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Paper 16
Entered: May 2, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

ASTRAZENECA AB,
Patent Owner.

Case IPR2015-01340
Patent RE44,186 E

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

ELLURU, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 (Paper 3, 1 "Pet.") of RE44,186 E (Ex. 1001, "the '186 patent"). Astrazeneca AB ("Patent Owner") filed a Patent Owner Preliminary Response. Paper 7 ("Prelim. Resp."). We subsequently ordered Petitioner to respond to certain arguments raised in the preliminary response. Paper 10. Petitioner filed the authorized Reply to Patent Owner's Preliminary Response. Paper 11 ("Reply").

We denied institution of an *inter partes* review of all the challenged claims. Paper 12, 14. Petitioner subsequently filed a Request for Rehearing (Paper 13), which we granted in an Order concurrently issued with this Decision. Paper 15.

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the current record, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of challenged claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent. Therefore, we institute an *inter partes* review of the challenged claims of the '186 patent.

A. Related Matters

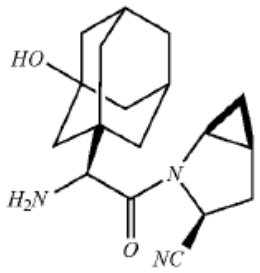
According to Petitioner, the '186 patent is at issue in numerous district court actions. Pet. 16; Papers 2, 5.

B. The '186 patent (Ex. 1001)

The '186 patent is directed to "cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV" ("DP-IV"). Ex. 1001, 1:19–20. DP-IV 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-IV-mediated enzymatic cleavage. *Id*. at 1:55–64. Inhibitors of DP-IV *in vivo* may, therefore, increase endogenous levels of glucagon, and serve to ameliorate the diabetic condition. *Id*. at 1:64–67.

C. Illustrative Claim

For the purposes of this Decision, claim 25[1] is illustrative of the challenged claims and is drawn to the compound shown below, or a pharmaceutically acceptable salt thereof.



This 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

[1] All the challenged claims are directed to compounds, compositions, and methods relating to the specific compound recited in claim 25.

"saxagliptin." *See* Pet. 3; Prelim. Resp. 22–23; Ex. 1003 ¶ 15; Ex. 2047, 9.

D. Prior Art Asserted by Petitioner

Pursuant to 37 C.F.R. § 42.104(b), Petitioner identifies the following prior art as the basis for challenging claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent. S*ee* Pet. 5–6.

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").

Petitioner also refers to the Declaration of David P. Rotella, Ph.D. ("Dr. Rotella"). Ex. 1003.

E. Asserted Grounds

Petitioner challenges claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent on the following grounds. Pet. 2–3, 22, 46, 50, 53.

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, 19, 20, and 21

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (mem.) (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Petitioner contends that the claims use conventional terminology. Pet. 18–19. Patent Owner does not contest the construction of any claim term.

For the purposes of this Decision, we need not expressly construe any claim terms.

B. Ground 1 (claims 1, 2, 4, 6–11, 25–28, 32–35, 39, and 40)

Petitioner contends that claims 1, 2, 4, 6–11, 25–28, 32–35, 39, and 40 would have been obvious over Ashworth I, Villhauer, Raag, and Hanessian I. Pet. 22–46.

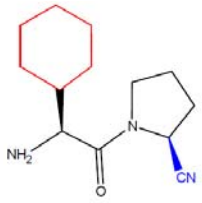
Petitioner contends that each of claims 1, 2, 4, 6–11, 25–28, 32–35, 39, and 40 either defines the saxagliptin compound or encompasses saxagliptin within its scope. Pet. 22–23. Petitioner further asserts that claim 25 is directed to the saxagliptin compound, or a pharmaceutically salt thereof. *Id*. at 23. "Thus, if the saxagliptin compound (and its use to treat type II diabetes) is obvious under 35 U.S.C. § 103, then all of these claims are obvious." *Id*. Accordingly, with respect to this asserted ground, we focus on whether Petitioner has established a reasonable likelihood that it would prevail in showing that claim 25 is unpatentable.

In resolving the question of the obviousness of the claims, we consider the following underlying factual determinations: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; and (3) the level of skill in the art; and (4) secondary considerations of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). 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).

Applying this analysis, Petitioner contends that one of ordinary skill in the art[2] would have selected Ashworth I's compound 25 ("compound 25") as a lead compound in the development of DP-IV inhibitors "because of its superior combination of potency and stability." Reply 1 (citing Pet. 24–25).

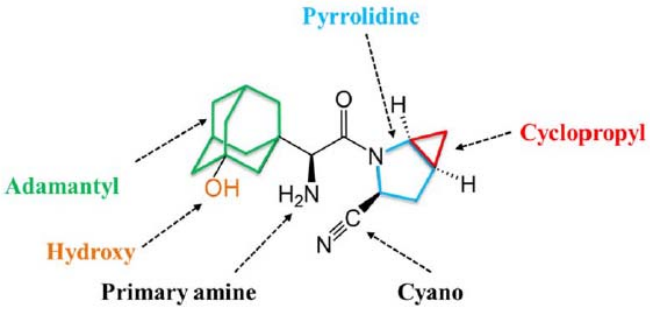
Compound 25 is illustrated below.



Pet 7, 25. 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. Pet. 7.

The chemical structure of saxagliptin is shown below.

[2] At this stage of the proceeding, we accept Petitioner's contention that a person of ordinary skill in the art would typically "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 less education but considerably more professional experience. Pet. 12; *see* Prelim. Resp. 31.



Prelim. Resp. 23. The structure of saxagliptin differs from compound 25 in having 3-hydroxyl adamantyl in place of the cyclohexyl group and a cyclopropyl fusion of the pyrrolidine ring[3]. *Id*.

