

Filed on behalf of: Teva Pharmaceuticals USA, Inc.  
By: Gary J. Speier  
Iain A. McIntyre  
Carlson, Caspers, Vandenburg, Lindquist & Schuman  
225 South Sixth Street  
Suite 4200  
Minneapolis, MN 55402  
Tel.: 612-436-9600  
Fax: 612-436-9605  
Email: gspeier@carlsoncaspers.com  
Email: imcintyre@carlsoncaspers.com

UNITED STATES PATENT AND TRADEMARK OFFICE  

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Teva Pharmaceuticals USA, Inc.,  
Petitioner,

v.

ASTRAZENECA AB,  
Patent Owner

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Inter Partes Review No.: Unassigned  
Patent No. RE44,186  

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**PETITION FOR INTER PARTES REVIEW**  
**OF REISSUE PATENT NO. RE44186**

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## **I. INTRODUCTION**

Pursuant to the provisions of 35 U.S.C. § 311 and § 6 of the Leahy-Smith America Invents Act (“AIA”), and to 37 C.F.R. Part 42, Teva Pharmaceuticals USA, Inc. (“Petitioner”) hereby requests review of United States Reissue Patent No. RE44,186 to Robl (hereinafter “the ’186 patent,” Ex. 1001) that issued on April 30, 2013, and is currently assigned to AstraZeneca AB (“Patent Owner”). This Petition demonstrates, by a preponderance of the evidence, that there is a reasonable likelihood that claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 of the ’186 patent are unpatentable for failing to distinguish over prior art. Thus, claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 of the ’186 patent should be found unpatentable and canceled.

## **II. OVERVIEW**

The Board has already issued its Decision Instituting *Inter Partes* Review (“Decision”) on all challenged claims of the ’186 patent on the same grounds raised herein. *Mylan Pharmaceuticals Inc., v. AstraZeneca AB*, Case IPR2015-01340 (Paper 16). In its Decision, the Board found that Petitioner Mylan Pharmaceuticals Inc. (“Mylan”) had demonstrated a reasonable likelihood that claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 of the ’186 patent are unpatentable for failing to satisfy the nonobviousness requirement of 35 U.S.C. § 103. *Id.* The Board instituted IPR of the challenged claims on four separate grounds:

Ground 1: Claims 1, 2, 4, 6-11, 25-28, 32-35, 39 and 40 are obvious over Ashworth, Villhauer, Raag and Hanessian;

Ground 2: Claims 12-16, 29, 30, 36, 37, 41 and 42 are obvious over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the GLUCOPHAGE Label;

Ground 3: Claims 12, 17, 18 and 22 are obvious over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the XENICAL Label; and

Ground 4: Claims 12 and 19-21 are obvious over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the MEVACOR Label.

IPR2015-01340 (Paper 16). Petitioner Teva hereby files its own petition on the same grounds and concurrently seeks to join the instituted IPR proceedings on these challenged claims.

#### **A. Brief Overview of the '186 Patent**

The '186 patent is entitled "Cyclopropyl-Fused Pyrrolidine-Based Inhibitors of Dipeptidyl Peptidase IV and Method." Ex. 1001. In a general sense, the '186 patent discloses compounds said to inhibit the enzyme dipeptidyl peptidase IV ("DP-IV" also referred to in the claims as "DP4). This enzyme is responsible for the metabolic cleavage of certain peptides found in the body, including glucagon, a peptide of 29 amino acids. *Id.*, at col. 1, l. 30-34. The glucagon peptide has multiple actions *in vivo*, including the stimulation of insulin secretion, inhibition of

glucagon secretion, promotion of satiety, and the slowing of gastric emptying. *Id.*, at col. 1, l. 40-44. Glucagon is rapidly degraded in the body, and the DP-IV enzyme has been shown to be the primary degrader of glucagon. *Id.*, at col. 1, l. 49-54. Thus, inhibitors of DP-IV *in vivo* should increase endogenous levels of glucagon, and serve to attenuate the diabetic condition. *Id.*, at col. 1, l. 56-59. The '186 patent discloses an extremely large genus of compounds which are termed "cyclopropyl-fused pyrrolidine-based compounds." *Id.*, col. 1, l. 65-66. In essence, these compounds are a cyclopropyl-fused pyrroline-based core with a wide variety of optional substituents. The '186 patent also discloses various pharmaceutical compositions formed from the compounds, as well as methods of treatment for diabetes and an extremely wide variety of other diseases and conditions said to be related to diabetes. *Id.*, col. 3, l. 44 – col. 3, l. 18. The '186 patent provides no evidence of testing any of the compounds in *in vivo* animal trials or clinical trials in humans for any such diseases or related conditions.

The original patent from which the '186 reissued, US 6,395,767 (the '767 patent), was based on an application filed February 16, 2001, which itself claimed the benefit of a provisional application, 60/188,555 ("the '555 application"), filed March 10, 2000. Ex. 1001, p. 1. Nine years after the '767 patent issued, then-owner Bristol-Myers Squibb Company ("BMS") filed a reissue application which, *inter alia*, added new claims 25-40. Ex. 1006 (reissue prosecution history) at

[0612]. BMS stated that the error it sought to correct was its failure to claim the compound of claim 25 specifically. Ex. 1006v2 at [0564]. BMS subsequently amended or canceled other claims, and added more claims, 41-45. These claims were subsequently allowed. *Id.* at [0584]. Reissued claims 1-43 are the claims presently in the '186 patent. Claims 1, 2, 4, 6-22, 25-30, 32-37 and 39- 42 of the '186 patent are shown in this petition to be unpatentable for failing to distinguish over prior art.

Claim 1 of the '186 patent is directed to the large genus of compounds, and dependent claims 2-10 define various subgenera. Claim 12 is directed to a pharmaceutical combination comprising a compound of claim 1 and an anti-obesity agent, a lipid-modulating agent, or an anti-diabetic agent other than a DP-IV inhibitor. Claims 13-20 depend directly or indirectly from claim 12 and are directed to various combinations of drug therapies.

Independent claim 25 is directed to a specific compound that is encompassed by claim 1 [Ex. 1003, ¶14; Ex. 1028, ¶14].<sup>1</sup> The compound of claim 25 is also known as (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile.

For convenience, the species compound defined by the structure set forth in claim 25 will hereafter be referred to as “saxagliptin.” Ex. 1003, ¶15; Ex. 1028,

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<sup>1</sup> This Petition is accompanied by the Declaration of David P. Rotella, Ph.D. (Rotella Dec. (Ex.1003)), and the Declaration of Dr. Ramaiah Muthyala (Muthyala Dec. (Ex.1028)).

¶15. This petition and supporting evidence demonstrate that the species of claim 25 is obvious over the prior art. When a species is obvious over the prior art, broader claims which encompass the species are also obvious. *In re Muchmore*, 433 F.2d 824, 824-25 (CCPA 1970) (“Since we agree with the board's conclusion of obviousness as to these narrow claims, the broader claims must likewise be obvious.”); *accord Soverain Software LLC v. Victoria’s Secret Direct Brand Mgmt., LLC*, 778 F.3d 1311, 1315 (Fed. Cir. 2015).

