Trials@uspto.gov
571-272-7822

Paper No. 79
Entered: August 18, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG, TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A. INC., and SUN PHARMACEUTICALS INDUSTRIES, LTD., SUN PHARMA GLOBAL FZE
and AMNEAL PHARMACEUTICALS LLC,
Petitioners,

v.

ASTRAZENECA AB,
Patent Owner.

Case IPR2015-01340
Patent RE44,186 E[1]

Before MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judge*, RAMA G. ELLURU and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

Opinion for the Board filed by Administrative Patent Judge ELLURU.

Opinion Concurring filed by Vice Chief Administrative Patent Judge TIERNEY.

ELLURU, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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[1] Wockhardt from IPR2016-01029, Teva from IPR2016-01122, Aurobindo from IPR2016-01117, and Sun/Amneal from IPR2016-01104 have each been joined as a Petitioner to this proceeding.

I. INTRODUCTION

A. Background

Mylan Pharmaceuticals Inc. ("Mylan") filed a Petition to institute an *inter partes* review of claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of U.S. Patent No. RE44,186 E (Ex. 1001, "the '186 patent"). Paper 3, 17 ("Pet."). Astrazeneca AB ("Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp."). We subsequently ordered Mylan to respond to certain arguments raised in the Preliminary Response. Paper 10. Mylan filed an authorized Reply to Patent Owner's Preliminary Response. Paper 11.

We initially denied institution of an *inter partes* review of all the challenged claims. Paper 12, 14. Mylan subsequently filed a Request for Rehearing. Paper 13. On May 2, 2016, we granted the Request for Rehearing in an Order (Paper 15) and concurrently instituted an *inter partes* review of all the challenged claims (Paper 16, 34–35 ("Dec.")). Patent Owner timely filed a Response to the Petition. Paper 28 ("PO Resp."). Mylan subsequently timely filed a Reply to Patent Owner's Response. Paper 41 ("Pet. Reply").

Subsequent to our Institution Decision, Wockhardt Bio AG ("Wockhardt"), Teva Pharmaceuticals USA, Inc. ("Teva"), Aurobindo Pharma U.S.A., Inc. ("Aurobindo"), and Sun Pharmaceutical Industries, Ltd., Sun Pharma Global FZE, and Amneal Pharmaceuticals LLC ("Sun/Amneal") (collectively, "follow-on Petitioners") each filed separate follow-on Petitions for *inter partes* review challenging claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent based on the same grounds of unpatentability presented by Mylan. *See* IPR2016-01029, Paper 1 (Wockhardt Petition); IPR2016-01122, Paper 1 (Teva Petition); IPR2016-

01117, Paper 1 (Aurobindo Petition); IPR2016-01104, Paper 3 (Sun/Amneal Petition). Each of the follow-on Petitioners also requested joinder with the *inter partes* review initiated based on Mylan's Petition. Pursuant to 35 U.S.C. § 315(c), we determined that the follow-on Petitions warranted institution and joined the follow-on Petitioners as parties to this proceeding, subject to the requirement that all Petitioners would present consolidated filings, evidence, and arguments, and not seek any additional discovery from Patent Owner.[2] *See* Papers 34, 38, 39, and 53.

Petitioners rely on the Declarations of Dr. David P. Rotella (Exs. 1003 (in support of Pet.), 1074 (in support of Pet. Reply)), Dr. Robert J. Tanenberg (Ex. 1041), and Dr. Deforest McDuff (Ex. 1060). Patent Owner relies on the Declarations of Dr. Ann E. Weber (Ex. 2056), Dr. M. James Lenhard (Ex. 2057), Dr. Christine S. Meyer (Ex. 2059), and Dr. Jeffrey Robl (Ex. 2173).

An oral hearing for this proceeding was held on January 25, 2017, a transcript of which has been entered in the record. Paper 77 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine Petitioners have not established, by a preponderance of the evidence, that claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent are unpatentable.

[2] Mylan, Wockhardt, Teva, Aurobindo, and Sun/Amneal will be collectively referred to as "Petitioners" in this Decision.

B. Related Proceedings

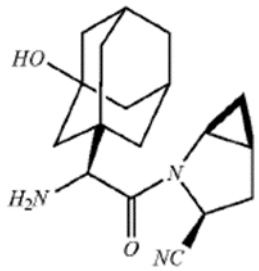
Petitioners and Patent Owner identify the following district court proceedings involving the '186 patent: *AstraZeneca AB v. Mylan Pharmaceuticals Inc.*, 14-cv-00696 (D. Del. 2014); *AstraZeneca AB v. Mylan Pharmaceuticals Inc.*, 14-cv-00094 (D.W. Va. 2014); *AstraZeneca AB v. Aurobindo Pharma Ltd. et al.*, 14-cv-01469 and 14-cv-00664 (D. Del 2014); *AstraZeneca AB v. Actavis Laboratories FL, Inc.*, 14-cv-01356 (D. Del. 2014); *AstraZeneca AB v. Sun Pharma Global FZE et al.*, 14-cv-00694 (D. Del. 2014); *AstraZeneca AB v. Amneal Pharmaceuticals LLC.*, 14-cv-00697 (D. Del. 2014); and *AstraZeneca AB v. Wockhardt Bio AG et al.*, 14-cv-00696 (D. Del. 2014). Pet. 16; Paper 2; Paper 5, 1. Patent Owner additionally identifies *AstraZeneca AB v. Watson Laboratories, Inc.*, 14-cv-00666 (D. Del. 2014) as involving the '186 patent. Paper 5, 1.

C. The '186 Patent (Ex. 1001)

The '186 patent is directed to "cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV (DP-4) ["DP 4"], and to a method for treating diabetes." Ex. 1001, 1:19–21. DP 4 is responsible for the metabolic cleavage of certain endogenous peptides including glucagon. *Id.* at 1:34–42. Glucagon is a peptide with multiple physiologic roles, including the stimulation of insulin secretion, the promotion of satiety, and the slowing of gastric emptying. *Id.* at 1:44–48. Glucagon is rapidly degraded in the body, primarily by DP 4-mediated enzymatic cleavage. *Id.* at 1:55–64. Inhibitors of DP 4 *in vivo* may, therefore, increase endogenous levels of glucagon, and serve to ameliorate the diabetic condition. *Id.* at 1:64–67.

D. Illustrative Claim

We instituted a review of claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42. Claims 1, 8, 10, 25, 32, and 39 are independent claims. For purposes of this Decision, claim 25 is illustrative of the challenged claims and is drawn to the compound shown below, or a pharmaceutically acceptable salt thereof.



Id. at 91:18–33. The illustrated compound is known as (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile or "saxagliptin."[3] *See* Pet. 3; Ex. 1003 ¶ 15; Ex. 2047, 9[4]. Petitioners state that each claim challenged under "Ground 1," claims 1, 2, 4, 6–11, 25–28, 32–35, 39, and 40, either defines the saxagliptin compound or includes saxagliptin within its scope. Pet. 22–23. Petitioners further contend that the species of claim 25 is obvious over the prior art, and thus, broader claims which also encompass the species are also obvious. Pet. 3–4 (citation omitted). All the challenged claims are directed to compounds, compositions, and methods relating to the specific compound recited in claim 25. *See* Pet. 4–5, 22–23; PO Resp. 68–69; Tr. 7:12–8:5. Thus, our

[3] Saxagliptin is the active pharmaceutical ingredient in two FDA-approved drugs, Onglyza and Kombiglyze XR, for the treatment of diabetes. PO Resp. 1.

[4] Cites to exhibits refer to a document's original page numbers.

inquiry focuses on whether Petitioners have shown by a preponderance of the evidence that claim 25 would have been obvious to a skilled artisan. We determine, for the reasons explained below, that Petitioners have not carried their burden.

E. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following asserted references.

Ashworth et al., *2-Cyanopyrrolidides as Potent, Stable Inhibitors of Dipeptidyl Peptidase IV*, 6(10) BIOORGANIC & MED. CHEM. LETT. 1163–66 (1996). Ex. 1007 ("Ashworth I").

Villhauer, WO 98/19998, published May 14, 1998. Ex. 1008 ("Villhauer").

Raag, et al., *Crystal Structures of Cytochrome P-450$_{CAM}$ Complexed with Camphane, Thiocamphor, and Adamantane: Factors Controlling P-450 Substrate Hydroxylation*, 30 BIOCHEM. 2647–84 (1991). Ex. 1009 ("Raag").

Hanessian et al., *The Synthesis of Enantiopure w-Methanoprolines and w-Methanopipecolic Acids by a Novel Cyclopropanation Reaction: The "Flattening" of Proline*, 36(17) ANGEW. CHEM. INT. ED. ENGL. 1881–84 (1997). Ex. 1010 ("Hanessian I").

Bachovchin et al., WO/99/38501, published Aug. 5, 1999. Ex. 1011 ("Bachovchin").

Center for Drug Evaluation and Research, Application Number: NDA 20-357, Revised Package Insert, available by FOIA Jan. 8, 1998. Ex. 1012 ("GLUCOPHAGE Label").

Center for Drug Evaluation and Research, Application Number: NDA 20-766, Package Insert, available by FOIA Aug. 9, 1999. Ex. 1013 ("XENICAL Label").

Center for Drug Evaluation and Research, Application Number: NDA 19-643/S-033, Package Insert, available by FOIA Sept. 15, 1994. Ex. 1014 ("MEVACOR Label").

We instituted review of claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 based on the following grounds.

References	Basis	Claims Challenged
Ashworth I, Villhauer, Raag, and Hanessian I	§ 103(a)	1, 2, 4, 6–11, 25–28, 32–35, 39, and 40
Ashworth I, Villhauer, Raag, Hanessian I, Bachovchin, and GLUCOPHAGE Label	§ 103(a)	12–16, 29, 30, 36, 37, 41, and 42
Ashworth I, Villhauer, Raag, Hanessian I, Bachovchin, and XENICAL Label	§ 103(a)	12, 17, 18, and 22
Ashworth I, Villhauer, Raag, Hanessian I, Bachovchin, and MEVACOR Label	§ 103(a)	12 and 19–21

Dec. 34–35.

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable constructions in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2146 (2016). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Petitioners contend that the claims use conventional terminology. Pet. 18–19. Patent Owner does not contest the construction of any claim term. For purposes of this Decision, we need not expressly construe any claim terms.

B. Level of Ordinary Skill in the Art

According to Petitioners' expert, Dr. Rotella, a person of ordinary skill in the art, with respect to and at the time of the '186 patent,

> would likely have some combination of the following skills and experience: (i) designing target compounds towards drug discovery; (ii) designing and preparing formulations of drugs that exhibit inhibitory activity; (iii) understanding the biological aspects of drug development, including the drug's effect on the whole animal; and (iv) understanding work presented or published by others in the field, including the patents and printed publications discussed in this declaration

and "could have an advanced degree (e.g., a Ph.D.) in pharmaceutics, pharmaceutical chemistry, medicinal chemistry or a related field and at least 2–3 years of practical experience in the design of drugs," or, alternatively, "less education but considerable professional experience." Ex. 1003 ¶ 35–36.