Petitioner argues that one of ordinary skill in the art would have been motivated to modify compound 25 by 1) replacing the 6-carbon cyclohexyl group at the 2-position with a 10-carbon adamantyl moiety;[4]
2) hydroxylating the adamantyl moiety at a specific position; and 3) adding a cyclopyropyl ring to the pyrrolidine portion of compound 25 in the 4S,5S configuration. Pet. 25–33. As discussed in more detail below, at this point in the proceeding, we are persuaded that a skilled artisan would have made each of these modifications with a reasonable expectation of success in arriving at the compound.

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[3] Patent Owner explains that DP-IV inhibitors were typically designed with two groups, generally referred to as a "P1 group" and "P2 group." Prelim. Resp. 9 (citation omitted). Saxagliptin features a dipeptide format comprising P1 and P2 groups in which the "P1" core is made up of a cyclopropyl group fused to a pyrrolidine ring at the 4, 5 position and the pyrrolidine ring further has a cyano group in the S configuration. *Id*. at 22. The P2 group consists of an adamantyl group, with a hydroxy group in its 3 position. *Id.* The "backbone" of P1 and P2 include a primary amine. *Id*.
[4] Adamantyl is a (C_{10}) tricycloalkyl. Ex. 1003 ¶ 102.

As a preliminary matter, and for purposes of this Decision, we accept Petitioner's assertion that a person of ordinary skill would have chosen to modify compound 25. At this point in the proceeding, we credit Dr. Rotella's testimony that a skilled artisan would have selected compound 25 as a lead compound. Ex. 1003 ¶¶ 105–107. 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). In determining whether a skilled artisan would have selected a prior art compound as a lead, our analysis is guided by evidence of the compound's pertinent properties. *Otsuka Pharmaceutical,* 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*.

Patent Owner argues that at the time of the invention, researchers in the field of DP-IV inhibitors were pursuing a "broad range" of inhibitor structures. Prelim. Resp. 31. According to Patent Owner, "[t]he number of possibilities and combinations was vast." *Id*. Patent Owner refers generally to other DP-IV inhibitors that were explored in the late 1990s as possible lead compounds that a skilled artisan would have chosen. *Id*. at 9–14. As analyzed further below, we disagree that Petitioner "fails to explain why a skilled artisan would have ignored the compounds [referenced by Patent Owner] . . . and, instead, would have focused on the Ashworth I

compounds." *Id*. at 32. Indeed, even if the other compounds identified by Patent Owner were viable lead compound candidates, "the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi Sankyo v. Matrix Labs*., 619 F.3d 1346, 1354 (Fed. Cir. 2010).

Petitioner asserts that a skilled artisan would have reasonably selected Ashworth I's compound 25 as a lead DP-IV inhibitor at the time of the invention "because of its superior combination of potency[5] and stability."[6] Pet. 24–26; Reply 1–4; Ex. 1007, Table II. Ashworth I evaluated chemical modifications in a series of DP-IV inhibitors having a 2-cyanopyrroline core and reported the effects of these modifications on potency and stability. Ex. 1007, 1164–66, Table II. Based on the potency and stability data presented in Ashworth I's Table II, we are persuaded on this record that a skilled artisan would have had reason to choose compound 25 as a lead compound. Specifically, Table II identifies compounds 24 and 25 as having the best

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[5] 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; Reply 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. Reply 1; Ex. 1003 ¶ 64; Prelim. Resp. 10 n.2. "Thus, an inhibitor with a K_i of 10^{-9} M is ten times more potent than one with a K_i of 10^{-8} M." Prelim. Resp. 10 n.2. For the purpose 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).").

[6] 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; Reply 1–2.

DP-IV inhibition potencies, with both having the same lower K_i limit of 0.9 nM, but of the two, compound 25 is illustrated as more stable with a half-life of >48. Ex. 1007, Table II; *see* Reply 2–3. Table II identifies compounds 25 and 27 as being the most stable compound with both having half-lives of >48, but of the two, compound 25 is illustrated as having a higher potency. *Id*.

Patent Owner argues that even if a skilled artisan focused on Ashworth I, compound 25 would not have been selected as a lead compound. Prelim. Resp. 32–34. Specifically, Patent Owner argues that Ashworth I identifies compounds 24–27 as having good potency and good stability, but a contemporaneous publication discussing Ashworth I reported that the most potent compound in Ashworth I is compound 24, and, thus, a skilled artisan would have chosen compound 24. *Id*. at 33. We are not persuaded by this argument because as discussed above, Ashworth I identified compounds 24 and 25 as having the same lower K_i limit, an indicator of potency. Thus, based on the data disclosed by Ashworth I itself, we are more persuaded by Petitioner's argument on this record. Patent Owner also argues that Ashworth I only discloses *in vivo* data for compound 26, and, thus, a skilled artisan would have chosen compound 26. Prelim. Resp. 33. We are not persuaded by this argument because Ashworth I does not explain why compound 26 was selected for *in vivo* testing, and, thus, we agree with Petitioner that without more there would have been no reason to select compound 26 as a lead compound over compound 25. Reply 3–4.

Further, Patent Owner argues that Ashworth II[7] (Ex. 2001), which provides data for a series of DP-IV inhibitors with a different chemical core than the Ashworth I compounds, identified compounds that were up to "5-fold more active" than their Ashworth I 2-cyanopyrrolidine compounds and were characterized as containing the "optimum C-terminal [P1] residue." Prelim. Resp. 34–35 (citing Ex. 2001, 2746) (emphasis omitted). Thus, contends Patent Owner, a skilled artisan without knowledge of the claimed compound at issue would have selected one of the Ashworth II compounds. *Id*. at 35. This argument is not persuasive because, as Petitioner responds (Reply 4), none of the compounds evaluated in Ashworth II exhibited both high potency and stability, as compared to compound 25.