Independent claim 1 defines a genus of compounds. Ex. 1001 at 86:24-87:47. Saxagliptin is but one species within this large genus. *Id.*, at 88:23-30; Ex. 1003, ¶150-151; Ex. 1028, ¶150-151. Independent claim 8 defines an eight-member genus (counting structures), one of which is the saxagliptin species. Ex. 1001 at 88:43-89:29; Ex. 1003, ¶13; Ex. 1028, ¶13.

Independent claim 10 defines a genus of compounds based on either of two structures (Ex. 1001 at 89:33-67), one of which defines a subgenus that includes the saxagliptin species. Ex. 1003, ¶163; Ex. 1028, ¶163.

Independent claims 32 and 39 define methods of treating diabetes-related conditions in mammals using the saxagliptin compound. Ex. 1001, 91:51-92:16 and 92:27-43; Ex. 1003, ¶172; Ex. 1028, ¶172.

## **B. Brief Overview of the Prosecution History**

The challenged '186 patent reissued on April 30, 2013, from the '767 patent originally granted on May 28, 2002. The '767 patent was based on application 09/788,173 (the '173 application), filed on February 16, 2001, that claimed the benefit of the '555 provisional application filed March 10, 2000. Ex. 1001, cover. Only one substantive Office Action was issued by the Office during prosecution of the '173 application. In that action, certain claims were rejected under 35 U.S.C. 102(b) as being anticipated by a Hiltmann reference. Ex. 1005, p. 0295. The Examiner's rejection consisted of one sentence and no substantive reasons for the rejection were provided. *Id.* Following an amendment to claim 1, the Examiner allowed the claims.

The reissue application filed by BMS in 2011 amended original claim 13, deleted original claims 23 and 24, and added claims 25-40. Ex. 1006 (reissue prosecution history) at [0079-81]. BMS stated that the error it sought to correct was its failure to claim the compound of claim 25 specifically. *Id.* at [0056] and Ex. 1006v2 at [0564]. BMS subsequently amended or canceled other claims, and added claims 41-45. Only one Office Action was issued by the Office against the reissue application. No prior art references were asserted against the claims in that Office Action, and the Examiner subsequently allowed the claims. Ex. 1006v2 at [0584]. These claims, renumbered as claims 1-22 and 25-43, are the claims presently in the '186 patent.

## **C. Brief Overview of the Scope and Content of the Prior Art**

### **1. The Dipeptide Substrate Targeted By The DP-IV Enzyme**

Dipeptidyl peptidase IV, variously referred to in the art as DP-IV, DPP-IV, or DP-4, was well known by the mid-1990s as a serine protease enzyme.

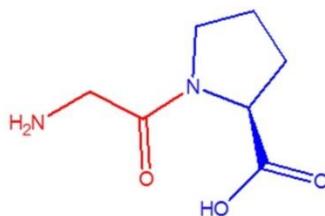
Ashworth (1996), Ex. 1007, p. 1163; Ex. 1003 ¶¶64; Ex. 1028, ¶¶64. It cleaves two amino acid peptides, or dipeptides, from certain larger peptides or proteins. *Id.* The enzyme targets substrates having a proline or alanine amino acid as the second residue from the N-terminus. *Id.*

DP-IV was known to inactivate glucagon-like peptide-1 (GLP-1), a major stimulator of pancreatic insulin secretion. *Id.* The art recognized that to inhibit DP-IV would result in increasing GLP-1 bioactivity. As GLP-1 was a major stimulator of pancreatic insulin secretion, DP-IV inhibitors would have direct benefits on glucose disposal. Villhauer (1998), Ex. 1008, p. 1. Thus, the art pursued inhibitors of DP-IV's protease activity for GLP-1 as a potential treatment for type II diabetes mellitus and related conditions, including obesity. Ex. 1008 (Villhauer), pp. 1, 18; Ex. 1003, ¶¶41; Ex. 1028, ¶¶41.

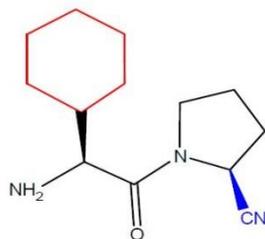
DP-IV functions by recognizing as its substrate either proline or alanine in the second (carboxyl, or C-terminus) position from the N-terminus, and then cleaving the dipeptide from the peptide or protein chain. Analogues of dipeptides which inhibited DP-IV, were described by Ashworth (1996)(Ex. 1007), Villhauer

(1998)(Ex. 1008), and others (mentioned in Ashworth, Ex. 1007, at p. 1163-1164).

Central to the substrate analogues described by both Ashworth and Villhauer is a modified first amino acid, glycyl, bonded to a modified proline as the second amino acid. Glycyl-proline is illustrated below, where glycyl is the portion in red and proline is in blue. Ex. 1007, p. 1163-1166; Ex. 1003, ¶101; Ex. 1028, ¶101.



Ashworth stated that substrates and inhibitors of DP-IV “require a free N-terminus.” Ex. 1007, p. 1163. Ashworth recognized, however, that a free amine at the N-terminus made the molecule prone to intramolecular cyclization, which would adversely affect stability of the analogue inhibitor. Ex. 1007, p. 1163; Ex. 1003, ¶60,112; Ex. 1028, ¶60,112. Ashworth added bulky side groups near the N-terminus, such as a (S)-cyclohexyl or a cyclopentyl group, and found that this provided improved stability in an aqueous solution. Ex. 1007, pp. 1165-1166. One example is shown below, which differs from glycyl-proline by adding the bulky cyclohexyl group (red) on the  $\beta$ -carbon of the glycyl, as described in Table II’s Compound **25** of Ashworth (“Chg”, abbreviation for Cyclohexylglycyl).



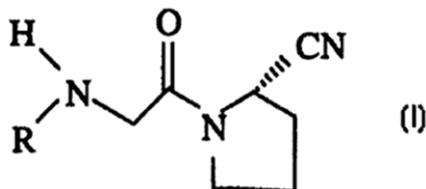
Ashworth's Compound **25** (above) differs in another aspect from glycylproline in that the carboxy group on the proline has been replaced with a nitrile (CN; blue). Ashworth recognized that a nitrile group provided biological activity comparable to the best previously tested DP-IV inhibitors ("these compounds were potent inhibitors of DP-IV"). Ex. 1007, p. 1165, and p. 1166, referring to a series of dipeptide nitriles, compounds 24-29, in Table II.

Thus, Ashworth published in 1996 two routes for optimizing a glycylproline based DP-IV inhibitor: placing large substituents such as cyclohexyl and cyclopentyl on the glycol moiety, and modifying the pyrrolidine ring of the proline moiety by replacing the carboxyl group with a nitrile. Ex. 1003, ¶71; Ex. 1028, ¶71. These substituents provided potent DP-IV inhibition and improved stability in an aqueous solution. Ex. 1007, 1163-64; Ex. 1003, ¶71; Ex. 1028, ¶71.