According to Patent Owner's expert, Dr. Weber, a person of ordinary skill in the art relevant to the '186 patent "is a medicinal chemist with a Ph.D. in chemistry and several years of practical experience working with pharmaceutical chemical compounds for potential and eventual clinical use in patients," "may also have a B.S. or M.S. degree in chemistry with significantly more experience," and "also has familiarity with the spectrum of properties needed for a successful drug, the potential difficulties associated with attaining them, and the potential effects of pharmaceuticals in the human body." Ex. 2056 ¶ 137.

The parties' formulations as to the level of ordinary skill in the art are similar, and neither side identifies with specificity an error in the opposing side's formulation. *See* PO Resp. 21; Pet. Reply 10. On the record presented, we hold that the cited prior art is representative of the level of

ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the level of ordinary skill in the art may be evidenced by the cited references themselves). Specifically, the references are consistent with the parties' formulations and demonstrate the level of skill in the art. Our determinations regarding the patentability of the challenged claims would remain the same under either side's proposed formulation.

C. *Credibility of the Experts*

We give more weight to the testimony of Patent Owner's expert, Dr. Weber, over that of Petitioners' expert, Dr. Rotella, with respect to testimony that is in direct conflict. We favor Dr. Weber's testimony because of her extensive experience in the design and development of DP 4 inhibitors for type-2 diabetes treatment. *See* Ex. 2056 ¶¶ 9–12; Ex. 2210, 1–2. Moreover, Dr. Weber entered the DP 4 field at the relevant time, i.e., the time of invention, around 2000. Ex. 1073, 108:16–21; Tr. 35:16–22. We find that her testimony has been consistent, not just throughout this proceeding, but also with evidence predating this proceeding. *See, e.g.*, Ex. 2056 ¶¶ 88, 115–118; 154–162; Ex. 1073, 51:2–54:14, 113:6–16, 119:19–121:9; Ex. 2161, 558.

Starting in 2000, Dr. Weber spearheaded the chemistry effort and discovery program at Merck & Co. ("Merck") that was targeting DP 4 as a type-2 diabetes treatment. Ex. 2056 ¶ 9; Ex. 1073, 40:5–8. In the early 2000s, Merck and several other pharmaceutical companies were developing DP 4 inhibitors to treat type-2 diabetes. Ex. 2056 ¶¶ 119, 257. Dr. Weber's work led to the development of sitagliptin, the first marketed and FDA-approved DP 4 inhibitor for treatment of type-2 diabetes. Ex. 2056 ¶ 9; Ex. 1073, 40:13–21; Tr. 35:11–13. When she began working on the DP 4

program, Dr. Weber surveyed the scientific and patent literature, including Ashworth I, to select a lead compound for further development. Ex. 1073, 43:2–11, 111:12–112:13; Tr. 35:19–36:5. That is, she "faced the problem the person of ordinary skill in the art would do," "did it the way a person skilled in the art would," and "went through the lead compound analysis" at the time of the invention. Tr. 36:1–5. Ultimately, Dr. Weber's review of the prior art led her not to Ashworth I, but to P32/98, one of only two DP 4 inhibitors that had advanced to clinical studies, for a lead compound. Ex. 2056 ¶¶ 88, 116–118; Ex. 1073, 50:9–52:21; Ex. 2161, 558. Following the discovery of sitagliptin, Dr. Weber continued to lead Merck's DP 4 inhibitor discovery program, resulting in further developments on DP 4 inhibitors for diabetes treatment. Ex. 1073, 40:22–41:9; Ex. 2056 ¶¶ 9–10. Dr. Weber has authored dozens of publications and has dozens of patents relating to DP 4. Ex. 1073, 110:19–111:10; Tr. 35:13–15; Ex. 2210, 3–13. In contrast, Dr. Rotella's experience with DP 4 inhibitors is limited to working with co-inventors of the '186 patent at Bristol-Meyers Squibb ("BMS") after the invention of saxagliptin.[5] Ex. 2221, 109:4–8, 113:7–116:25; Tr. 37:13–22.

Therefore, for the reasons discussed above and because, as discussed below, Dr. Weber's testimony is more consistent with the evidence, where there is a direct conflict between expert testimonies, we give more weight to Dr. Weber's testimony.

[5] The subject matter of the '186 patent (saxagliptin) was invented by researchers at BMS, the original owner of the '186 patent. Prelim. Resp. 6 n.1; Pet. 2. The '186 patent was later purchased by Patent Owner. Prelim. Resp. 6 n.1.

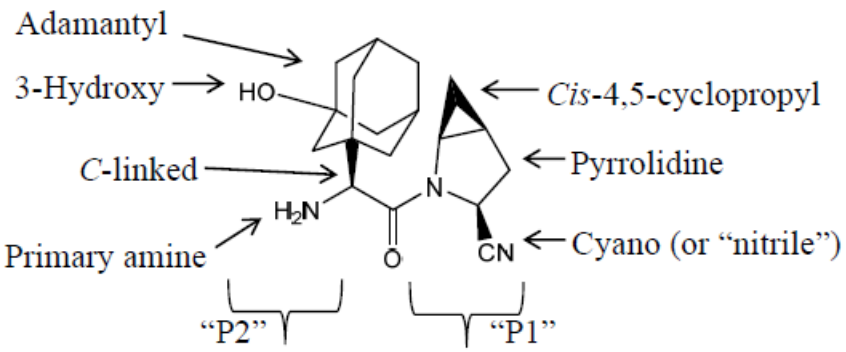
D. *Law of Obviousness*

"Section 103(a) forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 405 (2007). A determination of whether a new chemical compound would have been obvious over the prior art typically follows a two prong inquiry considering first, whether one of ordinary skill would have selected one or more lead compounds for further development and, second, whether the prior art would have supplied sufficient motivation to modify a lead compound to arrive at the compound claimed with a reasonable expectation of success. *See Otsuka Pharm. Co., Ltd., v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012). Identifying each element of a claimed compound in the prior art is insufficient to show that the compound as a whole would have been obvious. *Eli Lilly and Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). "[W]here the prior art, at best, gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible." *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012) (internal citations and quotation marks omitted); *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013). "Where . . . a defendant urges an obviousness finding by 'merely throw[ing] metaphorical darts at a board' in hopes of arriving at a successful result, but 'the prior art gave either no indication of which parameters were critical or no direction as

to which of many possible choices is likely to be successful,' courts should reject 'hindsight claims of obviousness.'" *Cyclobenzaprine*, 676 F.3d at 1070–71 (citing *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). An invention is not invalid for obviousness if all the prior art suggested "was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903.

E. Obviousness of Saxagliptin

The chemical structure of saxagliptin is shown below.



PO Resp. 4. The figure above is Patent Owner's annotated illustration of saxagliptin. Patent Owner explains that saxagliptin is a dipeptide-based structure consisting of "so-called 'P1' and 'P2' groups." *Id*. "The P1 group includes a cyano (or nitrile) substituent and a cyclopropyl substituent in the specific *cis*-4,5 configuration on a pyrrolidine ring." *Id*. "The P2 group is formed by an adamantyl group[6] which contains a hydroxy group in the 3-

[6] Petitioner explains that Adamantyl is a (C_{10}) tricycloalkyl. Pet. 26 (citation omitted).

position and is attached to a primary-amine-containing backbone through a carbon-carbon linkage (*C*-linked)." *Id*. (citing Ex. 2056 ¶ 95).

1. Lead Compound Analysis

Petitioners contend that one of ordinary skill in the art would have selected Ashworth I's compound 25 ("compound 25") as a lead compound in the development of DP 4 inhibitors "because of its superior combination of potency[7] and stability[8]." Paper 11, 1 (citing Pet. 24–25).

According to the Federal Circuit, 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 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). Our analysis as to whether a skilled artisan would have selected

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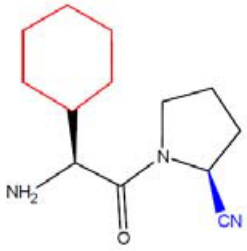
[7] Inhibitor potency is measured in terms of disassociation constant (K_i), which indicates the propensity of an inhibitor to disassociate from its target with smaller K_i values indicating greater potency. Ex. 1003 ¶ 64; *see* Pet. 31; Paper 11, 1. The parties agree that K_i, a measure of *in vitro* binding affinity, is indicative of inhibitor "potency," wherein a smaller K_i indicates greater potency. Paper 11, 1; Ex. 1003 ¶ 64; PO Resp. 7 n.2; Ex. 2056 ¶ 50. For purposes of this Decision, therefore, we apply the convention of equating inhibitor "potency" with *in vitro* binding affinity, represented by K_i. *See, e.g.*, Ashworth I (Ex. 1007, 1163) ("The most potent DP-IV inhibitors reported to date are the boroproline analogues 1, (K_i=2nM) and 2, (K_i =3nM).").

[8] Inhibitor stability is measured in terms of an inhibitor's half-life ($t_{1/2}$), with longer half-lives indicating greater stability. Ex. 1003 ¶ 64; *see* Pet. 31; Pet. Reply 1–2.

a prior art compound as a lead is guided by evidence of the compound's pertinent properties. *Otsuka*, 678 F.3d at 1292. Such relevant properties include positive attributes such as activity and potency, adverse effects, such as toxicity, and other relevant characteristics in evidence. *Id*. "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*. "[T]he lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi*, 619 F.3d at 1354.

Compound 25 of Ashworth I is illustrated below.



Pet. 7, 25. The illustration shows that compound 25 comprises a glycyl moiety having a primary amine (NH_2), a cyclohexyl group on the β-carbon (2-position) of the glycyl moiety, and a pyrrolidine ring having a cyano (nitrile) group, designated here as CN. *See* Pet. 7. Thus, the structure of saxagliptin (claim 25) differs from compound 25 in having 3-hydroxyl adamantyl in place of the cyclohexyl group and a cyclopropyl fusion of the pyrrolidine ring. *See* PO Resp. 29.

a) DP 4 Inhibitors at the Time of Invention

According to Dr. Weber, at the time of invention, the crystalline structure of DP 4 was unknown, leaving scientists without detailed knowledge of its active site for guidance in designing a DP 4 inhibitor. Ex. 2056 ¶ 89. Much of what was known about DP 4's binding requirements

came from structure-activity relationship ("SAR") studies with substrates and inhibitors of varying structure in an attempt to characterize what chemical features the enzyme would or would not tolerate. *Id*. ¶ 90.

b) Whether Ashworth I's Compound 25 Would Have Been Selected as a Lead Compound

According to Ashworth I, the "most potent DP-IV inhibitors" reported as of the date of Ashworth I were boroproline analogues, but they were considered unstable. Ex. 1007, 1163. Ashworth I discloses 2-cyanopyrrolidines as DP 4 inhibitors and focuses on their potency and stability. Pet. 24 (citing Ex. 1007, 1163–64). Ashworth I reported that "[a] number of dipeptide analogue, incorporating a 2-cyanopyrrolidide, were found to have K_i values of less than 5nM versus human DP-IV and half-lives of >48h in aqueous solution (pH 7.4)." *Id*. at 1163. Ashworth I also states that DP 4 inhibitors require a free N-terminus, and certain potential inhibitors, including C-terminal aldehydes, are inherently unstable at neutral pH due to intramolecular cyclization.[9] *Id*. at 1163. Of the disclosed compounds, Ashworth I identifies compounds 24–27 as "possess[ing] activity comparable to the boroprolines" and having "excellent half-lives ($t_{1/2}$) in aqueous solution (pH 7.4) at room temperature." *Id*. at 1165. With respect to the disclosed compounds, Ashworth I states that "[f]urther work on optimization of the pyrrolidine ring will be reported shortly." *Id*. at 1165. Petitioners argue that Ashworth I provided a skilled artisan "with reasons—specifically, potency and stability—to have selected compound 25

[9] As Patent Owner explains (PO Resp. 8), the free amine in the peptide backbone reacts with the electrophile, the "cyano" group (CN), in an intramolecular cyclization reaction to form an inactive compound.