Lastly, Patent Owner argues that "no one in the prior art—Ashworth or otherwise—expressed or recognized a preference for compound 25." Prelim. Resp. 33 (emphasis omitted). In support, Patent Owner refers to the "Ferring patent," which Patent Owner asserts provides activity data for a total of 15 putative DP-IV inhibitors, but not for compound 25, and the potencies for other compounds disclosed exceed values reported for compound 25. *Id*. at 11, 33. Of all the DP-IV inhibitors illustrated in Ashworth I, the significance of compound 25's potency and stability was recognized. For example, Ashworth I reported that "[a] number of dipeptide analogues, 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)." Ex. 1007, 1163. As Petitioner contends (Reply 3), only

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[7] 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").

compounds 25 and 27 satisfy these criteria highlighted by Ashworth I, but of the two, Ashworth I illustrates compound 25 as having better potency than compound 27. *Id*. at Table II. Therefore, at this stage in the proceeding, we are persuaded that a skilled artisan had reason to choose compound 25 as a lead compound.

Accepting that compound 25 is a lead compound, it nevertheless "remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus.,* 492 F.3d at 1357. 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 Pharms., Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Furthermore, unexpected beneficial properties in the claimed compounds must be considered in the analysis. *Id*. at 1378. As discussed in more detail below, at this point in the proceeding, we are persuaded that a skilled artisan would have made each of Petitioner's proposed modifications to arrive at saxagliptin with a reasonable expectation of success.

1. Replacing the 6-carbon cyclohexyl group at the 2-position with a 10-carbon adamantyl moiety

Petitioner refers to Ashworth I and Villhauer in arguing that a skilled artisan would have had reason to modify compound 25 by substituting its cyclohexyl substituent with an adamantyl group. Pet. 24–27. Based on the current record, we are persuaded by Petitioner's argument.

Ashworth I describes DP-IV inhibitors incorporating 2-cyanopyrollindine. Ex. 1007, 1163–64. Ashworth I taught that DP-IV

inhibitors require a free N-terminus, but that these compounds are inherently unstable due to intramolecular cyclization. Ex. 1007, 1163. As Patent Owner acknowledges, "molecules with a 'primary amine' group in the backbone, particularly if the core included a 'cyano' group, were vulnerable to a reaction called 'intramolecular cyclization,' in which the nitrogen in the primary amine became linked to the carbon of the cyano group." Prelim. Resp. 18 (citing Ex. 2007, 314).

Petitioner's witness, Dr. Rotella, opines that a skilled artisan "would have been motivated to limit intramolecular cyclization when optimizing Ashworth compound 25." Ex. 1003 ¶ 111. Dr. Rotella explains that the cyclization reaction of the free N-terminus amino group with the reactive site of the inhibitor requires the molecule to assume the "cis" confirmation. Ex. 1003 ¶ 111 (citation omitted). According to Dr. Rotella, a skilled artisan "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." *Id*. ¶ 112. Dr. Rotella reasons that "[s]election of the trans conformation advantageously places the reactive cyano and amine groups farther from each other" and "[a]dding a steric group to the compound would be expected to restrict its range of motion," thereby limiting intramolecular cyclization. *Id.* Referring to compounds 28 and 25 in Table II of Ashworth I, Dr. Rotella opines that changing the substituent at the 2-position of the acetylpyrrolidine-2-carbonitrile from a straight chain alkyl moiety (i.e,, a lysine moiety), in compound 28, to a more bulky cycloalkyl moiety (i.e., a cyclohexyl moiety) in compound 25, increased the stability of the compound from 24 hours to greater than 48

hours. *Id*. ¶ 115. Dr. Rotella concludes that "[g]iven this teaching, one of ordinary skill in the art would have been motivated to try even larger, bulkier alkyl groups" at the 2-position of the acetyl-pyrrolidine-2-carbonitrile compound, such as adamantyl, in order to bias the compound towards the trans configuration and increase stability. *Id.* ¶¶ 113, 115.[8]

In addition, Petitioner argues that Ashworth II's attempt to increase the potency of Ashworth I compounds 24 and 25, by modifying the pyrolidine ring to include a sulfur, decreased the stability of the compounds. Req. Reh'g 6–8 (citing Ex. 2001, 2748, Table II) (comparing half-lives of Ashworth I compound 24 to Ashworth II compound 13 and Ashworth I compound 25 to Ashworth II compound 14). Thus, contends Petitioner, based on this disclosure, a skilled artisan would have had reason to *improve* the stability of compound 25 while improving potency, despite the fact that Ashworth I described compound 25 as stable. *Id*. at 7. We are not persuaded by this argument. Petitioner itself acknowledges that Ashworth II attempted to improve the DP-IV inhibition potency of Ashworth I compounds 24 and 25 by modifying the pyrrolidine ring to *include a sulfur*. Req. Reh'g 7; *see also* Prelim. Res. 15–16 (discussing other modifications

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[8] Referring to data from Table I from Ashworth I, Petitioner argues that a skilled artisan would have reason to substitute the cyclohexyl group with a larger alkyl group because Ashworth I allegedly teaches that "lipophilic amino acids" gave more potent compounds. Pet. 25 (citing Ex. 1003 ¶ 116; Ex. 1007, 1165, Table I). This argument is unpersuasive because as Patent Owner argues (Prelim. Resp. 44), this data relates to DP-IV inhibitors with a different chemical core than compound 25—one that lacks the cyano group. Given this composition difference, Petitioner has not sufficiently explained the relevance of this data to the modifications Petitioner proposes a skilled artisan would have made to compound 25 to arrive at saxagliptin.

discussed in Ashworth II, such as addition of a methyl group instead of one of the hydrogens on the cyanopyrrolidine core and replacing the five-membered pyrrolidine ring with a six-membered piperidine ring). Petitioner does not sufficiently explain the relevance of stability data resulting from the modification disclosed in Ashworth II (e.g., modifying the pyrrolidine ring to include a sulfur) to the modifications Petitioner proposes a skilled artisan would have made to compound 25 (replacing the cyclohexyl group with a hydroxylated adamantyl group and adding a cylopyropyl ring to the pyrrolidine portion). *See* Pet. 25–33.