## **2. Substituting Hydroxyadamantyl onto the glycol moiety**

Following Ashworth, Novartis AG (Villhauer, Ex. 1008) described other large substitutions on the glycol moiety of a DP-IV dipeptide analog. Despite DP-IV's preference for a free amine on the N-terminal, Villhauer produced analogues

with large substitutions on the amine itself (base structure (I) shown below). Ex. 1008, cover page; Ex. 1003, ¶74; Ex. 1028, ¶74.



Adamantyl was among the substitutions Villhauer described for **R**, and adamantyl was identified as one of a small subset of “[e]ven more preferred compounds.” Ex. 1008, p. 5. The adamantyl-containing compound was made and characterized. Ex. 1008, pp. 11-13 (Example No. 47).

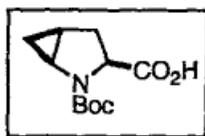
Raag (1990) had previously described adamantane (below) and its metabolites. Ex. 1009, p. 2674; Ex. 1003, ¶¶78-80; Ex. 1028, ¶¶78-80.



Because adamantane is symmetric and its tertiary carbons (i.e. the carbons bound to three other carbons) are more reactive than its secondary carbons, it metabolizes to 1-hydroxyadamantane, i.e., a hydroxyl on any of the four tertiary carbons. Ex. 1009, p. 2678; Ex. 1003, ¶80; Ex. 1028, ¶80. Metabolites are known in the art to impart improved stability for therapeutic compounds, among other advantages. Ex. 1003, ¶129; Ex. 1028, ¶129.

### 3. Adding Cyclopropyl to the Pyrrolidine ring

Proline's pyrrolidine ring had been modified by both Ashworth and Villhauer to increase DP-IV inhibition by dipeptide analogues. Hanessian (1997) described adding a three-carbon cycle, cyclopropyl, (or "x,y-methano") to pyrrolidine's ring, thus creating 4,5-methanoproline, (trans-conformation depicted below, Fig. 8 in Hanessian's Scheme 1; Ex. 1010, p. 1882). Hanessian noted that proline had "figured prominently as a component of therapeutic agents, in drug design, and in probing enzymatic activity." Ex. 1010, p. 1881.



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Hanessian's publication of conformationally altered ring variants of proline was described as having "important consequences in biological recognition, in cis/trans conformation changes, [and] in the susceptibility of the secondary amide bonds to enzymatic cleavage." Ex. 1010 at 1883.

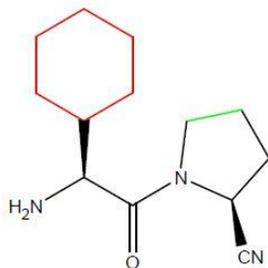
On the glycyL-2-cyanopyrrolidine modified as described in Ashworth (Ex. 1007), the 3,4 and 4,5 locations on the proline ring are available for cyclopropanation as described in Hanessian without interfering with the other bonds on the ring. Ex. 1003 ¶83; Ex. 1028, ¶83. Two possible enantiomers at each position results in only four possible cyclopropanations. Ex. 1003, ¶141; Ex. 1028, ¶141.

To summarize, more than a year prior to the earliest priority date of the '186 patent, those of ordinary skill in the art had all of the elements needed to make a compound glycyyl-2-cyanopyrrolidine with an (S)-3-hydroxyadamantyl on the  $\beta$ -carbon and with a 4S, 5S-cyclopropanation on the cyanopyrroline, i.e., “saxagliptin.” Moreover, the skilled worker had strong reasons to combine those elements with a reasonable expectation of success in creating a dipeptide analogue that inhibited DP-IV. Based on potent DP-4 inhibition and stability in aqueous solution, attributes of analogues described by Ashworth, such a compound would reasonably be expected by the skilled worker to be useful therapeutically, including in the treatment of type II diabetes mellitus and its related conditions.

**D. Overview of Differences Between the Prior Art and the Claims**

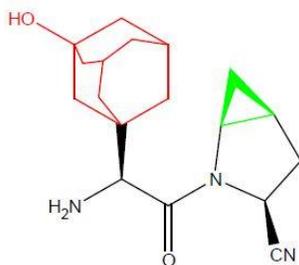
Pursuant to the requirements of *Graham v. John Deere Co.*, 383 U.S. 1, 17, 36 (1966), Petitioner provides an overview of the differences between the prior art asserted against the '186 claims and the claims.

Taking Ashworth Compound **25** (below) as a lead compound, the compound of claim 25 (saxagliptin) differs in two ways.



First, the claim 25 compound has a hydroxyadamantyl in place of the Ashworth's cyclohexyl (in red). Ex. 1003, ¶102; Ex. 1028, ¶102. Second, the claim 25 compound has a cyclopropanation at the 4 and 5 carbons (in green) of Ashworth's 2-cyanopyrrolidine. Ex. 1003, ¶102; Ex. 1028, ¶102.

For comparison, the compound of claim 25 of the '186 patent is reproduced below showing these modifications. Ex. 1001 at 91:20.



The references are discussed more in depth in the context of the specific grounds of challenge.

### **E. Level of Skill in the Art**

At the time of the invention, a person having ordinary skill in the art would have some combination of the following skills and experience: designing target compounds towards drug discovery; designing and preparing formulations of drugs that exhibit inhibitory activity; understanding the biological aspects of drug

development, including the drug's effect on the whole animal; and understanding work presented or published by others in the field, such as references discussed by Drs. Rotella and Muthyala in their declaration in Ex. 1003, at, e.g., ¶¶60-94 and Ex. 1028, ¶¶60-85, representing the state of the art, and including the references asserted in grounds 1-4 in this petition. Ex. 1003, ¶60; Ex. 1028, ¶60.

Typically, a person of ordinary skill in the relevant field in March 2000 would have an advanced degree (e.g., a Ph.D.) in pharmaceuticals, pharmaceutical chemistry, medicinal chemistry or a related field and at least 2-3 years of practical experience in the design of drugs. Alternatively, a person of ordinary skill in the relevant field might have less education but considerable professional experience. Ex. 1003, ¶36; Ex. 1028, ¶36.

Petitioner Teva's expert, Dr. Ramaiah Muthyala, is currently the Associate Professor in the Department of Experimental Clinical Pharmacology at the University of Minnesota. Ex. 1028, ¶¶1-2; Ex. 1029. From 1969-1999 Dr. Muthyala was a research scientist at multiple pharmaceutical companies, including at Indian Drugs and Pharmaceuticals Ltd., Schering Plough Dow Chemical Company and 3M/Imation Corporation. Ex. 1028, ¶3; Ex. 1029. Dr. Muthyala's industry experience focused on drug discovery and development. He received a Ph.D. in natural products from Sagar University, India, in 1970 and a Ph.D. in heterocyclic chemistry from the University of East Anglia, UK in 1975. Dr. Muthyala was a

Postdoctoral Scholar at the University of North Wales, UK, 1971-1972 and at Wayne State University, MI, 1974-1976. 1028, ¶4; Ex. 1029. Dr. Muthyala is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge to assist in an understanding of the evidence presented herein, as well as possessing the ability to address background art and common knowledge in the art.