(cyclohexylglycyl-2-pyrrolidine) as a lead compound and provided good reason to have expected that other β-branched α-amino acid derivatives would also be worth exploring." Pet. 25.

On the full record before us, we determine that Petitioners have not demonstrated by a preponderance of the evidence that a skilled artisan would have chosen Ashworth I's compound 25 as a "lead compound." Although Ashworth I indicates that compounds 24–29 were non-toxic in T cell assays up to 72 hours, and further indicates compound 25 was one among four compounds that were comparable to boroprolines, no further data is provided to guide the skilled artisan to select compound 25 among the other 2-cyanopyrrolidides as a lead compound for further modification to develop a DP 4 inhibitor. Ex. 1007, 1165–66. More importantly, the data reported in Ashworth I was based on *in vitro* data at room temperature, not *in vivo* data. PO Resp. 25 (citing Ex. 2174, 82:23–83:11). Indeed, Dr. Rotella states, "those studies were carried out at room temperature, which is roughly 20 degrees [Celsius]. I'll point out that body temperature is higher than that, and that temperature has a direct effect on half-life. As you elevate temperature, you can expect half-life to decrease." Ex. 2174, 82:23-83:11. Dr. Rotella further admits that he is not aware of any disclosure describing testing of Ashworth compounds in humans. Ex. 2174, 60:23-61:9. In addition, Ashworth I acknowledged that these compounds exhibited an intramolecular cyclization problem and that further work on optimization of the pyrrolidine ring was necessary and would be reported shortly. Ex. 1007, 1163–65. Others in the prior art also continued to seek solutions to the problem of intramolecular cyclization, such as those posed by Ashworth I compounds. *See* PO Resp. 27–28.

The evidence shows that compound 25 would have presented additional concerns to the skilled artisan seeking to develop a DP 4 inhibitor. For example, the cyano group in the compound presented the concern of toxic cyanide release *in vivo*. Ex. 2056 ¶¶ 116–18, 162. Furthermore, as noted above, the known stability data of compound 25 was based on *in vitro* tests at room temperature, which would not have provided reliable information about *in vivo* stability. Indeed, as Dr. Rotella acknowledged, not much was known about the pharmaceutical properties of compound 25 at the time of the invention. Dr. Rotella testified that "nothing is known, at least at this point in time, about other properties associated with compound 25, [and that] you'd want to understand what those properties were and adjust them as need be. Generally speaking, those properties are things we call, collectively, pharmaceutical properties." Ex. 2174, 115:21–116:17; Ex. 2056 ¶¶ 157, 171.

Ashworth II[10], which was a continuation of Ashworth I's disclosure, and also considered prior art to the '186 patent, does not further recognize compound 25 as a promising DP 4 inhibitor candidate and instead focuses on another series of compounds. Ex. 2056 ¶ 164 (Dr. Weber stating that Ashworth II was a continuation of Ashworth I and that a skilled artisan would have considered the teachings of both as a whole). Ashworth II states that "[a] series of stable, very potent inhibitors of [DP 4] has been developed." Ex. 2001, Abstract. Ashworth II concludes that the 4-cyanothiazolidine (a sulfur-containing ring) was approximately 5-fold more

[10] Ashworth et al., *4-Cyanothiazolidides as Very Potent, Stable Inhibitors of Dipeptidyl Peptidase IV*, 6(22) BIOORGANIC & MED. CHEM. LETT. 2745 (1996). Ex. 2001 ("Ashworth II").

potent than Ashworth I's 2-cyanopyrrolidine inhibitors and concluded that the 4-cyanothiazolidides were the "optimum" P1 core. Ex. 2056 ¶ 165 (citing Ex. 2001, 2746); *see* PO Resp. 26. We are persuaded by Dr. Weber's opinion that a skilled artisan would not have had reason to choose compound 25 as a lead compound given the disclosure in Ashworth II of a preference to cyanothiazolidides by the same authors that originally disclosed cyanopyrrolidines in Ashworth I. Ex. 2056 ¶ 170; *see Daiichi*, 619 F.3d at 1353–54 (accepting as true all evidence that the proposed lead compounds exhibited remarkable potency and activity, but nevertheless rejecting the proposed leads over more potent second-generation compounds).[11]

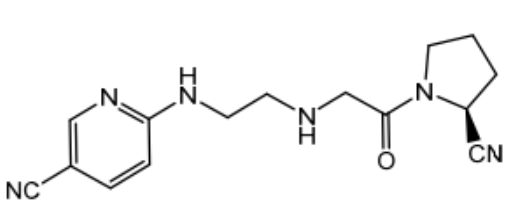
Petitioners' Reply acknowledges that "[Ashworth II's] [s]ulfur substitution at the 4-position on the proline ring made the inhibitor more potent" and preserved a saturated 5-membered ring. Pet. Reply 12. Nonetheless, Petitioners argue that cyclopropanation of the ring would also have preserved the saturated 5-membered ring, and, thus, Ashworth II did not teach *away* from compound 25, but rather was a modification *consistent* with cyclopropanating proline. *Id*. (citing Ex. 1074 ¶ 40). Petitioners' argument is unconvincing. Ashworth II does not disclose why the addition of sulfur in the proline ring made the compound more potent. Thus, Dr. Rotella's testimony that the addition of sulfur to the proline ring is allegedly

[11] In support of its argument that a skilled artisan would have had reason to choose compound 25, Petitioners reply that "Ashworth [I] itself discloses several compounds in the prior art over which it improves, *e.g.*, boroprolines." Pet. Reply 10 (citing Ex. 1007, 1163). This argument is unpersuasive because it does not take into account Ashworth II's disclosure that 4-cyanothiazolidides were the "optimum" P1 core. In our assessment of obviousness, we have considered *all* the prior art and evidence of record, and not simply the disclosure of Ashworth I in isolation.

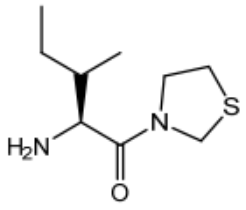
comparable to cyclopropanating because both modifications retain a statured 5-membered pyrrolidine ring is, at best, tenuous and suggests improper hindsight bias. *See* Ex. 1074 ¶ 40.

In addition to Ashworth II's disclosure that 4-cyanothiazolidides were the "optimum" P1 core, other DP 4 inhibitor candidates in the prior art with significantly different P1 structures than compound 25 were already in clinical trials. As Patent Owner argues, "the [lead compound] analysis still 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*, 619 F.3d at 1354 (emphasis added).

In particular, at the time of the invention, NVP-DPP728 and P32/98 were the only DP 4 inhibitor candidates that had advanced to clinical trials for evaluation in humans. PO Resp. 14 (citing Ex. 2056 ¶¶ 88, 143; Ex. 2057 ¶¶ 40–41). According to Dr. Weber, because of the available data on these two compounds and their ongoing clinical trials, NVP-DPP728 and P32/98 were recognized in the art as the most promising DP 4 inhibitors at the time of the invention. Ex. 2056 ¶¶ 154–59. Notably, each of these compounds have different structures than Ashworth I's compound 25, as depicted below:



NVP-DPP728



P32/98

Ex. 2056 ¶ 88; Ex. 2016; Ex. 2078. As shown above, NVP-DPP728 has an

"N-linked" dipeptide backbone, meaning that the alkyl group is attached directly to the amine nitrogen in the peptide backbone, as opposed to attached to a carbon, as in a "C-linked" compound like compound 25. PO Resp. 11 (citing Ex. 2056 ¶ 59). Also, as shown above, P32/98 is a C-linked compound with a thiazolidine ring (i.e., sulfur in the pyrrolidine ring like the Ashworth II compounds) in the P1 position, and isoleucine in the P2 position. PO Resp. 13 (citing Ex. 2056 ¶¶ 118, 155; Ex. 2078, 308); Ex. 2056 ¶ 162).

Both these clinical candidates avoided the stability issues associated with the Ashworth I compounds. With respect to NVP-DPP728, the N-linkage reduced stability concerns because the secondary amine backbone was less likely to interact with an electrophile in the P1 group, and thus, was viewed as a solution to the intramolecular cyclization problem disclosed in Ashworth I. Ex. 2056 ¶¶ 54, 113, 125. Also, because P32/98 did not have an electrophile (e.g., a cyano group) in the P1 position, that structure eliminated the risk of intramolecular cyclization altogether. PO Resp. 13 (citing Ex. 2056 ¶¶ 116–117). Before the time of the invention, both of these compounds showed positive data in humans. Ex. 2056 ¶¶ 156, 159. Notably, both NVP-DPP728 and P32/98 are less potent than compound 25, and yet were chosen for clinical trials, suggesting that the skilled artisan would not have selected a compound for further development as a DP 4 inhibitor merely based on its higher potency. Ex. 2056 ¶¶ 88, 172; *see also id.* at ¶¶ 157, 159, 169.

In our evaluation of the evidence, we find Dr. Weber's testimony that a skilled artisan would not have selected compound 25 as a lead compound to be more persuasive than Dr. Rotella's testimony to the contrary. Dr.

Weber testifies that a skilled artisan would have been led towards NVP-DPP728 or P32/38 and away from Ashworth I's compound 25. This testimony is consistent with Dr. Weber's prior experience. Indeed, well before this proceeding, Dr. Weber herself performed a similar lead compound analysis while working at Merck to develop a DP 4 inhibitor at the time of the invention. Ex. 2056 ¶¶ 116–118, 154–171; Tr. 41:15-20; Ex. 2161, 1–2. When Dr. Weber began working on DP 4 inhibitors in 2000, she first reviewed and studied the prior art, including specifically Ashworth I. Ex. 1073, 111:12–112:20; Tr. 35:19–22. Based on her own survey of the scientific and patent literature at that time, P32/98 was selected as a lead compound because it had available human clinical data, among other factors. Ex. 2056 ¶¶ 116–118; Ex. 2161, 2; Ex. 1073, 50:9–10, 119:19–121:9. This is consistent with her current testimony that, "given the available data, NVP-DPP728 and P32/98 were recognized by one of skill in the art as the most promising, natural starting points for further development efforts." Ex. 2056 ¶ 149. Dr. Rotella, on the other hand, worked with co-inventors of saxagliptin and was provided with at least the Ashworth I and Hanessian I references by BMS to develop a backup molecule to saxagliptin. Ex. 2174, 25:10–25; Ex. 2221, 109:4–116:21; Tr. 38:1–15. Accordingly, we find that Dr. Rotella's lead compound selection of Ashworth I's compound 25 was more likely to be prejudiced by hindsight bias.