To the extent Petitioner argues that any modification to compound 25 in an attempt to increase potency would diminish stability, we are not persuaded based on this evidence. *See* Req. Reh'g 6 ("Ashworth II highlights the potential *instability* of compound 25 when making changes to the pyrrolidine ring portion of the molecule (e.g., to improve potency) and motivates further improvement to the stability of compound 25 of the kind established in the Petition."); *id.* at 7 ("In view of the teachings of Ashworth II, one of ordinary skill would have been highly motivated to improve the stability of compound 25 while improving potency"). In any event, Petitioner need not show that a skilled artisan had a reason to *increase* the stability of compound 25. It is sufficient that, based on this record, we are persuaded the prior art disclosed that adamantyl was a larger alkyl group than cyclohexyl and a suitable substitute on a DP-IV inhibitor, discussed further below, and a skilled artisan had a reasonable expectation that such a substitution on compound 25 would successfully yield a compound that was at least as stable as compound 25.

Petitioner further argues that a skilled artisan would have had reason

to substitute the cyclohexyl group of compound 25 with the even larger cycloalkyl adamantyl group disclosed by Villhauer. Pet. 26. Dr. Rotella further opines that "the art taught adamantyl as an obvious alternative to cyclohexyl." Ex. 1003 ¶ 118. Villhauer discloses examples of alkyl groups, a cyclohexyl group, and an adamantyl group, attached to the amino moiety of 2-cyano pyrrolidides. Ex. 1008, p. 12–13 (Example Nos. 28, 47, 52); Ex. 1003 ¶ 118.

Based on 1) Ashworth I's recognition that a free N-terminus on a DP-IV inhibitor makes compound 25 prone to cyclization, and, thus, instability; 2) Dr. Rotella's testimony that a skilled artisan would have had reason to add a large, steric group to compound 25 at the 2-postion to limit intramolecular cyclization; 3) the stability data disclosed in Ashworth I, Table II and relied upon by Dr. Rotella in opining that a larger alkyl group at the 2-position increased the stability of compound 25; and 4) the prior art teaching of adamantyl as a larger alkyl group that can be substituted for a cyclohexyl group, as disclosed in Villahauer, we are persuaded that Petitioner has made a sufficient showing that a skilled artisan would have had reason to modify Ashworth I's compound 25 by substituting a larger, bulkier alkyl group at the 2- position of the acetyl-pyrrolidine-2-carbonitrile compound, such as an adamantyl group. With respect to predictable results, Dr. Rotella states that "[i]n the context of the '186 patent, one of ordinary skill in the art 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." Ex. 1003 ¶ 122. Based on the current record, particularly the unrebutted testimony of Dr. Rotella, we are

persuaded that a skilled artisan would have had a reasonable expectation of success in substituting the cyclohexyl group with an adamantyl group on compound 25.

Patent Owner argues that a skilled artisan would not have reason to substitute the cyclohexyl group of compound 25 with an adamantyl group. Specifically, Patent Owner argues that Petitioner's reliance on Ashworth I's disclosure relating to the potency of DP-IV inhibitors with a chemical core that did not include a cyano group is not relevant because those compounds did not have an intramolecular cyclization problem. Prelim. Resp. 44; Pet. 24 (Petitioner stating that "Ashworth found that lipophilic amino acids, particularly β-branched α-amino acid derivatives were the most potent."). We do not find the evidence in Table I of Ashworth I persuasive because there is insufficient explanation as to the relevance of compounds that do not contain a cyano group to saxagliptin. We, thus, agree with Patent Owner that the potency data in Ashworth I, Table I does not sufficiently support Petitioner's argument at this point in the proceeding. Patent Owner's argument that the potency date is irrelevant, however, does not refute the stability data in Ashworth I, Table II and Dr. Rotella's corresponding testimony, relied on by Petitioner.

Patent Owner also argues that the stability data in Ashworth I, Table II, contradicts Petitioner's theory because compounds 24–27 exhibit "comparable stability with half-lives of about 48 hours, no matter the substituent in the P2 position." Prelim. Resp. 45 (citing Ex. 1007, 1165–66, Table II). The stability data in Table II of Ashworth I, however, is indicated by ranges. Thus, as Petitioner argues, Ashworth I indicates that cyclohexylated compound 25 is more stable (with a half-life of >48 hours)

than smaller cyclopentylated compound 24 (with a half-life of 48 hours). Req. Reh'g. 10. Petitioner asserts that "[t]he extent to which it is more stable is unknown based on the data presented in Ashworth I," as the data shows only that compound 25 has a longer half-life than compound 24. *Id*. We agree with Petitioner, and, thus, are unpersuaded by Patent Owner's argument.

Referring to Ashworth II, Table II data, Patent Owner also argues that compounds with the more bulky liphophilic cyclohexane group and the cyclopentane group at the 2-position display lower stability, with a lower half-life, than the compounds with the less bulky isoleucine. Prelim. Resp. 45–46 (citing Ex. 2001, Table II). Thus, concludes Patent Owner, this data indicates that by "increasing lipophilicity," the compound's potency and stability is decreased, contradicting the Petitioner's proposed reason for modification. *Id*. at 46. We are not persuaded by Patent Owner's argument because, as discussed above, the modifications discussed in Ashworth II are not proposed by Petitioner. Req. Reh'g. 7. Petitioner readily admits that stability was diminished by Ashworth II's modifications to compound 25. *Id*. In sum, Patent Owner has not sufficiently explained, based on the current record, how the stability and potency data for compounds in Ashworth II are relevant to the modifications Petitioner proposes a skilled artisan would have had reason to make to compound 25 of Ashworth I. Although Patent Owner asserts that "[a]t worst, the data reinforce[s] the inability to predict the impact on potency and stability when modifying the structures of these molecules," Patent Owner does not explain sufficiently the relevance of the unpredictability of the modifications described in Ashworth II to the modifications Petitioners contends that a skilled artisan

would have had reason to make. Prelim. Resp. 46.