The lack of specific guidance in the '186 patent confirms the high level of skill in the art. For example, the '186 patent includes only a limited description of the various pharmaceutical combinations that it claims. There are no validated or tested dosages for those combinations and no examples describing any actual combinations produced by the inventors.

Rather than providing specific guidance regarding dosages for the claimed combinations, the '186 patent invites those of ordinary skill in the art to turn to the knowledge and resources available to them when selecting and formulating combinations of known drugs. In one example, rather than providing specific guidance for combination dosages, the patent provides extremely broad dosage ranges (Ex. 1001 at 4:48-53), providing essentially no guidance for selecting dosages or treatment regimens. Hence, the '186 patent relies on a high level of skill in the art to enable practicing the invention. Ex. 1003, ¶37; Ex. 1028, ¶37.

In many instances, the '186 patent states that other known agents or treatment mechanisms, not described in detail in the '186 patent, can be used in combination with the selected compound. Examples include “other known mechanisms for therapeutically treating lipid disorders” (Ex. 1001 at 4:43-45); “other known sulfonylureas or other antihyperglycemic agents” (*id.* at 15:5-12); “squalene synthetase inhibitors” (*id.* at 17:47-56); “hypolipidemic agents” (*id.* at 18:1-20); and “known beta 3 agonists” (*id.* at 20:12-18). Furthermore, the '186 patent repeatedly defers to standard resources for guidance in determining dosages and other treatment parameters for the claimed combinations, including 15 citations to the Physician’s Desk Reference (PDR) (*id.* at 15:60-61; 16:4-5; 19:3 and 35; 20:43, 50, 57 and 67; 21:9, 15, 24, 41, 47 and 54). The patent states that “[t]he amounts and dosages employed will be as indicated in the Physician’s Desk Reference[.]” *Id.* at 19:2-4. The PDR is well known in the art as a resource for established dosing and treatment regimens for approved drugs. Ex. 1003, ¶40; Ex. 1028, ¶40.

Villhauer (Ex. 1008) similarly indicates a high level of skill in the art by relying on that skill to select from the many options described as well as options known to those in the art. Ex. 1008 at, *e.g.*, pp. 2-3 (large and diverse *Markush R* groups), p. 3 (pharmaceutically acceptable salts and isomers), p. 7 (“The process of the invention may be effected in conventional manner.”), p. 8 (starting materials

known or prepared in known or conventional manner) and p. 20 (pharmaceutically acceptable carriers, adjuvants and modes of administration, and conventional preparation of same). Villhauer reflects the conventional approach in the art of preparing promising variants of lead compounds and comparing the results. Ex. 1003, ¶38; Ex. 1028, ¶38.

Thus, as shown above, the '186 patent and the prior art confirm the high level of ordinary skill in the art as of March 10, 2000, the earliest date to which the '186 patent claims priority. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *accord Ex parte Jud*, 85 USPQ2d 1280, 1282 (BPAI 2007) (expanded panel) (holding the applicant's disclosure, the cited references, and any declaration testimony may be used to establish the level of skill in the art).

### **III. GROUNDS FOR STANDING**

Petitioner certifies that, under 37 C.F.R. § 42.104(a)) the '186 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting *inter partes* review of the '186 patent on the grounds identified.

### **IV. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8**

Real parties-in-interest (§42.8(b)(1)): Teva Pharmaceuticals USA, Inc. is a real party-in-interest. Teva Pharmaceuticals USA, Inc. is a subsidiary of Teva Pharmaceuticals Industries, Inc.

Related Matters (§42.8(b)(2)): Petitioner is aware of the following matters:

The '186 patent is involved in *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-014696 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). Neither Teva Pharmaceuticals USA, Inc. nor Teva Pharmaceuticals Industries, Inc. is a party to any of these lawsuits.

**Lead and Back-Up Counsel** (§42.8(b)(3))

Lead Counsel: Gary J. Speier (Reg. No. 45,458)

Back-Up Counsel: Iain McIntyre (Reg. No. 40,337)

**Service Information** (§42.8(b)(4)) Mylan consents to electronic service.

<b>Lead Counsel</b>	<b>Backup Counsel</b>
Gary J. Speier gspeier@carlsoncaspers.com Carlson, Caspers, Vandenburg, Lindquist & Schuman 225 South Sixth Street, Suite 4200 Minneapolis, MN 55402 Tel.: 612-436-9600 Fax: 612-436-9605	Iain A. McIntyre imcintyre@carlsoncaspers.com Carlson, Caspers, Vandenburg, Lindquist & Schuman 225 South Sixth Street, Suite 4200 Minneapolis, MN 55402 Tel.: 612-436-9600 Fax: 612-436-9605

Petitioner agrees to service by email.

**V. STATEMENT OF PRECISE RELIEF FOR EACH CLAIM CHALLENGED**

Petitioner requests review of claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 of the '186 patent under 35 U.S.C. § 311 and AIA § 6. Petitioner challenges claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 on the grounds that each of the claims should be canceled as unpatentable under 35 U.S.C. § 103 (2012) as follows:

<b>Ground</b>	<b>Claims</b>	<b>Description</b>
1	1, 2, 4, 6-11, 25-28, 32-35, 39 and 40	Obvious under 35 U.S.C. § 103 over Ashworth, Villhauer, Raag and Hanessian
2	12-16, 29, 30, 36, 37, 41 and 42	Obvious under § 103 over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and Glucophage® Label
3	12, 17, 18, 22	Obvious under § 103 over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and Xenical® Label
4	12, 19, 20, 21	Obvious under § 103 over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and Mevacor® Label

The '186 patent claims the benefit of a provisional application filed March 10, 2000. Ashworth (Ex. 1007) was published in 1996; Villhauer (Ex. 1008) was published on May 14, 1998; Raag (Ex. 1009) was published in 1991, and Hanessian (Ex. 1010) was published in 1997. Each reference for ground 1 is available as prior art against the challenged claims under 35 U.S.C. § 102(b) (2012).

Bachovchin (Ex. 1011) published on August 5, 1999, and thus is prior art under §102(a). GLUCOPHAGE Label information (Ex. 1012) was publicly available from FDA under the Freedom of Information Act (“FOIA,” 5 U.S.C. § 552) by January 8, 1998, and thus is available as prior art under §102(b).

XENICAL Label information (Ex. 1013) was publically available from FDA under FOIA at least by August 9, 1999, and thus is prior art under §102(a). MEVACOR Label information (Ex. 1014) was publically available from FDA under FOIA by at least September 15, 1994, and thus is available as prior art under §102(b).

## **VI. CLAIM CONSTRUCTION**

A claim subject to *inter partes* review receives the broadest reasonable construction or interpretation in light of the specification of the patent in which it appears, because among other reasons, the patent owner has an opportunity to amend the claims. *See* 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279-82 (Fed. Cir. 2015).