In view of the full record, and given Petitioners' burden to prove unpatentability by a preponderance of the evidence, we determine that Petitioners have not established sufficiently that a skilled artisan would have chosen compound 25 as a lead compound.

c) Accepting That a Skilled Artisan Would Have Selected Compound 25 as a Lead Compound for Further Development

Even accepting Petitioners' assertion that a skilled artisan would have chosen compound 25 as a lead compound, Petitioners must further demonstrate that a skilled artisan would have had reason to modify compound 25 with a reasonable expectation of success to arrive at the claimed saxagliptin. *See Otsuka*, 678 F.3d at 1291–92; *see Daiichi*, 619 F.3d at 1352 ("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.").

Petitioners argue that one of ordinary skill in the art would have had reason to modify compound 25 by 1) adding a cyclopropyl ring to the pyrrolidine portion of compound 25 in the 4S,5S configuration; 2) replacing the 6-carbon cyclohexyl group at the P2 position with a 10-carbon adamantyl moiety; and 3) hydroxylating the adamantyl moiety. Pet. 25–33. On the full record, we determine that Petitioners have not met their preponderance of the evidence burden with respect to each of the three proposed modifications and all three modifications taken together.

d) Modifying Compound 25 by Adding Cyclopropyl in the Cis-4,5 Configuration

Referring to Hanessian I, Petitioners argue that a skilled artisan would have had reason to modify compound 25's proline pyrrolidine ring by adding a three-carbon cyclopropane (cyclopropyl ring) to create cis 4,5-

methanoproline, in order to increase the compound's stability and potency with a reasonable expectation of success. Pet. 9–11, 28–29. As discussed below, we find there is an insufficient basis in the prior art or expert testimony to support a finding that a skilled artisan at the time of the invention would have reasonably expected that modifying compound 25 by cyclopropanating its pyrrolidine ring would have successfully increased its stability or potency.

(1) Hannesian's Disclosure

Hanessian discloses that cyclopropanation of proline at the 4,5-carbons "flattens" the ring, i.e., reduces the bond angles within the ring compared to unmodified proline. Ex. 1010, 1882. One consequence of the cyclopropanation was that the carbon with the carboxyl group (Cα or 1-carbon) was the out-of-plane carbon rather than C_β (2- carbon), as is the case with unmodified proline. *Id*. Cyclopropanation also affects the *cis*/*trans* conformation of the proline with respect to the *tert*-butoxycarbonyl (Boc) protecting group bonded to the nitrogen in the proline ring. *Id*. at 1883 and Table 1 (figure of compound 8).

(2) Petitioners' Contentions

Petitioners aver that it was known that DP 4 inhibitor instability was attributable to intramolecular cyclization between the free amino group of the P2 group and the electrophile attached to the proline mimic of the P1 group. Paper 11, 5 (citing Ex. 1007, 1163; Ex. 2007, 314). Petitioners further contend that proline was known to have significant conformation effect on peptides and that "conformationally constrained" proline is used extensively in peptidomimetic research. Pet. 28. According to Petitioners, a well-known strategy at the time of the invention for modulating the

orientation of a substituent bound to a proline ring would have been to fuse the substituent-bearing ring with another ring, such as cyclopropyl. Pet. 21 (citing Ex. 1021, 243); Ex. 1003 ¶¶ 135, 137. Petitioners refer to Hanessian I's teaching of 4,5-methanoproline, in which the proline has a second ring, a cyclopropane, sharing the bond between the 4- and 5-carbon of the proline. *Id*. at 28–29 (citing Ex. 1010, 1881–82).

Dr. Rotella explains that Hanessian I teaches modifying a substituted proline ring, specifically a 2-carboxyl substituted proline, to produce a 4,5-methano-modified substituted proline "with the 2-substitutent orientation modified" with respect to the proline ring. Ex. 1003 ¶ 143. In the case of 2-cyanoproline, such as compound 25, the α-carbon bears a nitrile, and thus, Petitioners, referring to Hanessian, argue that a skilled artisan would have reasoned that flattening would push the nitrile-bearing carbon out of the plane defined by the rest of the proline ring. Pet. 29; Ex. 1003 ¶ 141; Tr. 31:14–22 (Petitioners arguing that a skilled artisan would have tried to improve compound 25 by changing the orientation of the molecule in space so that the free amino group on the P2 would be prevented from "attacking" the cyano group). Dr. Rotella also opines that a skilled artisan "would have had reason to try modifying the 2-cyano substituted proline portion of the Ashworth compound 25, to produce a 4,5-methanoproline ring system in order to 'flatten' the proline ring as taught in Hanessian, thereby adjusting the orientation of the cyano substituent to the proline ring and minimizing or preventing intramolecular cyclization, as taught by Ashworth [I]." Ex. 1003 ¶ 143. Petitioners contend that "[c]hanging the position of the nitrile relative to the rest of the dipeptide would have been expected to have an effect on both the inhibitor's interaction with DP-IV and on the risk of intermolecular

cyclization (and thus on stability)." Pet. 29 (citing Ex. 1003 ¶ 143). With respect to specific positioning of the cyclopropane, Petitioners state that Hanessian I identified three locations on the proline ring where cyclopropanation could occur, with two resulting stereoisomers each, for a total of six possible cyclopropanations of the proline ring to try; thus, argue Petitioners, with only six possibilities, a skilled artisan would have had reason to try each to determine which provided the best activity and stability. *Id*. (citing Ex. 1003 ¶ 139).

(3) Chiou Does Not Support Petitioners' Position

In support of the contention that a skilled artisan would have been motivated to select cyclopropyl fusion as a means for modulating the interaction between a DP 4 inhibitor and DP 4, Petitioners and Dr. Rotella refer to Chiou. Pet. 21–22; Ex. 1003 ¶¶ 135, 137 (citing Ex. 1021, 243). Chiou, however, does not disclose fusing two rings, or specifically the fusion of a cyclopropyl group to a second ring. Ex. 2056 ¶¶ 177–78. Rather, as Patent Owner argues (PO Resp. 31–32), Chiou describes substituting a cyclopropyl group for a single carbon-carbon bond in acetylcholine so that the substituents that were attached to each of the carbon atoms become ring-bound substituents attached to the cyclopropyl. Ex. 2056 ¶ 177; Ex. 1021, 244 (Fig. 1). Petitioners do not provide sufficient evidence as to how or why a skilled artisan would have applied this teaching to fusing a cyclopropyl ring to a pyrrolidine ring that already has ring-bound substituents in a compound that has a vastly different structure than acetylcholine. *See* Pet. 21–22.

(4) No Reasonable Expectation of Increasing Stability

We are not persuaded that the skilled artisan would have had a reasonable expectation of success in achieving increased stability of Ashworth I's compound 25 based on Hanessian I's teachings concerning the cyclopropanation of proline. *See* Pet. 29. There was no disclosure in the prior art of cylopropanating the pyrrolidine ring of compound 25, or any similar compound. Indeed, Dr. Rotella admitted "that there wasn't anything in the literature prior to the invention of saxagliptin that actually suggested that cyclopropanation of an Ashworth-One type DPP4 inhibitor would improve its stability." Ex. 2174, 142:3-9. In addition, there is not sufficient evidence as to how the modified cyano-moiety would have been understood to affect compound 25's stability. Given the structural differences, we find there is insufficient evidence suggesting that the skilled artisan could have reasonably predicted how cyclopropanating compound 25's P1 group (as opposed to the proline compound discussed in Hanessian I) would have affected the cyano moiety's (as opposed to the substituent in Hanessian I) orientation in space. Furthermore, there is insufficient evidence as to whether that modified orientation would have sufficiently decreased intramolecular cyclization. Indeed, Dr. Rotella testified that:

> [I]n the process of that modification of orientation in space [when you fuse two rings together], you may observe effects on potency, you may observe effects on solution stability, you may observe other effects on other properties that one might measure in connection with a drug discovery project.

Ex. 2174, 119:10–120:2. When asked, "[a]nd those effects might be either positive or negative; correct?" Dr. Rotella replied, "[t]hey might be, yes." Ex. 2174, 120:3–5. Dr. Rotella also testified that at the time of the

invention, the objective of adding a cyclopropyl substituent to the pyrrolidine ring of compound 25 would have been exploratory. He testified:

> Q. Well, what is the objective of putting the cyclopropane on the molecule, in your opinion?
> A. There are two possible objectives based on the data -- there are at least two possible objectives based on the data available surrounding compound 25.
> Q. And what are they?
> A. One would be to *explore* whether or not you could improve potency. A second would be whether or not you could improve solution stability. One might also *explore* how that -- those changes, either by themselves or in combination with two changes, might also improve or change -- sorry -- to improve solid-state stability. Furthermore, *since nothing is known, at least at this point in time, about other properties associated with compound 25, you'd want to understand what those properties were and adjust them as need be*. Generally speaking, those properties are things that we call, collectively, pharmaceutical properties.

Ex. 2174, 115:11–116:13 (emphasis added). This testimony does not sufficiently support Petitioners' contention that a skilled artisan would have reasonably expected cyclopropanating the pyrrolidine ring of compound 25 to increase its stability.

(5) No Reasonable Expectation of Increasing Potency

Likewise, there is insufficient evidence that the proposed modification would have been reasonably expected to increase DP 4 inhibitor activity at the time of the invention. Hanessian I does teach the synthesis and conformational effect of "flattening" a proline ring *like that* of compound 25 by fusing a cyclopropyl ring to the proline ring. *See* Dec. 24. However, as Patent Owner contends with support from its expert, Hanessian I does not teach what the effect of such flattening would have been on a DP 4 inhibitor

and its potential inhibitory activity. PO Resp. 33 (citing Ex. 2056 ¶ 181). Petitioners' expert acknowledges that Hanessian I's teaching does not relate to any particular system, particularly a DP 4 inhibitor. *See* 2056 ¶¶ 184–85. In particular, Dr. Rotella testified:

> Q: Now, Hanessian doesn't tell you in this article what the effect of that flattening is going to be in any particular system; correct?
> Dr. Rotella: He does not.

Ex. 2174, 127:1–4. As Patent Owner's expert, Dr. Weber confirms, although "Hanessian-I reports that cyclopropanation flattens a proline ring, it does not teach what, if any, effect flattening would have on the physico-chemical or biological properties of the cyanopyrrolidine compounds of Ashworth." Ex. 2056 ¶ 181. Similar to our analysis above, we find the relevance of cyclopropanating the proline group of compound 25 to increasing DP 4 inhibitor activity that Petitioners propose is based on hindsight knowledge of saxagliptin's structure. *See Otsuka*, 678 F.3d at 1295 (requiring a showing that the prior art "predicted the results")

(6) Unpredictability of Modifications

Petitioners' arguments and Dr. Rotella's opinions that a skilled artisan would have made the proposed cyclopropanation modification with a reasonable expectation of success are unconvincing, particularly given the unpredictability of the prior art. As an initial matter, Dr. Weber provides supporting opinion evidence that the specific modification proposed by Petitioners would have been unpredictable at the time of the invention: "the effect of a cyclopropyl group on the reactivity of the resultant methano pyrrolidine nitrile toward cyclization had never been explored and was entirely unpredictable." Ex. 2056 ¶ 191. Indeed, there was no disclosure in

the prior art at the time of the invention of cyclopronating a five-membered ring, as attested to by Dr. Weber:

> Q. In the course of your work in developing DPP-4 inhibitors at Merck, did you or any of your colleagues consider adding a cyclopropyl group at the P1 position of your DPP-4 compounds?
> A. No, we never did, and to the best of my knowledge nobody other than the chemists at BMS ever did that.