Lastly, Patent Owner argues that Villhauer does not cure the deficiencies in Petitioner's argument with respect to a reason to modify and expectation of success because Villahauer's compounds are structurally different from compound 25. *Id*. Patent Owner notes that Villhauer describes compounds having a "secondary amine" (NH) backbone without the "intramolecular cyclization" problems noted in the art in connection with "primary amine" compounds, like those described in Ashworth I. Prelim. Resp. 4–5. Petitioner does not appear to be relying on Villhauer's disclosure with respect to solving the problem of intramolecular cyclization. Rather, Petitioner only refers to Villhauer for its description of an alkyl group that is larger than cyclohexyl and can be substituted for cyclohexyl on a DP-IV inhibitor. Pet. 25–27.

Thus, based on the current record, we are persuaded that a skilled artisan would have had reason to replace the 6-carbon cyclohexyl group at the 2-position on compound 25 with a 10-carbon adamantyl moiety.

2. Hydroxylating Adamantyl

Petitioner avers that a skilled artisan would have had reason to use a hydroxylated adamantyl metabolite to improve solubility and bioavailability of the compound. Pet. 27–28. Specifically, Petitioner asserts that those skilled in the art routinely investigated metabolites of a lead compound, especially when looking for ways to improve metabolic stability. Pet. 27 (citing Ex. 1003 ¶ 54). According to Petitioner, it was also known that metabolites can have other advantages, such as increasing solubility, absorption and bioavailability. *Id*. (citing Ex. 1003 ¶ 54). Petitioner refers

to Raag, which notes that adamantane is consistently metabolized into 1-hydroxadamantine and is not very soluble. Pet. 27 (citing Ex. 1009, 2675, 2678). Dr. Rotella opines that a skilled artisan, given the teaching of Raag, would have had reason to block metabolism of a substituted adamantyl ring at the 3-position by placing a group such as a hydroxyl group at that position because blocking metabolism at the 3-position would be expected to result in greater metabolic stability. Ex. 1003 ¶ 127. Dr. Rotella further opines that it was well known that metabolites (such as 3-hydroxy substituted adamantyl compounds) could provide improved metabolic stability to a compound. Ex. 1003 ¶ 129. Petitioner concludes that a skilled artisan would have had reason to use a hydroxylated adamantyl metabolite, as taught by Raag, to improve solubility and bioavailability because Ashworth I taught that a large lipophilic substituent was advantageous for N-glycyl-2-cyanopyrollidine stability, and Villahauer taught using adamantyl as a large substituent, but Raag taught that adamantane is not very soluble. Pet. 27–28 (citations omitted). We determine that this reasoning is persuasive and adopt it as our own for purposes of this decision.

Patent Owner contends that a skilled artisan would not have had reason to hydroxylate the adamantyl group. Prelim. Resp. 47–51. Patent Owner first argues that Petitioner's reasoning is flawed because "[Petitioner] argues that the adamantyl group was a logical substitution [for the cyclohexyl group] because it is more lipophilic (oil loving), and then immediately suggests making that substituent less lipophilic through incorporation of a hydroxyl group." Prelim. Resp. 47. We do not find this argument persuasive because Petitioner argues that a skilled artisan had reason to use a large lipophilic substituent at the 2-position on N-glycl-2-

cyanopyrrolidine for *stability*, but contends that a skilled artisan would had reason to hydroxylate the adamantyl group to increase *solubility* and *bioavailability*. The modifications are for different reasons and we are not persuaded that they contradict each other. Patent Owner further argues that there are other ways to improve the metabolic stability of a lead structure, the results of metabolism are unpredictable and often undesirable, and adamantyl is metabolized into other metabolites. Prelim. Resp. 48–50. These arguments are not persuasive in light of Petitioner's evidence that hydroxylating adamantyl was known to yield a more soluble and bioavailable compound.

3. Modifying compound 25 to add cyclopropyl

Referring to Hanessian I, Petitioner argues 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 4,5-methanoproline. Pet. 9–11, 28–29. We are persuaded by Petitioner's argument at this point in the proceeding and adopt its rationale here.

As discussed above, Petitioner avers that it was known that DP-IV inhibitor instability was attributable to intramolecular cyclization between the free amino group of P_2 and the electrophile attached to the proline mimic of P_1. Reply 5 (citing Ex. 1007, 1163; Ex. 2007, 314). And Petitioner further avers that the trans, versus cis, conformation for a DP-IV inhibitor was favored. Ex. 1003 ¶ 133. According to Petitioner, a well-known strategy at the time of the invention for modulating the orientation of a ring-bound substituent 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. It was known that fusion between two rings flattened the ring and was expected by those skilled in the art to affect the orientation of ring bound substituents. Ex. 1021, 243; Ex. 1003 ¶¶ 135–36, 143.

Hanessian I described the synthesis and conformation effect of fusing a cyclopropyl ring to a proline ring, like that of compound 25. Ex. 1010, 1882–83. Hanessian I found that cyclopropanation of a proline constrains the proline ring by flattening the ring, i.e., reducing the bond angles within the ring compared to unmodified proline. *Id*. at 1882. One of the consequences of ring flattening is that the α carbon substituent (the cyano moiety in the case of compound 25) is pushed out of the plane defined by the rest of the proline ring. Reply 7 (citing Ex. 1010, 1882; Ex. 1003 ¶ 143); Pet. 29. Dr. Rotella opines that changing the position of the cyano moiety relative to the rest of the dipeptide would have been expected to decrease the risk of intramolecular cyclization, and, thus, increase stability. Ex. 1003 ¶¶ 143, 145; Pet. 29; Reply 7.