The claims use conventional terminology. Ex. 1003, ¶42; Ex. 1028, ¶42. The patent disclosure offers specific definitions (Ex. 1001 at 4:3-47), but these definitions are conventional. Ex. 1003, ¶42; Ex. 1028, ¶42. For example, the specification defines “[t]he term ‘lipid-modulating’ agent as . . . agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or [sic, employ] other known mechanisms for therapeutically

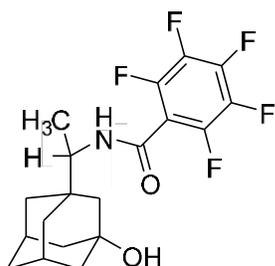
treating lipid disorders.” Ex. 1001 at 4:43-47. The specification includes anti-atherosclerosis agents in this class. Ex. 1001 at 4:30-31 (“one or more lipid-modulating agents (including anti-atherosclerosis agents)”).

## **VII. BACKGROUND KNOWLEDGE IN THE ART PRIOR TO MARCH 10, 2000**

The Background section of the '186 patent discloses that “inhibitors of dipeptidyl peptidase IV [(DP-IV) are known to] . . . treat[ ] diabetes, especially Type II diabetes.” Ex. 1001 col. 1, ll. 19-21. Lin (1998)(Ex. 1015) described common features of DP-IV inhibitors. For example, Lin reported that “[DP-IV] substrates require the presence of a proline at the P1 position as well as a protonated free N terminus.” Lin also described what was generally known in the art in March 2000 regarding DP-IV’s preference for substrates and inhibitors in the trans conformation: “[DP-IV] possesses a high conformational specificity for a trans amide bond between the P1 and N-terminal P2 residues.” Ex. 1015, p. 14020. Ex. 1003, ¶46; Ex. 1028, ¶46. Lin addressed the importance of the trans conformation for compound stability and its effect on DP-IV inhibition as follows: “Many of the problems associated with inefficient inactivation of [DP-IV] are a consequence of the **importance of the trans conformation** of the P1-P2 amide bond and the requirement for a protonated free N terminus. **The cyclization reaction of the free N-terminal amino group with the reactive inhibitor . . . require[s] the molecule assume the cis conformation.**” [pp. 14020-14021

(emphasis added)].

Hoffman (1988) (Ex. 1016) had described the use of a large, steric adamantyl group in the antiviral drug, rimantadine and reported that the adamantyl moiety was known to be metabolized to a hydroxylated derivative at the 3-position as shown below:



3-hydroxy rimantadine

Lipinski (Ex. 1017), Hansch (Ex. 1018) and Cates (Ex. 1019) had published strategies for enhancing the drug-like properties of a compound, such as by reducing a compound's partition coefficient, and thus potentially increasing its solubility in aqueous solution. According to Lipinski (1997), the use of hydroxyl groups on drugs increases their water solubility. *See*, Ex. 1017, p. 17. Also, adding a hydroxyl group to a lipophilic group should also reduce the compound's Log P and thus improve its solubility. Ex. 1017, pp. 8 and 15. *See also*, Hansch (1979)(Ex. 1018), pp. 48-54, 52, describing hydroxyl groups as lowering Log P when added as a compound substituent. Cates (1981)(Ex. 1019) had described a process of approximating whether or not a drug is soluble in water and how modifications to such a drug will affect the solubility of the drug. Ex. 1003, ¶53;

Ex. 1028, ¶53. Furthermore, prior to March 2000 it was known in the art that identification of candidate drug metabolites “can guide structural modifications, thereby improving the activity and/or bioavailability.” Korfmacher *et al.*, *Drug Discovery Today*, 1992, pp. 532-537 (Ex 1020). 3-Hydroxy adamantane is a known metabolite of adamantane. Ex. 1016; Ex. 1003, ¶49; Ex. 1028, ¶49.

Further, Korfmacher taught the following advantages of metabolite identification:

Metabolite identification in drug discovery provides early information that can lead to structural changes in the current lead compound . . . .  
Early metabolite identification can provide information on how to improve the metabolic stability of the lead structure. In this way, future lead compounds might be a metabolite identified from the previous lead drug or an analog of the previous drug designed to block the major route of metabolism.

Ex. 1020, p. 534. Thus, according to Korfmacher, one of ordinary skill in the art would have been motivated to make and test a known metabolite when optimizing a lead drug.

A well-known strategy prior to March 2000 for modulating the orientation of a ring-bound substituent would have been through fusion of the substituent-bearing ring with another ring. Chiou (1969), Ex 1021, p. 243. Fusion between two rings can result in significant changes in ring flexibility, including ring flattening. *Id.* These changes in turn would have been expected by one of ordinary skill in the art

to affect the orientation of ring-bound substituents. *Id.* Cyclopropyl is one of the most commonly used ring fusion agents because: (i) addition of a cyclopropyl ring has a negligible effect on compound molecular weight, which is an important contributor to better drug-like qualities (*see, e.g., Ex 1021, p. 243*); (ii) cyclopropyl has an exceedingly small footprint, meaning it adds a minimal steric effect on the rest of the compound to which it is attached (*see, e.g., Ex 1021, p. 243*) and (iii) cyclopropyl provides greater conformational restriction than larger ring fusions, resulting in fewer conformations (*see, e.g., Ex 1021, p. 243*). *Ex. 1003, ¶57; Ex. 1028, ¶57.*

It was also well known in the art prior to March 2000, that an enzyme and its respective substrates and inhibitors typically fit together in a manner analogous to a hand in a glove. *See, e.g., Koshland (1994), Ex. 1022, p. 2377.* Closer degrees of matching often result in greater affinity (with respect to a substrate) or greater inhibition (with respect to an inhibitor). *Id.* at 2376. Thus inhibitor conformation and functional group orientation are important to effective interactions between enzymes and their inhibitors. *Id.* Like other enzymes, DP-IV inhibition would have been expected to be improved when the active site and inhibitor fit closely. *Ex. 1003, ¶58; Ex. 1028, ¶58.*

## **VIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY**

### **A. [Ground 1] Claims 1, 2, 4, 6-11, 25-28, 32-35, 39 and 40 Are**

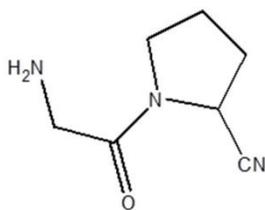
**Obvious Under 35 U.S.C. § 103 Over Ashworth, Villhauer, Raag and Hanessian**

Each claim challenged under this Ground 1 either defines the saxagliptin compound now called saxagliptin or includes saxagliptin within its scope. Before the earliest priority date of the '186 patent, a person having ordinary skill in the art would have considered it obvious to make this compound for use as a DP-IV inhibitor for treatment of type II diabetes mellitus and its related conditions. Hence, each claim challenged in this Ground 1 includes obvious subject matter.