Ex. 1073, 117:4–11. Dr. Weber further testified:

> Q. What was your reaction when you first learned that saxagliptin had a cyclopropyl group on the pyrrolidine ring?
> A. I was very surprised when I saw the patent when it was first published. I was first surprised that they had actually tried it, and I was even more surprised that it worked.

Id. at 117:12–20.

In addition, the art taught that even minor changes to the P1 position of Ashworth I's compounds were not well tolerated. For example, the prior art taught that "flattening" the pyrrolidine ring of a DP 4 inhibitor by insertion of a double bond resulted in a loss of potency. Ex. 2056 ¶¶ 180–83; Ex. 2151, 302–03, Table I; Ex. 2221, 58:21–24. Ashworth II also taught that adding a sixth carbon to Ashworth I's five-membered pyrrolidine ring, whether by increasing the ring size or adding a methyl substituent, decreased activity against DP 4. Ex. 2001, 2747, Table I; Ex. 2056 ¶¶ 173–174 (comparing K_i values for different compounds).[12] Petitioners reply that

[12] In our Decision on Institution we questioned the relevance of Ashworth II data to Petitioners' proposed modifications (Dec. 24), but as Patent Owner argues (PO Resp. 36), we agree that this data is relevant to showing that Ashworth II explored modifying the pyrrolidine ring of Ashworth I's compounds and found that any modification, other than adding a Sulfur atom, was unsuccessful to potency. Ex. 2056 ¶ 107.

"[t]hese teachings corroborate Dr. Rotella's testimony that a POSA would have *explored* a ring-fusion strategy." Pet. Reply 17 (emphasis added) (citing Ex. 1003 ¶ 55). Exploration, however, does not by and of itself support a finding of a reasonable expectation of success. *See In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (obviousness not established where "what was 'obvious to try' was to *explore* a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it") (quoting *O'Farrell*, 853 F.2d at 903 (emphasis added)). Other references in the prior art reflect similar unsuccessful results. For instance, Augustyns reported that changing the five-membered pyrrolidine ring size of a DP 4 inhibitor or introducing a substituent reduced inhibitory activity, with only one exception: a "'fluorine, isosteric to hydrogen, is allowed.'" PO Resp. 35 (citing Ex. 2151, 303; Ex. 2056 ¶¶ 173-175). According to Dr. Weber, "one skilled in the art would understand that fluorine is closer in size to a hydrogen atom (*i.e.*, isosteric) and therefore would have a minimal effect on the size of the P1 moiety." Ex. 2056 ¶ 175. Petitioners reply that Augustyns explained that such a substitution would be permitted only at the ring's 3-position. Pet. Reply 18 (citation omitted). Dr. Rotella explained, however, that the "3-position" can be either one of two carbon positions. Ex. 2221, 52:10–18, 53:3–11; Ex. 1073, 85:2–86:4 (Dr. Weber testifying that a medical chemist would understand that Augustyns was suggesting that substituting at one of the two carbons that is not attached to the nitrogen would not be preferred).

In addition, Ashworth II, in an attempt to improve the potency of DP 4 inhibitors by modifying the pyrrolidine ring, discloses that all tested

modifications to the P1 position of Ashworth I's compounds resulted in loss of activity, except thiazolidide (Sulfur substituted five-membered ring), which was identified as the "optimum" *C*-terminal residue. Ex. 2056 ¶¶ 173–174; Ex. 2001, 2746–7, Table I. In its Reply, Petitioners argue that this teaching showed that "modest increases in ring size are tolerated and can even result in greater potency." Pet. Reply 17–18. Petitioners' argument is unavailing, however, because Petitioners do not adequately show that the increased activity of Ashworth II's sulfur containing ring was due merely to its "modest" increase in size, as alleged by Petitioners, as opposed to some other contributing factor of the sulfur substituent. For example, Ashworth II shows that compound 4 (a five-membered cyano ring containing sulfur) and compound 5 (a five-membered cyano ring not containing sulfur) do not have significantly different potency, with K_i values of 1.70 nM ± 0.50 and 2.2 nM ± 0.50, respectively. Ex. 2001, 2747, Table I; Ex. 2221, 35:15–19 (Dr. Rotella agreeing that the K_i values for compounds 4 and 5 are not substantially different). Ashworth II also shows the K_i values for compounds 3 and 4, both of which are sulfur-substituted five-membered rings, albeit with the sulfur in different locations. Ex. 2001, 2747, Table. I; Ex. 2221, 38:6–12 (Dr. Rotella agrees that the rings of compounds 3 and 4 would have been expected to be the same size). Yet, these two compounds have significantly different K_i numbers, 0.41 nM ± 0.15 and 1.7 nM ± 0.50, respectively (about a four-fold difference). Ex. 2001, 2747, Table. I. Dr. Weber confirms that while thiazolidine is preferred in one position, it is not preferred in a second position, "indicating that something other than size is contributing to the greater potency of that compound." Ex. 1073, 104:3–13, 121:14–122:1.

We find the relevance of cyclopropanating the cyanopyrrolidine ring of compound 25 to increasing stability or potency, as Petitioners propose, is based on hindsight knowledge of saxagliptin's structure, as opposed to the predictability of the proposed modification. *See Otsuka*, 678 F.3d at 1295 (requiring a showing that the prior art "predicted the results"). Viewing the evidence in its entirety, we find that Petitioners have not shown by a preponderance of the evidence that a skilled artisan would have reasonably expected that cyclopropanating the pyrrolidine ring of compound 25 would have increased the stability or potency of the compound.

e) Modifying Compound 25 by Substituting an Adamantyl Group for the Cyclohexyl Group

Referring to Ashworth I and Villhauer, Petitioners argue that a skilled artisan would also have had reason to modify compound 25 by substituting its cyclohexyl substituent with an adamantyl group in order to increase its stability and potency.[13] Pet. 25–27, 30–33. As discussed below, we find there is insufficient evidence to support a finding that a skilled artisan would have reasonably expected that modifying compound 25 by substituting its cyclohexyl substituent with an adamantyl group would have successfully increased its stability or potency.

(1) Petitioners' Contentions

Petitioners state that "Ashworth taught the advantages of placing a large[14] β-branched (S)-cycloalkyl on N-glycyl-2-pyrrolidine." Pet. 26

[13] The Petition does not adequately assert that a skilled artisan would have made the proposed modification to increase potency. *See* Pet. 25–27, 30–33. Nonetheless, we consider the argument for completeness.

[14] To the extent Petitioners refer to "large" as a substituent with more atoms,

(citing Ex. 1007, 1165; Ex. 1003 ¶ 68). Petitioners further aver that "[a]damantyl (C_{10}) [disclosed in Villhauer] is a tricycloalkyl even larger than cyclopentyl (C_5) or cyclohexyl (C_6)," and contends that a skilled artisan would have had reason to substitute adamantyl for cyclohexyl on compound 25 "due to the comparisons Ashworth had already made" using substituents taught by Villhauer. Pet. 26 (citation omitted). Petitioners further contend that the prior art described two key modifications, including "add[ing] a *bulky hindering* structure to the glycyl moiety to improve stability." Pet. 31 (citing Exs. 1007, 1008) (emphasis added). Petitioners also aver that the art had identified specific paths for each modification and states that "[t]he hindering structure would preferably be a large structure, particularly a cycloalkyl." *Id*.

(2) Ashworth I Disclosure

Ashworth I does not support a finding that a skilled artisan would have reasonably expected that modifying compound 25 by substituting the cyclohexyl with an adamantyl group would have further increased its stability or potency. Ashworth I states "β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid,

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Ashworth I teaches that a substituent with more atoms does not necessarily increase stability. *See* PO Resp. 46; Ex. 2056 ¶ 208; Ex. 2174, 154:13–155:15 (Dr. Rotella admitting that between compound 25 and compound 28, compound 28 "does contain more atoms"); Ex. 1007, 1166, Table II (compare $t_{1/2}$ >48h for compound 25 to $t_{1/2}$ 24h for compound 28). Petitioners reply that compound 28 does not necessarily have a steric effect and that a skilled artisan would not have considered it to be "'bulky.'" Pet. Reply 14. The Petition, however, does not explicitly distinguish between "large" and "bulky" alkyl substituents. *See* Pet. 25–27, 30–33. Dr. Rotella likewise does not explicitly distinguish between "large" and "bulky" alkyl groups. Ex. 1003 ¶ 115 (referring to "larger, bulkier alkyl groups").

(S)-cyclohexylglycine providing the most active pyrrolidide (compound 5 possessing a Ki value of 64 nM)." Ex. 1007, 1165. Ashworth I does not describe β-branched cycloalkyls as a "hindering" or "steric" structure that reduces intramolecular cyclization. In addition, although recognizing cyclohexyl as β-branched, Ashworth I does not expressly teach that further increasing the β-branching of the substituent would have resulted in increased stability or potency. Indeed, as Patent Owner explains (PO Resp. 47–48), Ashworth I's disclosure of compounds with a quaternary carbon is most relevant to an adamantyl group because adamantyl also has a quaternary carbon (a carbon with four-non-hydrogen groups attached to it). *Id*. at 47. In Ashworth I's pyrrolidides, compound 11 (with a quaternary carbon) is less potent than compounds 5, 7, and 9, each of which has a tertiary carbon (a carbon with three-non-hydrogen groups attached to it like compound 25's cyclohexyl). Ex. 1007, 1164, Table 1; Ex. 2056 ¶¶ 204–06. Similarly, Ashworth I's compound 27, with a t-butyl which contains a quaternary carbon, is less potent than compounds 24–26, each of which has a tertiary carbon. Ex. 1007, 1166, Table II; Ex. 2056 ¶¶ 205–06. Furthermore, Ashworth I does not teach that adamantyl would have been interchangeable with compound 25's cyclohexyl group. Ex. 2056 ¶ 196. Petitioners' Reply contends that "[b]oth Ashworth and Villhauer used cyclopentyl and cyclohexyl *to impede cyclization*" (emphasis added), but Petitioners do not provide factual support for this assertion. *See* Pet. Reply 14 (citing Pet. 26 (citing Ex. 1008, 5)). As further discussed below, Villhauer (Ex. 1008), cited by Petitioners in support, does not discuss impeding cyclization by the addition of cycloalkyls, and as noted above, neither does Ashworth I.