Patent Owner argues that a skilled artisan would not have been motivated to add cyclopropyl to compound 25. Prelim Resp. 36–40.[9] Patent Owner contends that Hanessian I's disclosure is unrelated to DP-IV inhibitors and the cyanopyrrolidine structure and Petitioner does not give a reason why a skilled artisan would have had a specific reason to flatten compound 25's proline ring. Prelim. Resp. 36. This argument is not

[9] Patent Owner contends that Petitioner's "flawed" argument as to why a skilled artisan would have modified compound 25 to add a cyclopropyl ring is another independent reason, in addition to Petitioner's "improper" lead compound theory, as to why Petitioner has failed to show that any claim of the '186 patent is likely unpatentable. Prelim. Resp. 4.

persuasive because Petitioner refers to Hanessian I for its description of the synthesis and conformational effect of fusing a cyclopropyl ring to a proline ring *like that* of compound 25. Reply 6. Specifically, Petitioner argues that a skilled artisan would have considered Hanessian I's disclosure of flattening and conformationally constraining a proline ring relevant to: 1) addressing the unintended intramolecular cyclization and potency of compound 25 due to the free amino group of P_2 and the electrophile of the cyano moiety on P_1, and; 2) the importance of compound 25's 2-cyano moiety for DP-IV inhibition, by pushing the cyano moiety out of the plane defined by the rest of the proline ring. Reply 5–7.

Patent Owner also argues that Ashworth II reported negative results from other optimizations that were not beneficial, but which had structural similarity to the cylopropyl addition. Prelim. Resp. 37–38. We are not persuaded by this argument because, as discussed above, Patent Owner has not sufficiently persuaded us that Ashworth II's disclosure, which describes different modifications to the proline ring than those proposed by Petitioner (Ex. 2001), is relevant to the modifications Petitioner contends a skilled artisan would have made to compound 25. Patent Owner also refers to Hanessian II[10] in arguing that introducing a cyclopropyl substituent would have had unpredictable and uncertain consequences on the activity of compound 25. Prelim. Resp. 38–39 (citing Ex. 2043). As Petitioner argues (Reply 8), however, Patent Owner has not sufficiently established the relevance of Hanessian II's evaluation of the interaction between 4,5-

[10] Hanessian et al., 37 TETRAHEDERON LETT. 8971, 8973 (1996) ("Hanessian II") (Ex. 2043).

methanoprolines and receptors that are not DP-IV inhibitors to our analysis. In addition, Patent Owner argues that Petitioner emphasizes the importance of DP-IV inhibitors being in the trans conformation, but Hanessian I teaches that compounds with the cyclopropyl group exist in the cis conformation, in the solid state, and in solution, as a mixture of conformations. Prelim. Resp. 39 (citing Ex. 1010, 1883). On the present record, we do not find this argument convincing because Hanessian I teaches that cis or trans conformations may predominate depending on the compound. Ex. 1010, 1883.

Lastly, Patent Owner argues that a skilled artisan would not have had reason to add cyclopropyl in the 4,5 cis configuration to compound 25. Patent Owner Resp. 42–44. We disagree on this record. Hanessian I identified three locations on the proline ring (2,3; 3,4; and 4,5), where cyclopropanation could occur, with two resulting stereoisomers, for a total of six possible cyclopropanations of the proline ring. Ex. 1003 ¶ 139. Petitioner argues that with only six possibilities, a skilled artisan would have had reason to try each in an effort to determine which provided the best activity and stability. Pet. Ex. 1003 ¶¶ 139–40. We are persuaded by Petitioner's argument. *See* Pet. 28–29; Reply 7.

In sum, on the current record, Petitioner has established a reasonable likelihood of prevailing with respect to claims 1, 2, 4, 6–11, 25–28, 32–35, 39, and 40 based on the asserted references for this ground.

C. Ground 2 (Claims 12–16, 29, 30, 36, 37, 41, and 42)

Petitioner contends that claims 12–16, 29, 30, 36, 37, 41, and 42 would have been obvious over Ashworth, Villhauer, Raag, Hanessian I, Bachovchin, and the GLUCOPHAGE label. Pet. 46–50.

Claim 12 defines a pharmaceutical combination comprising a DP-IV inhibitor defined in claim 1 with an *anti-diabetic agent* that is not a DP-IV inhibitor for treating diabetes and related diseases, an anti-obesity agent and/or a lipid-modulating agent; claim 13 depends from claim 12 and recites the pharmaceutical combination comprising the DP-IV inhibitor of claim 1 and an antidiabetic agent that is not a DP-IV inhibitor; claim 14 depends from claim 13 and limits the antidiabetic agent to a *Markush* group of antidiabetic agent types; and claim 15 depends from claim 14 and identifies metformin and acarbose (among others) as the anti-diabetic agent. *See* Pet. 47. Thus, claim 15 covers the pharmaceutical combination of the DP-IV inhibitor of claim 1 and metformin, and, thus its parent claims 12–14 also encompass this combination. *Id*.

Bachovchin states that an "object [of its invention] is to provide improved methods for reducing at least one of body fat stores, hyperlipidemia, hyperlipoproteinemia, and for abating atherosclerosis." Ex. 1011, 3:29–31. Bachovchin discloses that DP-IV inhibitors may be used "in combination with other oral agents such as metformin and related compounds or glucosidase inhibitors as, for example, acarbose." Ex. 1011, 46:29–31. In addition, GLUCOPHAGE indicates that metformin tablets are approved for treating type II diabetes mellitus. Ex. 1012, 0008. Given our determination above that Petitioner has demonstrated a reasonable likelihood that the DP-IV inhibitor of claim 1 would have been obvious, and in view of

Bachovchin's recommendation to use metformin (or acarbose) with a DP-IV inhibitor, we are persuaded by Petitioner's argument and Dr. Rotella's opinion that a skilled artisan would have considered combining saxagliptin with metformin or acarbose. Pet. 47 (citing Ex. 1003 ¶¶ 178–79).

Claims 29, 30, 36, 37, 41, and 42 are method claims and only add the requirement of a combination of saxagliptin (free or as a salt) with a carrier and with an anti-diabetic agent (claims 29, 36, and 41), specifically metformin (claims 30, 37, and 42). For the reasons discussed above, particularly with respect to claims 13 (anti-diabetic agent) and 15 (metformin), Petitioner has established a reasonable likelihood of prevailing with respect to these claims. Pet 47–48 (citing Ex. 1003 ¶¶ 176, 179, 180).