Claim 25 is directed to the saxagliptin compound itself, or a pharmaceutically acceptable salt thereof. As demonstrated below, claims 1, 2, 4, 6-8, 10 encompass the saxagliptin compound. Claims 9, 11 and 26-28 encompass a pharmaceutically acceptable salt of the saxagliptin compound or use of a pharmaceutically acceptable carrier with the saxagliptin compound. Claims 32-35, 39 and 40 encompass use of the saxagliptin compound (or its salt) with a pharmaceutically acceptable carrier to treat at least type II diabetes. 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. *Muchmore*, 433 F.2d at 824-85; *Soverain Software LLC*, 778 F.3d at 1315.

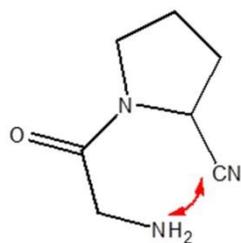
**1. Skilled Workers Were Motivated to Make Better DP-IV Inhibitors**

Villhauer explained that those in the art were looking for better DP-IV inhibitors, particularly for treating type 2 diabetes mellitus (which Villhauer calls “non-insulin dependent diabetes mellitus”) and related conditions, such as obesity. Ex. 1008, pp. 1, 18; Ex. 1003, ¶¶41, 77; Ex. 1028, ¶¶41, 77. Villhauer focused on N-glycyl-2-cyanopyrrolidine derivatives (illustrated below). Ex. 1008, p. 1.



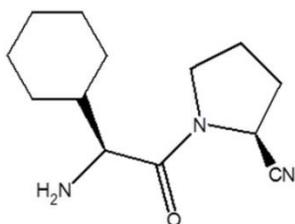
## 2. Ashworth Identified a Lead Compound

Ashworth also explored 2-cyanopyrrolidines as DP-IV inhibitors, with a particular focus on increasing potency and stability. Ex. 1007, pp. 1163-64. Ashworth noted that DP-IV requires a free N-terminus, but this makes the inhibitors prone to intramolecular cyclization (illustrated below). *Id.* at 1163.



Ashworth prepared a series of amino acid pyrrolidines as hydrochloride salts. *Id.* at 1165. Ashworth found that lipophilic amino acids, particularly  $\beta$ -branched  $\alpha$ -amino acid derivatives were the most potent, with (S)-cyclohexylglycine being most active. *Id.* Ashworth determined that the 2-

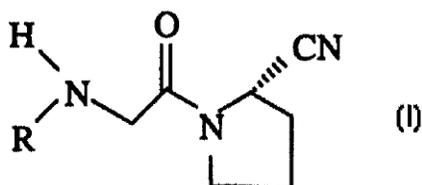
cyanopyrrolidine derivatives were potent DP-IV inhibitors, particularly four compounds (Compounds **24-27**)(Ex. 1007, pp. 1165-66) that were comparable to boroprolines, which were known to be effective DP-IV inhibitors but were unstable. *Id.* Ashworth's Compound **25**, the cyclohexylglycyl version (illustrated below), had one of the best potencies (expressed in  $K_i$  (nM)) and one of the best stabilities (expressed in  $t_{1/2}$  (h)). *Id.*



Drs. Rotella and Muthyala explain in their Declarations (Ex. 1003; Ex. 1028) that those skilled in the art would have understood that Ashworth's addition of cyclohexyl to the  $\beta$ -carbon of the glycyl helped to restrict the N-glycyl-2-cyanopyrrolidine to a conformation both preferred by DP-IV as a substrate and one less prone to cyclization. Ex. 1003, ¶¶100, 116; Ex. 1028, ¶¶100, 116. Ashworth provided a person having ordinary skill in the art with reasons—specifically, potency and stability—to have selected compound **25** (cyclohexylglycyl-2-pyrrolidine) as a lead compound and provided good reason to have expected that other  $\beta$ -branched  $\alpha$ -amino acid derivatives would also be worth exploring. Ex. 1003, ¶105, Ex. 1028, ¶105. Ashworth explained that they were also working on optimizing the pyrrolidine ring (i.e., the proline moiety). Ex. 1007, p. 1165.

### 3. Villhauer Identified a Large Adamantyl Group to Modify DP-IV Inhibitors

Villhauer also worked to improve 2-cyanopyrrolidines as DP-IV inhibitors, but by substitution on the terminal amine rather than on the  $\beta$ -carbon of the glycyl (below). Ex. 1008, Abstract.



Villhauer expressly contemplated adding (C3-12)cycloalkyl, preferably cyclopentyl or cyclohexyl (like Ashworth), either unsubstituted or monosubstituted with a small (C1-3)hydroxyalkyl, like hydroxyethyl. *Id.*, pp. 2 (see option b), 4. Villhauer also expressly contemplated using adamantyl instead at the same position. Ex. 1008, p. 3 (option g). Either 1-adamantyl or 2-adamantyl could be used. Ex. 1008, p. 4. Villhauer characterized as “[e]ven more preferred” a genus that includes adamantyl, but not unsubstituted cyclohexyl. Ex. 1008 at 5. Instead, one of Villhauer’ most preferred examples, compound **5**, used (1-hydroxymethyl)cyclopent-1-yl. Ex. 1008, p. 11 (table) and p. 21.

Adamantyl is a (C10)tricycloalkyl. Ex. 1003, ¶113; Ex. 1028, ¶113. As discussed above, Ashworth taught the advantages of placing a large  $\beta$ -branched (S)-cycloalkyl on Nglycyl-2-pyrrolidine. Ex. 1007, p. 1165; Ex. 1003, ¶67; Ex. 1028, ¶67. Adamantyl (C10) is a tricycloalkyl even larger than cyclopentyl (C5) or

cyclohexyl (C6). A person having ordinary skill in the art 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, and using additional candidates that Villhauer taught. Ex. 1003, ¶119; Ex. 1028, ¶119.

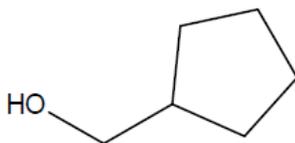
Villhauer also taught that the compound may be in free form or in acid addition salt form, where the salt could be from any pharmaceutically acceptable acid, with hydrochloride as a preferred option. Ex. 1008, p. 3; Ex. 1003, ¶76; Ex. 1028, ¶76. Similarly, Villhauer taught that any pharmaceutically acceptable carriers, adjuvants and enteral or parenteral administration forms (prepared by conventional means) could be used with any of the disclosed agents of the invention. Ex. 1008, p. 20; Ex. 1003, ¶76; Ex. 1028, ¶76.

#### **4. Raag Describes a Hydroxylated Adamantane Metabolite**

Those skilled in the art routinely investigated metabolites of a lead compound, especially when looking for ways to improve metabolic stability. Ex. 1003, ¶53; Ex. 1028, ¶53. It was also known that metabolites can have other advantages, such as increasing solubility, absorption and bioavailability. Ex. 1003, ¶53; Ex. 1028, ¶53. Raag described the oxidation of substrates, including adamantane, by the detoxifying enzyme P-450. Ex. 1009, p. 2674. Raag determined that adamantane is consistently metabolized to 1-hydroxyadamantane

because it has only two unique types of carbon: those bound to two other carbons and those bound to three other carbons, secondary and tertiary carbons, respectively. Because tertiary carbons are more reactive, adamantane was consistently metabolized by the enzyme on one of the tertiary carbons. Ex. 1009, p. 2678.