(3) Prior Art Does Not Teach or Suggest Modifying with a "Bulky" Substituent

Petitioners' Reply emphasizes "bulky" substituents, as opposed to "β-branched" or "large" substituents referred to in the Petition, stating that "the petition's rationale [was] that bulky is better." *Compare* Pet. 26, *with* Pet. Reply 14–15; *see* Ex. 1074 (Dr. Rotella's second declaration) ¶ 23 ("As discussed above, the teaching of the art at the time of the invention was that *bulkier, not more branched,* alkyl groups were preferred) (emphasis added). Petitioners, however, do not cite to specific disclosure from either Ashworth I or Villhauer as expressly teaching the substitution of a "bulky" structure at the P2 position of an amino acyl pyrrolidine in order to reduce the intramolecular cyclization described by Ashworth I or to increase stability. *See* Pet. 25–33. Although Petitioners characterize the cyclohexyl group on compound 25 as "bulky" (Pet. 7; Ex. 1003 ¶ 115), Ashworth I itself does not refer to a "bulky" substituent. Moreover, neither the Petition nor Petitioners' Reply sufficiently explains what a "bulky" substituent encompasses or why a skilled artisan would understand Ashworth I's cyclohexyl and cyclopentyl alkyl substituents or adamantyl to have been "bulky." *See* Pet. 7, 25–27, 30–33. In addition, Petitioners do not sufficiently explain, based on express teachings of Ashworth I or Villhauer, why a skilled artisan would have concluded that the increased stability and potency of Ashworth I's compound 25, for example, was due to its alleged "bulkiness," as opposed to some other characteristic of compound 25.

According to Petitioners' Reply, "those in the art already knew that P2 should be 'bulky.'" Pet. Reply 13 (citing Ex. 2096, 833 ("Mentlein")). Petitioners, however, do not sufficiently explain the relevance of Mentlein to the proposed modification. Pet. Reply 13. Mentlein states that "[i]n the P_2

position bulky amino acids with an obligate free amino group are preferred" and "a bulky N-terminal amino acid with free amino group (P_2 position) as with Tyr or His in the peptides investigated here is optimal for high DPP-IV activity." Ex. 2096, 833. Petitioners do not cite disclosure from Mentlein teaching that further increasing the bulkiness of the substituent in the P_2 position would have resulted in increased stability or potency. In addition, Petitioners do not adequately explain how a skilled artisan would have reconciled Ashworth I's teaching that "β-branched α-amino acid derivatives were the most potent compounds" (Ex. 1007, 1165) with Mentlein's reference to "bulky" amino acids (Ex. 2096, 833). Thus, Petitioners do not adequately explain why this disclosure would have led a skilled artisan to reasonably expect that replacing compound 25's cyclohexyl with an adamantyl group, both allegedly bulky cycloalkyls, would have increased its stability or potency.

According to Dr. Rotella, Ashworth I discloses that changing the substituent at the 2-position of the acetylpyrrolidine-2-carbonitrile from a straight chain alkyl group such as lysine (compound 28) "to a more bulky cycloalkyl" group such as cyclohexyl (compound 25) increases the stability from 24 hours to greater than 48 hours. Ex. 1003 ¶ 115; *see id*. at ¶ 117 (referring to substituting with a "larger cycloalkyl moiety"). Dr. Rotella opines that given this teaching, a skilled artisan would have had reason to try even "larger, bulkier alkyl groups," such as substituting the cyclohexyl group of compound 25 with an adamantyl group, "in order to further minimize cyclization and increase the stability of the compound under similar conditions." *Id*. We are not sufficiently persuaded by Dr. Rotella's opinion, and determine that it is based on hindsight knowledge of

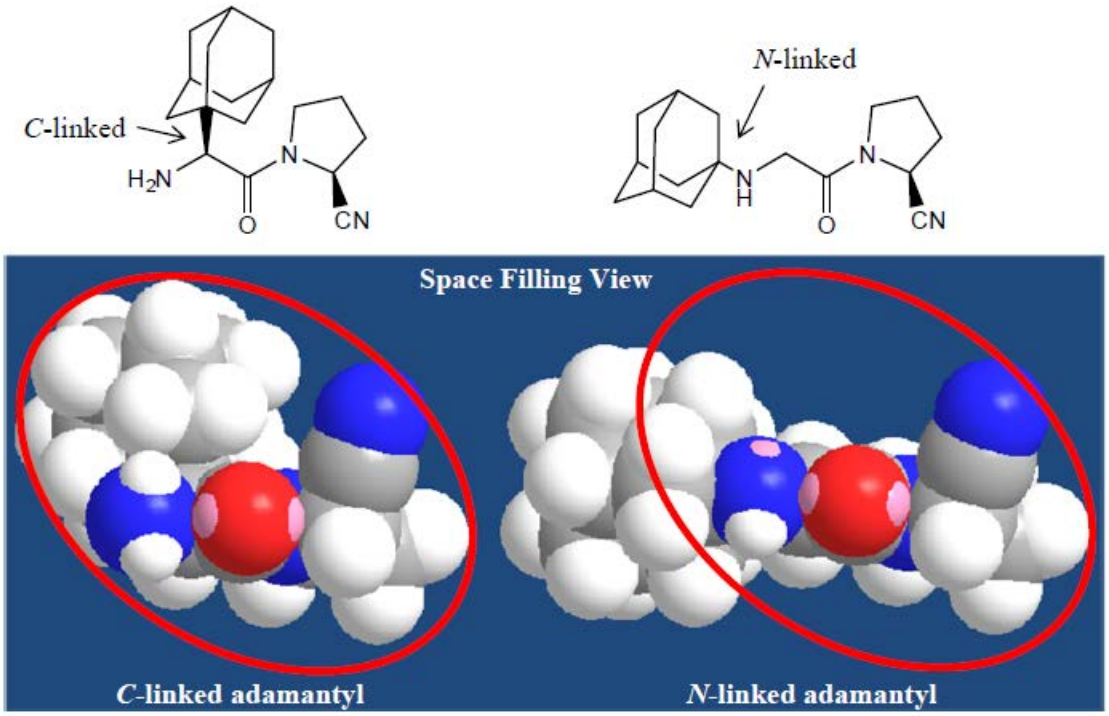
saxagliptin's structure. As discussed above, Ashworth I did not teach "bulky" substituents, nor did it teach that increasing the bulkiness of a substituent minimized cyclization or otherwise, increased stability. Thus, Petitioners have not adequately demonstrated that a skilled artisan would have reasonably expected that increasing the alleged bulkiness of the cyclohexyl group of compound 25 would have increased its stability or potency.

(4) Villhauer Does Not Support Petitioners' Position

Petitioners' reliance on Villhauer also does not establish that a skilled artisan would have had a reasonable expectation of success in increasing stability or potency. Pet. 26. As Petitioners admit, Villhauer contemplated substitution of cycloalkyl groups on the terminal amine (i.e., "N-linked") as opposed to on the β-carbon of the glycyl (i.e., "C-linked") of 2-cyanopyrrolidines. Pet. 25 (citing Ex. 1008, Abstract). Villhauer discloses substitution with ($C_{3–12}$) cycloalkyl, preferably cyclopentyl or cyclohexyl, with a small ($C_{1–3}$) hydroxyalkyl. Ex. 1008, 2, 4. Villhauer also discloses substitution with adamantyl, and characterizes as "[e]ven more preferred," a genus of substituents that includes adamantyl. Pet. 26 (citing Ex. 1008, 4, 5). According to Petitioners, a skilled artisan would have had good reason to employ Villhauer's "'even more preferred' adamantyl in place of Ashworth's cyclohexyl compound 25 due to the comparisons Ashworth had already made, using additional candidates that Villhauer taught." Pet. 26 (citing Ex. 1003 ¶ 101). Petitioners' Reply also avers that "Villhauer was pursuing similar modifications on the P2 nitrogen using *bulkier* substituents." Pet. Reply 13 (emphasis added) (citing Pet. 26).

Dr. Weber provides figures, reproduced below, of the structures

resulting from substituting C-linked and N-linked adamantyl groups onto Ashworth I's compound 25.



Ex. 2056 ¶ 200, Ex. 2259A. According to Patent Owner, the figures above illustrate C-linked and N-linked adamantyl substituents, including the different orientation of the substituents in three-dimensional space. PO Resp. 43 (citing Ex. 2056 ¶ 200). Petitioners do not explain sufficiently why a skilled artisan would have applied Villhauer's teaching of an N-linked adamantyl to a C-linked substitution of compound 25. Pet. 26–27, 30–33; Ex. 1074 ¶ 20 (Dr. Rotella summarily stating that a skilled artisan "could reasonably expect to obtain a potent DPP 4 inhibitor by moving the adamantyl group from nitrogen to carbon on this template"). For example, Petitioners do not explain adequately why a skilled artisan would have reasonably expected that the stabilities of the two would be similar despite the difference in orientation of N-linked and C-linked substituents on 2-

cyanopyrrolidines. *See* Ex. 2056 ¶¶ 198–200; Ex. 2221, 22:23–23:8 (Dr. Rotella expressing no opinion on what position the N-linked and C-linked substituents groups would occupy in space). Indeed, Dr. Weber opines that a skilled artisan would have understood that N-linked P2 groups increased stability because the more sterically hindered secondary amine is less likely to react with an electrophile in the P1 group. PO Resp. 11–12 (citing Ex. 2056 ¶ 54); Ex. 2056 ¶¶ 190, 207.

Villhauer does not teach modifying the P2 group with a "bulky" substituent, as Petitioners argue, to increase stability or potency. Petitioners do not cite disclosure from Villhauer characterizing the disclosed substituents on the P2 groups as "bulky" or as providing steric hindrance. Furthermore, Dr. Weber states that Villhauer disclosed many alkyl groups that a skilled artisan would have recognized as having more than the 6 carbons of cyclohexyl in compound 25 (i.e., "bulkier" than compound 25). Ex. 2056 ¶ 203; PO Resp. 45. And as Petitioners recognize, Villhauer characterizes an entire genus of substituents that includes adamantyl as "[e]ven more preferred." Pet. 26; Ex. 2221, 21:7–14 (Dr. Rotella agreeing that the number of molecules that are embraced by the class of compounds is many of hundreds). Petitioners do not sufficiently show why a skilled artisan would have reasonably expected adamantyl, over these other allegedly "bulky" compounds, to increase stability or potency. Furthermore, Petitioners' conclusion that because both Ashworth and Villhauer used cyclopentyl and cyclohexyl to impede cyclization and Villhauer characterized adamantyl as even more preferred than unsubstituted cyclohexyl, a skilled artisan would have understood that adamantyl's "extra bulk must be the basis for this preference" is speculative. Pet. Reply 14.

Petitioners reason that "both adamantyl and cyclohexyl are N-linked in Villhauer so the linkage cannot be the reason for Villhauer's preference." *Id*. Neither Ashworth I nor Villhauer discusses "imped[ing] cyclization," and as noted above, Villhauer identifies a genus of substitutes that includes adamantyl as "[e]ven more preferred." Petitioners do not point to specific disclosure in Villhauer for the preference.