Claim 16 depends from claim 13 and requires a weight ratio of DP-IV inhibitor to non-DP-IV anti-diabetic agent in the range of 0.01 to 100:1. We are persuaded on this record by Petitioner's argument based on the disclosures of Villhauer and the GLUCOPHAGE label, and Dr. Rotella's opinion that a skilled artisan formulating a composition with saxagliptin and metaformin (a composition covered by claim 16 given its dependency from claim 13) would have had reason to try weight ratios overlapping the claimed range of claim 16. Pet. 49 (citations omitted); Ex. 1003 ¶ 196. *See Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (determining appropriate drug combination formulations is routine in the art and is obvious absent an unexpected result).

In sum, on the current record, Petitioner has established a reasonable likelihood of prevailing with respect to claims 12–16, 29, 30, 36, 37, 41, and 42 based on the asserted references for this ground.

D. Ground 3 (Claims 12, 17, 18, and 22)

Petitioner contends that claims 12, 17, 18, and 22 would have been obvious over Ashworth, Villhauer, Raag, Hanessian I, Bachovchin, and the XENICAL label. Pet. 50–53.

As noted above, claim 12 defines a pharmaceutical combination comprising a DP-IV inhibitor defined in claim 1 with an anti-diabetic agent that is not a DP-IV inhibitor for treating diabetes and related diseases, *an anti-obesity agent* and/or a lipid-modulating agent. Claim 17 depends from claim 12 and defines a *Markush* group of antiobesity agent types; and claim 18 depends from claim 17 and lists orlistat (XENICAL) as one of a *Markush* group of specific anti-obesity agents.

Petitioner argues that Bachovchin in combination with the XENICAL label teaches a pharmaceutical combination comprising the DP-IV inhibitor of claim 1 and orlistat, an anti-obesity agent. Specifically, Petitioner avers that Bachovchin identified obesity as a condition associated with type II diabetes. Pet. 50 (citing Ex. 1011, Abstract). Petitioner further argues that "Bachovchin contemplates conjoint administration of a DP-IV inhibitor with agents directed to related symptoms [of diabetes]," and acknowledges that Bachovchin does not specifically identify an anti-obesity agent. Pet. 50 (citing Ex. 1011, 45:23–46:31). Petitioner nevertheless argues that "given the association of obesity with type II diabetes mellitus, it would have been obvious to select an anti-obesity agent for conjoint administration." Pet. 50 (citing *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997); Ex. 1003 ¶¶ 172, 183–85). Petitioner also refers to the XENICAL label which discloses an anti-obesity agent known in the prior art as orlistat. Pet. 50. The XENICAL label indicates that XENECAL has been assessed in

clinical trials for its effect on comorbidities, including type II diabetes, and that XENECAL is indicated for obese patients with other risk factors, including diabetes. Ex. 1013, 0011, 0013, 0018.

Bachovchin teaches that a DP-IV inhibitor can be administered with "one or more other therapeutic agents." Ex. 1011, 45:23–24. And the XENECAL label teaches an anti-obesity agent. Ex. 1013, 0017–18. Thus, based on the current record, particularly the disclosures of Bachovchin and the XENECAL label, we are persuaded that a pharmaceutical composition combining the DP-IV inhibitor of claim 1 and an anti-obesity agent, such as XENCAL, would have been obvious because they treat related maladies (claim 18). Because we are persuaded that Petitioner has established a reasonable likelihood of prevailing with respect to claim 18, we are likewise persuaded with respect to its parent claims 12 and 17.

Claim 22 recites a pharmaceutical combination comprising a compound as defined in claim 1 and recites alternative agents, including an anti-obesity agent. Specifically, claim 22 recites "A pharmaceutical combination comprising a compound as defined in claim 1 *and* an agent for [recited maladies] . . . *and/or* an anti-obesity agent." Emphasis added. Petitioner argues that under the broadest reasonable interpretation, claim 22 requires a pharmaceutical combination comprising a compound as defined in claim 1 with any one of the recited agents, including an anti-obesity agent, or with any combination of the recited agents. Pet. 51–52. Thus, contends Petitioner, for the same reasons provided for claim 18, claim 22 is likewise obvious. Patent Owner does not provide an opposing construction for claim 22. At this point in the proceeding, we agree with Petitioner's construction of claim 22 based on the claim language, and, thus, are persuaded that

Petitioner has established a reasonable likelihood of prevailing with respect to claim 22.

In sum, on the current record, Petitioner has established a reasonable likelihood of prevailing with respect to claims 12, 17, 18, and 22 based on the asserted references for this ground.

E. *Ground 4 (Claims 12 and 19–21)*

Petitioner contends that claims 12 and 19–21 would have been obvious over Ashworth, Villhauer, Raag, Hanessian I, Bachovchin, and the MEVACOR label. Pet. 53–57.

As noted above, claim 12 defines a pharmaceutical combination comprising a DP-IV inhibitor defined in claim 1 with an anti-diabetic agent that is not a DP-IV inhibitor for treating diabetes and related diseases, *an* anti-obesity agent and/or a *lipid-modulating agent*. Claim 19 depends from claim 12 and requires selection of the lipid-modulating agent from a *Markush* group of lipid-modulating agent types; and claim 20 depends from claim 19 and lists a *Markush* group of specific lipid-modulating agents, including lovastatin.

Petitioner argues that Bachovchin "contemplated conjoint administration of a DP-IV inhibitor with a variety of other therapeutic agents, including agents that lower cholesterol, while increasing high-density lipoprotein ("HDL") levels." Pet. 53 (citing Ex. 1011, 45:23–33). Petitioner also refers to the MEVACOR label, which discloses the lipid-modulating agent lovastatin, and states that lovastatin reduces LDL and can increase HDL. Pet. 53–54 (citing Ex. 1014, 0007). The MEVACOR label also indicates that diabetes should be brought under control using another

therapy. Ex. 1014, 0010. Petitioner contends that a combination of two compounds that are often administered together would have been obvious. Pet. 54 (citing *Richardson-Vicks Inc.*, 122 F.3d at 1484).

