237:5 (Weber).) Specifically, Dr. Weber discussed two prior art publications: the Augustyns 1997 (JTX-125) and Ashworth II (JTX-126) references. These publications conclude that adding a cyclopropyl group to the five-member pyrrolidine rings was not something a POSA would want to do. (Tr. 236:33-237:5, 240:13-25 (Weber).) Therefore, the court concludes that the prior art does not suggest a motivation to add a cyclopropyl.

Third, Dr. Powers has failed to show a reasonable probability of success with this second modification. Although Aurobindo argues there were a limited number of options for positions to try cyclopropanating the five-membered ring, the experts agreed there was no way to predict from the prior art what the effect of cyclopropanation would be. (Tr. 249:17-250:3 (Weber); Tr. 115:19-116:6 (Powers).) In fact, Dr. Powers testified that there would not be a reasonable expectation of success in adding cyclopropyl: "it would not be obvious to say that . . . because it worked with ACE that it would give a better inhibitor with DPP-4. But I think it would be very optimistic." (Tr. 115:19-116:6 (Powers).)

Given the evidence adduced at trial, the court is convinced the prior art would not motivate a POSA to make the selection of vildagliptin, along with the proposed modifications. It remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound. *Takeda*, 492 F.3d at 1356-57. Here, the court finds that Dr. Powers' alleged motivations are at odds with the teachings of the prior art and, again, appear to be the product of a classic hindsight analysis. The court concludes asserted claims of the RE'186 patent are not obvious.

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In sum, Aurobindo has failed to present a *prima facie* case that the asserted claims of the patent-in-suit are invalid as obvious. [8]

B. AstraZeneca's Request for Attorney's Fees

Section 285 of the Patent Act provides that "[t]he court in exceptional cases may award reasonable attorney fees to the prevailing party." 35 U.S.C. § 285. The court has discretion to determine that a case is "exceptional" if under the totality of the circumstances, it is "simply one that stands out from others with respect to the substantive strength of a party's litigating position." *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 134 S.Ct. 1749, 1756 (2014). A litigant must prove entitlement to an award of attorney fees by a preponderance of the evidence. *Id.* at 1758.

AstraZeneca argues that this is an exceptional case because of the substantive weakness of Aurobindo's litigating position, and, therefore, AstraZeneca should be awarded its reasonable attorney fees. (D.I. 373 at 40.) AstraZeneca accurately notes that Aurobindo's case-in-chief suffered from hindsight bias and contradictions with the prior art. These facts, however, do not mandate a finding that this case is exceptional. This case, like most ANDA cases, hinged on the credibility of the expert witnesses, not a substantively weak litigation position. Although an exceptional case finding is no longer constrained to "inequitable conduct before the PTO; litigation misconduct; vexatious, unjustified, and otherwise bad faith litigation; a frivolous suit or willful infringement," *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1034 (Fed. Cir. 2002), the absence of such conduct also weighs against an award in this case. Under the totality

[8] Because Aurobindo has failed to establish a prima facie case of obviousness, the court does not address AstraZeneca's secondary considerations. *See Graham*, 383 U.S. at 17-18.

of the circumstances, the court finds that this is not an exceptional case and denies AstraZeneca's request for an award of attorney's fees.

IV. CONCLUSION

For the reasons stated above, the court concludes that none of the asserted claims of the patent-in-suit are invalid due to obviousness.

DATED: February 2, 2017

UNITED STATES DISTRICT JUDGE