(5) Dr. Rotella's Opinion Does Not Support Petitioners' Position

Dr. Rotella's opinion likewise does not sufficiently support a finding that a skilled artisan would have reasonably expected that the proposed modification would have increased compound 25's stability or potency. Dr. Rotella opines that "[o]ne of ordinary skill would have understood that intramolecular cyclization could be reduced by both selecting against a conformation that favors intramolecular cyclization (i.e., selecting against the cis conformation) and through the addition of a large, steric group to the compound" to restrict the compound's range of motion. Ex. 1003 ¶ 112; *see id*. at ¶¶ 111, 113. For the bases for his opinion, Dr. Rotella cites to Debnath Pal & Pinak Chakrabarti, *Cis Peptide Bonds in Proteins: Residues Involved, their Conformations, Interactions and Location*, 294 J. of Mol. Biol. 271 (1999), 274 (Ex. 1026, "Pal"). Ex. 1003 ¶ 112. Dr. Rotella, however, does not sufficiently explain Pal's relevance to modifying compound 25 to include an adamantly group on P1. *Id*. As Patent Owner notes (PO Resp. 42), Petitioners do not sufficiently point to specific disclosure in Pal studying the effect on stability by placing a large steric group in the alpha-position of the P2 residue of substituted pyrrolidines. *See* Ex. 2056 ¶ 209. Moreover, Pal does not discuss the cis conformation in the context of a small dipeptide molecule, such as a DP 4 inhibitor. *See* PO Resp. 42.

Dr. Rotella concludes that a skilled artisan "would have expected the modification to improve the characteristics of the compound, and particularly, to increase the potency and stability of the compound." Ex. 1003 ¶ 121. Dr. Rotella's basis for this conclusion is that a skilled artisan "would only need to verify the readily predicted results of adding an adamantyl group and removing the cyclohexyl group. Such a modification requires less experimentation than is invited by the specification of the '186 patent." *Id*. at ¶ 122. The prior art's invitation to experiment, however, does not sufficiently demonstrate a reasonable expectation of success in this case. *See Cyclobenzaprine*, 676 F.3d at 1073 (stating that "where the prior art, at best, gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible").

For the foregoing reasons, we determine that a skilled artisan would not have reasonably expected that modifying Ashworth I's compound 25 by substituting its cyclohexyl group with adamantyl would have increased its stability or potency.

f) Hydroxylating an Adamantyl-Substituted Compound 25

Referring to Raag, Petitioners argue that a skilled artisan would have had reason to modify compound 25 by using a hydroxylated adamantyl metabolite in order to improve stability and bioavailability of the compound. Pet. 27–28 (citing Ex. 1003 ¶ 124). As discussed above, we determine that the skilled artisan would not have had reason to incorporate an adamantyl group onto compound 25. Nonetheless, even assuming that initial modification, we find there is insufficient disclosure from the time of the

invention to support a finding that a skilled artisan would have reasonably expected that the proposed further modification of hydroxylating the adamantyl group would improve stability and bioavailability of the compound.

(1) Petitioners' Contentions

Petitioners argue that skilled artisans routinely investigated metabolites of lead compounds in order to improve metabolic stability and it was known that metabolites can have other advantages, including increasing solubility, absorption, and bioavailability. Pet. 27 (citing Ex. 1003 ¶ 54). According to Petitioners, Raag describes the oxidation of adamantane by the detoxifying agent P-450 and teaches that adamantane is consistently metabolized to 1-hydroxyadamantane. Pet. 27 (citing Ex. 1009, 2674, 2678). Petitioners further contend that Raag discloses that adamantane is not "very soluble," but Ashworth I taught "that a large lipophilic substituent was advantageous for N-glycyl-2-cyanopyrrolidine stability," and Villhauer "taught using adamantyl as a large substituent." Pet. 27 (citations omitted). Petitioners also aver that Villhauer teaches a hydroxylated 1-methylcylopentyl substituent. Pet. 27. Petitioners conclude that the prior art taught those skilled in the art that hydroxylation of "a large lipophilic substituent like adamantyl placed on a glycyl-proline dipeptide analogue would provide a reasonable expectation of working as a DP-IV inhibitor." Pet. 28 (citing Ex. 1003 ¶ 149).

(2) Unpredictability of Metabolism

We agree with Patent Owner that given the unpredictability of the metabolism of adamantyl-modified compound 25, a skilled artisan would not have reasonably expected that the proposed modification would have

improved stability and bioavailability of non-hydroxylated compound 25. *See* PO Resp. 52–53. As an initial matter, based on Raag, Petitioners assert that "adamantane is not very soluble." Pet. 27 (citing Ex. 1009, 2675). Petitioners do not sufficiently explain the relevance of adamantane's solubility profile to the question of whether a skilled artisan would have understood deshydroxy saxagliptin to be insoluble. *See* PO Resp. 52 (illustrating the two molecules). As Dr. Weber opines, "[a]damantane is a very different substrate from the adamantyl amino acid derivatives like saxagliptin (or in this case, its deshydroxy derivative) and one of skill in the art would not expect the metabolic profile of the two substrates to be the same." Ex. 2056 ¶ 212. Dr. Weber explains that "[w]here adamantane has only two types of unique carbon atoms capable of oxidation, the *C*-linked adamantyl cyclopropyl-fused cyanopyrrolidines have multiple potential oxidation sites, some of which are not on the adamantyl ring." *Id*. at ¶ 213. Dr. Rotella likewise testified as follows:

> Q. And adamantane is, by itself, not the molecule that's described in the Villhauer WO 98/19998 publication or in the patent in suit describing saxagliptin; correct?
> MS. STEINER: Objection to form.
> THE WITNESS: That's correct.

Ex. 2174, 164:19–24.

> Q. Those molecules have other structure attached to them; correct?
> A. Yes.
> Q. And the presence and nature of that other structure can affect the metabolic fate of that adamantane ring; correct?
> MS. STEINER: Objection. Form.
> THE WITNESS: Depending on the modifications, yes.

Id. at 165:1–9.

Petitioners reply that a skilled artisan "would expect oxidation, most likely at a tertiary carbon" and "adamantyl binds to the dipeptide at one tertiary carbon, leaving three interchangeable tertiary carbons for oxidation." Pet. Reply 15–16. Petitioners' contention, however, does not adequately address the metabolic unpredictability of the entire molecule. In addition, as Dr. Weber explains (Ex. 2056 ¶ 215), a prior art reference that studied the metabolic profile of rimantadine, a modified adamantine, reported that multiple ring-hydroxylated derivatives were formed. Ex. 1016, 1703. Dr. Weber states the same study showed the formation in a human patient of eight metabolites of amantadine, an adamantyl-containing compound, but none of them were a metabolite with hydroxylation on the adamantane ring. PO Resp. 53; Ex. 2056 ¶ 215 (citing Ex. 1016, 1703).

In its Reply, Petitioners state that Villhauer teaches hydroxyadamantyl in the P2 position. Pet. Reply 16 (citing Ex. 2013, 7:15–25). Given the difference of N-linked molecules disclosed in Villhauer from C-linked molecules like saxagliptin, Petitioners have not adequately established the relevance of this disclosure and how it establishes the predictability of the metabolism of adamantyl-modified compound 25. *See* Ex. 2056 ¶¶ 237, 241.

Thus, we agree that given the unpredictability of the metabolism of an adamantyl analog of Ashworth I's compound 25, a skilled artisan would not have reasonably expected the proposed modification to improve stability and bioavailability of the compound. *See* Ex. 2056 ¶ 216.

g) All of the Proposed Modifications Together

Even assuming Petitioners have established that each of the proposed modifications would have been obvious, Petitioners have not established that

a skilled artisan would have reasonably expected that all of the modifications as a whole would have been successful. 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).

As Patent Owner explains (PO Resp. 54–55), each of the proposed modifications to Compound 25 necessarily changes the structure of that compound, and would have resulted in an unknown and uncharacterized compound, yet Petitioners do not sufficiently take into account the reasonable expectation of success in making a subsequent modification given the previous modification. In particular, Patent Owner argues that Petitioners' Declarant, Dr. Rotella, "does not explain factually" the motivation for taking sequential, independent steps to reach saxagliptin, or consider whether the multiple modifications would have been made together with a reasonable expectation of success. PO Resp. 55–56 (citing Ex. 1003 ¶¶ 95, 118, 138, 146–148). Dr. Weber concludes that a skilled artisan would have had no reason to select compound 25 "and make the multiple modifications together to reach the claimed invention with a reasonable expectation of success." Ex. 2056 ¶ 259. We determine that Petitioners have not sufficiently accounted for the unpredictable effect of one modification on the other.

For example, Petitioners have not shown sufficiently how a skilled artisan would have reasonably predicted the effect of the modification on the P2 group, by substitution with a quaternary carbon, such as in saxagliptin, on the modification on the P1 group, by adding a cyclopropyl in the *cis*-4,5

orientation. *See* Ex. 2056 ¶ 231; Ex. 2237. As discussed above, Ashworth I discloses that compounds with a quaternary carbon substituent on the P2 group were less potent than compounds with a tertiary carbon substituent. Ex. 1007, 1164, Table 1, 1166, Table II; Ex. 2056 ¶¶ 204–06. But Petitioners do not show whether a skilled artisan would have reasonably predicted that this result would have been the same or different with the combined modification on the P1 group by the addition of a cyclopropyl in the *cis*-4,5 orientation. In other words, Petitioners do not show that a skilled artisan would have reasonably expected that the combined modifications would have been successful based on the predictability of the individual modifications. Indeed, Dr. Weber opines that "[t]he increase in potency observed by the *combination* of a cyclopropyl in the *cis*-4,5 orientation on the pyrrolidine ring in P1 and a quaternary carbon, such as in saxagliptin, on the P2 group could not have been predicted by one of skill in the art at the time of the invention." Ex. 2056 ¶ 231 (emphasis added).

Thus, we conclude that the Petitioners have not adequately established that a skilled artisan would have reasonably expected all the proposed modifications to compound 25 to have been successful as a whole.

2. Conclusion as to Alleged Obviousness of Claim 25

For the foregoing reasons, we determine that Petitioners have not shown by a preponderance of evidence that the subject matter of claim 25 would have been obvious.

3. Secondary Considerations of Nonobviousness

In addition to finding that Petitioners have not established by a preponderance of the evidence that the subject matter of claim 25 would have been obvious, we further determine that secondary considerations of

nonobviousness also weigh in favor of a finding of nonobviousness of claim 25. Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *Graham*, 383 U.S. at 17. "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). As the Federal Circuit noted, secondary considerations "may often be the most probative and cogent evidence" of nonobviousness. *Id*. "[T]he Board should give the objective indicia its proper weight and place in the obviousness analysis, and not treat objective indicia of nonobviousness as an afterthought." *Leo*, 726 F.3d at 1358.