Bachovchin teaches that a DP-IV inhibitor can be administered with "one or more other therapeutic agents," and provides as an example administering an inhibitor with agents that reduce cholesterol levels and increase HDL levels. Ex. 1011, 45:23–24, 30–33. And the MEVACOR label teaches a lipid modulating agent. Ex. 1014, 0007. Thus, based on the current record, particularly the disclosures of Bachovchin and the MEVACOR label, we are persuaded that a pharmaceutical composition combining the DP-IV inhibitor of claim 1 and a lipid-modulating agent, such as lovastatin, would have been obvious because they treat related maladies (claim 20). Because we are persuaded that Petitioner has established a reasonable likelihood of prevailing with respect to claim 20, we are likewise persuaded with respect to its parent claims 12 and 19.

Claim 21 depends from claim 19 and requires a weight ratio of DP-IV inhibitor to the lipid-modulating agent in the range of 0.01 to 100:1. We are persuaded on this record by Petitioner's argument based on the disclosures of Villhauer and the METAVACOR label, and Dr. Rotella's opinion that a skilled artisan formulating a composition with saxagliptin and lovastatin (a composition covered by claim 21 given its indirect dependency from claim 19) would have had reason to try weight ratios overlapping the claimed range of claim 16. Pet. 55 (citations omitted); Ex. 1003 ¶ 195. *See Merck*, 874 F.2d at 809.

In sum, on the current record, Petitioner has established a reasonable likelihood of prevailing with respect to claims 12 and 19–21 based on the asserted references for this ground.

F. Secondary Considerations of Nonobviousness

Patent Owner argues that objective evidence of nonobviousness ("secondary considerations") supports patentability of the challenged claims. Prelim. Resp. 51–55. Secondary considerations, when present, must "'be considered en route to a determination of obviousness.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (citation omitted). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

To be relevant, evidence of nonobviousness must be commensurate in scope with the claimed invention. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (citing *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971)); *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998).

Patent Owner argues that saxagliptin displays several unexpected properties that are the direct result of its unique structure. Prelim. Resp. 51. According to Patent Owner, these unexpected properties include synergistic potency, improved chemical stability, increased bioavailability, and distinctive tight binding characteristics of saxagliptin to DP-IV. *Id*. at 7, 51–54. Notably, Patent Owner argues that "[e]ven if a skilled artisan could rationalize one of the above-proposed modifications, [Petitioner] fails to

establish the predictability of implementing *all* of them together." Prelim. Resp. 6; *see also id*. at 23 (citations omitted) (Patent Owner stating that "the 'greatest improvement in stability' came from the addition of an adamantyl group on one side of the molecule, together with the addition of a cyclopropyl group at the 4,5 *cis* position on the pyrrolidine ring."). Patent Owner further emphasizes that "[t]he structural secret to saxagliptin's unusual binding properties was understood only after the fact through later crystallographic studies showing a series of highly specialized, previously unknown, chemical contacts with the DPP-IV enzyme that saxagliptin inhibits." *Id*. at 7; *see id*. at 24. Patent Owner further argues that these unpredictable and unexpected results resulted in the commercial success of saxagliptin. *Id*. at 54. Lastly, Patent Owner contends there were multiple failed attempts to make potent and stable DP-IV inhibitors. *Id*. at 54–55. At this point in the proceeding, without further supporting evidence, we are unpersuaded by Patent Owner's secondary considerations of nonobviousness arguments.

Moreover, our Decision on Institution is not a "determination of obviousness" in the same meaning as the Federal Circuit wrote in *Transocean*. Rather, a Decision on Institution decides whether a "reasonable likelihood" exists for such a determination to be made at a later time. *Compare* 35 U.S.C. § 314(a) (authorizing *inter partes* review only if "there is a reasonable likelihood that the petitioner would prevail"), *with* 35 U.S.C. § 316(e) (placing the burden on petitioner of "proving a proposition of unpatentability by a preponderance of the evidence"). Accordingly, our analysis in this Decision focuses on whether Petitioner has established a reasonable likelihood of success based on the current record. *Id.* § 314(a);

see also Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,765 (Aug. 14, 2012) ("The 'reasonable likelihood' standard is a somewhat flexible standard that allows the Board room to exercise judgment."). Given that we have determined that Petitioner has shown a reasonable likelihood of prevailing absent evidence of secondary considerations of nonobviousness, and Patent Owner's insufficient evidence of nonobviousness at this point in the proceeding, we further determine that it would be premature, at this stage, to do a complete weighing of all the evidence of obviousness and non-obviousness using the preponderance of the evidence standard.

III. CONCLUSION

We have considered Patent Owner's remaining arguments and remain persuaded that Petitioner has established a reasonable likelihood of prevailing with respect to the challenged claims. For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1, 2, 4, 6–22, 25–30, 32–37, and 39–42 of the '186 patent.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that *inter partes* review is instituted on the following grounds:

> Claims 1, 2, 4, 6–11, 25–28, 32–35, 39, and 40, under 35 U.S.C. § 103(a), as obvious over Ashworth I, Villhauer, Raag, and Hanessian I;

Claims 12–16, 29, 30, 36, 37, 41, and 42, under 35 U.S.C. § 103(a), as obvious over Ashworth I, Villhauer, Raag, Hanessian I, Bachovchin, and GLUCOPHAGE Label;

Claims 12, 17, 18, and 22 under 35 U.S.C. § 103(a), as obvious over Ashworth I, Villhauer, Raag, Hanessian I, Bachovchin, and XENICAL Label; and

Claims 12, 19, 20, and 21 under 35 U.S.C. § 103(a), as obvious over Ashworth I, Villhauer, Raag, Hanessian I, Bachovchin, and MEVACOR Label;

FURTHER ORDERED that the trial is limited to the grounds identified above, and no other ground is authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of U.S. Patent No. RE44,186 E is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

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