Raag also noted that adamantane is not very soluble. Ex. 1009, p. 2675. Yet Ashworth taught that a large lipophilic substituent was advantageous for N-glycyl-2-cyanopyrrolidine stability (Ex. 1007, p. 1165), and Villhauer taught using adamantyl as a large substituent. Ex. 1008, pp. 3, 5. A person of ordinary skill would have been motivated to use hydroxylated adamantyl metabolite, as taught by Raag (Ex. 1009, p. 2678), to improve solubility and HO bioavailability of the compound. Ex. 1003, ¶123; Ex. 1028, ¶123. Villhauer taught that a hydroxylated 1-methylcyclopentyl (illustrated below) substituent worked well.



Thus, the combined teachings of Ashworth, Villhauer and Raag informed those of skill 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. Ex. 1003, ¶150; Ex. 1028, ¶150.

## 5. Hanessian Describes Cyclopropyl Modification to the Proline Moiety

In addition to adding a bulky substituent group on glycyl's  $\beta$ -carbon, Ashworth described optimizing the proline portion of the glycyl-proline dipeptide analogue. Ex. 1007 at 1165. Ashworth found that adding a nitrile group to the pyrrolidine ring portion of proline yielded compounds with high inhibitory potency against DP-IV enzyme. *Id.*, 1165-1166.

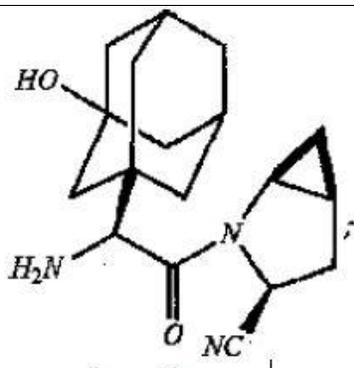
Proline is noted for its significant conformational effect on peptides such that proline often figures prominently as a component of therapeutic agents, in drug design and in probing enzyme activity. Hanessian, Ex. 1010, p. 1881. Conformationally constrained proline is used extensively in peptidomimetic research. *Id.* While others had studied 2,3- and 3,4-methanoproline, Hanessian focused on 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 1881-82. Hanessian found that cyclopropanation of the proline at the 4,5-carbons "flattens" the ring, i.e., reduces the bond angles within the ring compared to unmodified proline. *Id.* at 1882. One consequence was that the carbon with the carboxyl group ( $C\alpha$  or 1-carbon) was the out-of-plane carbon rather than  $C\beta$  (2-carbon) as is the case with unmodified proline. *Id.* In the case of 2-cyanoproline, the  $\alpha$ -carbon bears a nitrile instead so the flattening would push the nitrile-bearing carbon out of the plane defined by the rest of the proline ring. Ex. 1010, p. 1882;

Ex. 1003, ¶142; Ex. 1028, ¶142. Cyclopropanation also affected the *cis/trans* conformation of the proline with respect to the Boc protecting group bonded to the nitrogen in the proline ring. Ex. 1010, p. 1883 and Table 1 (figure of compound 8).

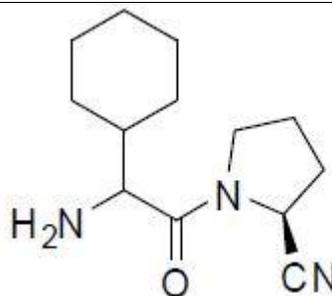
Hanessian identified three locations on the proline ring (2,3; 3,4 and 4,5) where cyclopropanation could occur, with two resulting stereoisomers, for a total of six possible cyclopropanations of the proline ring to try. Changing the position of the nitrile relative to the rest of the dipeptide would 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). Ex. 1003, ¶143; Ex. 1028, ¶143. With only six possibilities, those skilled in the art would have had reason to try each determine which provided the best activity and stability. Ex. 1003, ¶139-140; Ex. 1028, ¶139-140.

The following claim chart shows where each component of the compound of claim 25 is disclosed in the Ashworth, Villhauer, Raag and Hanessian references.

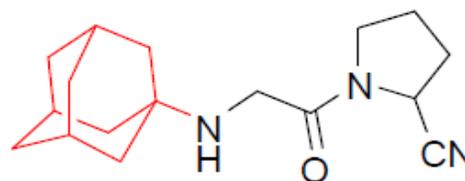
<b>U.S. Patent No. RE44,186 Challenged Claim 25</b>	<b>Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), and Hanessian (Ex. 1010)</b>
25. A compound that is	Ashworth discloses the following compound <b>25</b> :



or a pharmaceutically acceptable salt thereof.



(Ex. 1007, p. 1166, Table II). Villhauer discloses DP-IV compounds having cycloalkyl or alkyl groups attached to the amino moiety of 2-cyano pyrrolidides (Ex. 1008, pp. 12-13). *See also* Ex. 1008, p. 13, Example 47:



Raag discloses that “[a]damantane is . . . metabolized to a single product . . . [which] can be attributed to the existence of only two types of unique carbon atoms in adamantane, together with the greater reactivity of tertiary versus secondary carbons” (Ex. 1009, p. 2678). *See also*, Ex. 1009, Table III, col. 7.

Hanessian discloses the “highly stereocontrolled syntheses of the diastereomeric 4,5-methano-L-prolines . . . [by an] intramolecular cyclopropanation reaction” (Ex. 1010, 1882).

**6. The Compound of Claim 25 of the '186 Patent Was Obvious Over the Combined Teachings of the References**

The art recognized a need for a potent, stable DP-IV inhibitor for use as a therapeutic compound for type II diabetes mellitus as well as its related conditions. Exs. 1007; 1008; 1003 ¶¶63-65; Ex. 1028, ¶¶63-65. The art had identified the dipeptide N-glycyl-2- cyanopyrrolidine analogues as a promising solution. Exs. 1007, 1008. The art even described two key modifications: (1) add a bulky hindering structure to the glycyl moiety to improve stability, Exs. 1007, 1008; and (2) optimize the conformation of the proline ring. Exs. 1007, 1009, 1010, 1003¶145; Ex. 1028, ¶145. The art had also identified specific paths for each modification.

The hindering structure would preferably be a large structure, particularly a cycloalkyl, optionally hydroxylated. Ashworth (Ex. 1007, pp. 1165-66) disclosed cyclohexyl as a promising starting point. Villhauer (Ex. 1008, pp. 3, 5) described adamantyl and hydroxy(C1-3)alkylated cycloalkyls. Raag (Ex. 1009) reported that adamantyl has a hydroxylated metabolite, recognized in the art as a reasonable way to optimize a compound for therapeutic use. Ex. 1003, ¶127-129; Ex. 1028, ¶127-129.