Patent Owner argues that the objective indicia of non-obviousness include: 1) failure of others; 2) saxagliptin's properties were unexpected and unpredictable; 3) saxagliptin met a long-felt need; and 4) saxagliptin is commercially successful. PO Resp. 57–58. All types of objective evidence of nonobviousness must be shown to have a nexus to the claimed invention. *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (copying); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) (praise). The stronger the showing of nexus, the

greater the weight accorded the objective evidence of nonobviousness. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985).

a) Failure of Others

The claimed compounds of the '186 patent are directed "to a method for treating diabetes, especially Type II diabetes" as well as other conditions. Ex. 1001, 1:19–21. Dr. M. James Lenhard, M.D., Patent Owner's expert, notes that saxagliptin was the first invented DP 4 inhibitor to attain FDA approval, providing a new class of drugs for the treatment of type 2 diabetes. Ex. 2057 ¶ 60. Patent Owner emphasizes that not a single DP 4 inhibitor compound in the prior art has been FDA approved and that these failures were for various reasons. PO Resp. 58–59; Ex. 2056 ¶ 251. *See Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, Civ. No. 09-MD-2118-SLR, 2010 WL 3766530 (D. Del. Sept. 21, 2010) (recognizing the failure to obtain FDA approval is relevant evidence of failure of others). Patent Owner argues that failure of other DP 4 inhibitor compounds to obtain FDA approval "highlight[s] the difficulty and unpredictability in obtaining a DP 4 inhibitor with all of the properties necessary for a safe and effective treatment of type-2 diabetes" and, thus, suggests that saxagliptin is nonobvious. PO Resp. 58–59 (citing Ex. 2056 ¶¶ 141, 147–148, 251, 253–254). In particular, Patent Owner identifies Ashworth I's compounds, NVP-DPP728, P32/98, Vildagliptin, denagliptin, and compound E-3024 as being among "failures in this field." PO Resp. 58–60 (citing Exs. 2050, 2056, 2057, 2081, 2098, 2161).

Petitioners disagree that compound 25 was a failure, arguing that

"Ashworth recognized Compound 25 as a potent, stable and non-toxic DPP-4 inhibitor *in vitro*." Pet. Reply 18 (citing Ex. 1007, 1165–66). Petitioners also disagree that lack of FDA approval of a compound for any reason is indicative of failure and asserts that Patent Owner "shows no nexus between any prior art FDA failure and unexpected results" and "fails to show that the *closest* prior art (Compound 25) failed or would have failed to obtain FDA approval for clinical reasons." Pet. Reply 18–19 (citing, e.g., Ex. 2056 ¶ 251; Ex. 1073, 19:12–34:18 (claim 8), 34:19–37:20 (claim 10), 99:9–102:20).

We determine that the failure of others in the field of DP 4 inhibitors to obtain FDA approval for the treatment of diabetes is an objective indicia of nonobviousness of claim 25. We disagree that Ashworth I identified compound 25 as a candidate for further study as a DP 4 inhibitor, as evidenced by Ashworth II's focus on a different compound structure. Even assuming, however, that compound 25 could have obtained FDA approval, Petitioners do not sufficiently address the numerous other prior art DP 4 inhibitors that failed to obtain FDA approval. *See* Ex. 2056 ¶¶ 98–99. We further determine that the failure of others to obtain FDA approval for DP 4 inhibitors as a treatment for diabetes has a nexus to claim 25 and the other challenged claims because saxagliptin was directed to the treatment of diabetes. Ex. 1001, 1:19–21. Thus, we determine this consideration weighs in favor of the patentability of the challenged claims.

b) Unpredictable and Unexpected Properties

Patent Owner asserts that saxagliptin yielded the following unpredictable and unexpected features, compared to prior art DP 4 inhibitors, including compound 25:

> extended, slow, tight binding; 2) improved chemical stability under physiologic conditions; 3) an active metabolite that extends *in vivo* efficacy; 4) an extended pharmacodynamic profile; 5) formation of favorable binding interactions with DPP-4; and 6) the ability to use a low once-daily dosing regimen to safely and effectively treat patients with type-2 diabetes.

PO Resp. 60. According to Patent Owner, for example, saxagliptin's cis-4,5 cyclopropyl group imparts surprising improved chemical stability, as compared to Ashworth I's compounds. *Id*. at 61 (citation omitted). Patent Owner further avers that the combination of the cis-4,5 cyclopropyl group and "an entropically constrained quaternary P2 group resulted in an unexpected increase in potency." *Id*. at 62 (citation omitted). In addition, Patent Owner contends that saxagliptin's formation of an active metabolite in humans "bound to DPP-4 with slow tight binding kinetics" and resulted in an "an extended pharmacodynamic profile *in vivo*." *Id*. at 63. Specifically, contends Patent Owner, "while the parent saxagliptin molecule disappears from the blood, the pharmacodynamic effect continues by virtue of the active metabolite." *Id*. (citations omitted). Patent Owner posits that saxagliptin's properties are the result of "unexpectedly favorable binding interactions in the DPP-4 active site," due to the cyclopropyl group, and the C-linked positioning of the adamantyl group. *Id*. at 63–64 (citations omitted). Patent Owner concludes that saxagliptin's properties were unpredictable and unexpected by comparison to the available data for compound 25 and other more advanced inhibitors. *Id*. at 65.

Reasserting their arguments with respect to obviousness, Petitioners argue that saxagliptin reflects steady progress through modifications and optimizations, with a reasonable expectation of success. Pet. Reply 19–20

(citations omitted). In addition, Petitioners assert that Patent Owner fails to identify any claim limitation or support in the '186 patent specification that correlates with Patent Owner's proffered unexpectedly superior properties. *Id*. at 20. Petitioners further assert that "unexpected results must be differences in kind, not simply differences of degree," and that Patent Owner has not demonstrated that other gliptins lack sufficient binding or stability to be clinically effective. Pet. Reply 20–21 (citations omitted).

We determine that the unpredictable and unexpected results of saxagliptin's properties are objective indicia of nonobviousness of claim 25. Patent Owner sufficiently ties the unpredictable and unexpected binding of saxagliptin to DP 4 and its active metabolite to the structure of saxagliptin, including its cyclopropyl group and C-linked positioning of the adamantyl group. Thus, we determine this consideration weighs in favor of the patentability of claim 25.

c) Long-Felt Need

According to Patent Owner, saxagliptin was the second DP 4 inhibitor to obtain FDA approval, but was invented before the first DP 4 inhibitor to obtain FDA approval. PO Resp. 65 n.3. *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (holding that long-felt need is based on the filing date of the challenged invention). Patent Owner asserts that saxagliptin's "superior side effect profile" and "efficacy as both a monotherapy and in combination with other type-2 diabetes drugs" satisfied a long-felt need for a safe type-2 diabetes alternative treatment. PO Resp. 65 (citation omitted).

Petitioners argue that a skilled artisan "familiar with these applications would not have appreciated that any need had been met other

than the proffering of yet another DPP-4 inhibitor candidate" and "the need in October 2000 was for a new treatment for type-2 diabetes, and that need continues today." Pet. Reply 22–23 (citation omitted). Petitioners also contend that saxagliptin was not specifically recognized and was not specifically claimed until the 2011 reissue application. *Id*. at 22–23. Petitioners further argue that, even if there was a need for a DP 4 inhibitor, it was first met by the invention of vildagliptin, before saxagliptin. Pet. Reply 23 (citation omitted). Petitioners also assert that, although regulatory approval is not a test for patentability, vildagliptin and sitagliptin both received regulatory approval prior to saxagliptin. Pet. Reply 23–24 (citations omitted).

We determine that saxagliption's satisfaction of a long-felt need is objective indicia of nonobviousness of claim 25. That other DP 4 inhibitors also satisfied this need does not diminish saxagliptin's satisfaction of this need. Thus, we determine this consideration weighs in favor of the patentability of claim 25.

d) Commercial Success of Saxagliptin

Patent Owner argues that the substantial sales and market share of its products Onglyza and Kombiglyze XR ("the Onglyza Family") are due to the active ingredient, saxagliptin, and all of its associated properties. PO Resp. 66–67 (citation omitted). According to Patent Owner, since the launch of Onglyza in August 2009, the Onglyza Family of products has generated over $3.5 billion in total sales through September 2015, and the number of dispensed prescriptions totaled approximately 12.8 million between August 2009 and October 2015. *Id*. at 66 (citation omitted).

Petitioners do not materially dispute the $3.5 billion in sales number.

Tr. 129: 8–12. Petitioners, however, argue that Patent Owner's sales figure is inflated because "'it does not take into account discounts and rebates that are unearned by the selling companies.'" Pet. Reply 24–25 (citations omitted). Petitioners further dispute that Patent Owner's market share indicates nonobviousness. Pet. Reply 25–27 (citations omitted). Petitioners aver that "saxagliptin's relatively small market share proves saxagliptin has not distinguished itself from competing gliptins." *Id*. at 26; Tr. 128:19–22 (Petitioners' counsel estimated the Onglyza Family of products has approximately 13% market share).

We determine that Patent Owner's evidence of saxagliptin's commercial success is not as persuasive as the other secondary considerations, given Petitioners' arguments with respect to discounts and the market share for the Onglyza Family of products.

e) Conclusion as to Secondary Considerations

In sum, the secondary considerations of nonobviousness raised by Patent Owner weigh in favor of the patentability of claim 25.

4. Conclusion

As discussed above, we determine that Petitioners have not established that claim 25, a saxagliptin-specific claim, would have been obvious and that the secondary considerations weigh in favor of the patentability of claim 25. Petitioners contend that "all involved claims should fall with the so-called saxagliptin-specific claims [claims 25–28, 32–35, 39, and 40]." Pet. Reply 27. Thus, we determine that Petitioners have not established, by a preponderance of the evidence, that all the challenged claims, claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent, are unpatentable.

III. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the ’186 patent have not been shown to be unpatentable by a preponderance of the evidence; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG, TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A. INC., and SUN PHARMACEUTICALS INDUSTRIES, LTD., SUN PHARMA GLOBAL FZE
and AMNEAL PHARMACEUTICALS LLC,
Petitioners,

v.

ASTRAZENECA AB,
Patent Owner.

Case IPR2015-01340
Patent RE44,186 E

Before MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judge*, RAMA G. ELLURU and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

TIERNEY, *Vice Chief Administrative Patent Judge*, concurring in the result.

I concur in the result. Specifically, I agree with the majority that Petitioners have failed to establish that a skilled artisan would have had reason to make the proposed modifications with a reasonable expectation of success in arriving at the claimed compound.

FOR PETITIONER MYLAN:

Steven Parmelee
sparmelee@wsgr.com
Richard Torczon
rtorczon@wsgr.com
Jad A. Mills
jmills@wsgr.com
Douglas H. Carsten
dcarsten@wsgr.com

FOR PETITIONER AUROBINDO:
Sailesh K. Patel
SPatel@schiffhardin.com
George Yu
gyu@schiffhardin.com

FOR PETITIONER SUN/AMNEAL:
Samuel Park
spark@winston.com
Andrew Sommer
asommer@winston.com

FOR PETITIONER WOCKHARDT:
Patrick Gallagher
pcgallagher@duanemorris.com

FOR PETITIONER TEVA:
Gary Speier
gspeier@carlsoncaspers.com
Iain McIntyre
IMcIntyre@carlsoncaspers.com

FOR PATENT OWNER:
Charles Lipsey
Charles.lipsey@finnegan.com
David Weingarten
David.weingarten@finnegan.com
Eric Grondahl

egrondahl@mccarter.com
John Livingstone
Jonh.livingstone@finnegan.com
Anthony Hartmann
Anthony.hartmann@finnegan.com