Hanessian (Ex. 1010) recognized substituents at the 4-carbon of the proline ring as beneficial. Hanessian also recognized that cyclopropanation of the proline ring, particularly at the 4,5-carbons, would affect both the conformation of the dipeptide and the positioning of the nitrile. Given the limited number of possible

cyclopropanations (six overall, four involving the 4-carbon), those skilled in the art would have had reason to try them all. Ex. 1003, ¶¶139-140; Ex. 1028, ¶¶139-140. One of these, the (4*S*,5*S*)-methanopyrrolidine derivative, is present in saxagliptin. Compare the cyclopropanated proline ring of the compound of claim 25 with Hanessian, Ex. 1010, p. 1882 (compound **8**); Ex. 1003 ¶¶146; Ex. 1028, ¶¶146.

The art proceeded by taking a promising lead structure, making promising modifications and then comparing the results. Ashworth, Villhauer, and Hanessian all took this approach: exploring a genus of related modifications. Ex. 1003, ¶¶67, 75, 83; Ex. 1028, ¶¶67, 75, 83. In the case of Ashworth and Villhauer, and even the '186 patent, the lead structure is essentially the same: N-glycyl-2-cyanopyrrolidine. Ex. 1003, ¶¶12, 68, 75; Ex. 1028, ¶¶12, 68, 75. Using the guidance that Ashworth, Villhauer, Raag and Hanessian provide, those skilled in the art would have had reason to pursue the modifications leading to the same compound, as recited in claim 25, with a reasonable expectation of success, following the same protocols common to these references, and customary practices in the art. Ex. 1003, ¶¶145-148; Ex. 1028, ¶¶145-148. The level of guidance provided in the prior art compares favorably with the guidance in the patent specification. *Cf. Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 n.3 (Fed. Cir. 2008) (explaining that, if the lack of guidance in the patent did not indicate obviousness, then it would indicate that the patent lacked enablement).

The present petition sets forth the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and how a person of ordinary skill would have modified the prior art to reach the claimed invention. *See Graham v. John Deere Co.*, 313 U.S. 1, 17 (1966). A prior art reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect. *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985). Further, it is well-established that a determination of obviousness based on teachings from multiple references does not require an actual, physical substitution of elements.” *In re Mouttet*, 686 F.3d 1322, 1332 (Fed. Cir. 2012) (citing *In re Etter*, 756 F.2d 852, 859 (Fed. Cir. 1985) (en banc) (noting that the criterion for obviousness is not whether the references can be combined physically, but whether the claimed invention is rendered obvious by the teachings of the prior art as a whole).

In *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007), the Court confirmed that obviousness determinations require an expansive, flexible and functional approach. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has a good reason to pursue the options known in the art. If this leads to the anticipated success, it is *likely* the product not of innovation but of ordinary skill and common sense. *Id.* at 421. Obviousness is “necessarily a

reconstruction based upon hindsight reasoning,” but so long as it is based on the knowledge and content of the art rather than on the patent disclosure, that is permissible. *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

The structure of the compound of claim 25 is Ashworth compound **25** (2-cyclohexylglycyl-2-cyanopyrrolidine), with hydroxyadamantyl substituted for the cyclohexyl (as Villhauer and Raag suggest) and with the 2-cyanopyrrolidine modified to have a (4S,5S)-cyclopropyl ring (as Hanessian suggests). Ex. 1003 ¶132-146; Ex. 1028, ¶132-146. Villhauer taught that N-glycyl-2-cyanopyrrolidine DP-IV inhibitors could be in free form or in acid addition salt form, where the salt could be from any pharmaceutically acceptable acid. Ex. 1008, p. 3. Thus, as either the free form or the salt form, the compound of claim 25 would have been obvious to a person of ordinary skill in the art prior to March 10, 2000.

#### **7. Claims 26-28**

Claim 26 specifies that the salt is hydrochloride salt. Claims 27 and 28 define compositions of the compounds of claims 25 and 26, respectively, with a pharmaceutically acceptable carrier. Villhauer (Ex. 1008, p. 3) identified hydrochloride as the preferred salt for such compounds. Villhauer also taught that one or more pharmaceutically acceptable carriers could be used in such compositions. *Id.* at 20. Thus, claims 26-28 are obvious in view of the combined teachings of Ashworth, Villhauer, Raag and Hanessian.

The following claim chart shows where each element of the compound of claim 26, and of the pharmaceutical compositions of claims 27 and 28, is disclosed in the Ashworth, Villhauer, Raag and Hanessian.

<b>U.S. Patent No. RE44,186 Challenged Claims 26-28</b>	<b>Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), and Hanessian (Ex. 1010)</b>
26. The compound as defined in claim 25, wherein the pharmaceutically acceptable salt is the hydrochloride salt.	The compound of claim 25 is discussed in its respective claim chart. Ashworth discloses the “subsequent acid catalyzed deprotection (4N HCl/dioxane) afforded the inhibitor as its hydrochloride salt.” (Ex. 1007, p. 1165).
27. A pharmaceutical composition comprising the compound of claim 25 and a pharmaceutically acceptable carrier therefor.	The compound of claim 25 is discussed above.
28. A pharmaceutical composition comprising the compound of claim 26 and a pharmaceutically acceptable carrier therefor.	“Together with at least one pharmaceutically acceptable carrier...” (Ex. 1008, p. 20).

### **8. Genus Claims 1, 2, 4, 6 and 8-11 Are Obvious As Encompassing The Compound Species of Claim 25**

The genus of compounds encompassed by claim 1 of the '186 patent is extremely large, covering several orders of magnitude more compounds than are described in the '186 patent itself. Ex. 1003, ¶150; Ex. 1028, ¶150.

Claim 1 includes the compound of claim 25 with the following R-group elections: x = 0, y = 1, n is 0, X is CN, R<sup>1</sup> is cycloalkyl, R<sup>2</sup> is hydrogen and R<sup>3</sup> is hydrogen. Ex. 1003, ¶14; Ex. 1028, ¶14. According to the '186 patent, “the term

‘cycloalkyl’ . . . includes . . . adamantyl . . . which . . . may be optionally substituted with 1 to 4 substituents such as . . . hydroxy.” Ex. 1001, col. 9, l. 48 – col. 10 l. 21. Claim 1 further recites hydroxy as a possible substituent (“R<sup>1</sup> . . . [is] selected from . . . cycloalkyl . . . optionally substituted . . . [with] hydroxy”).

Because it would have been obvious to one of ordinary skill in the art to modify compound **25** of Ashworth, as described above for claim 25, the structures of claim 1 of the ’186 patent which encompasses the compound of claim 25, would also have been obvious for at least the reasons set forth above with respect to claim 25. In re Soverain Software LLC, 778 F.3d at 1315; Muchmore, 433 F.2d at 681.

Moreover, DP-IV inhibition was well described in the art by March 2000, as evidenced by prior art references disclosing such inhibitors. *See e.g.*, Ex. 1007 and Ex. 1008. From within these references, one of ordinary skill in the art prior to March 2000, could have relied on a number of possible combinations for a teaching of the elements of the compound of 25 and to provide motivation to combine those references discussed above. For example, even the mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound **25** (the lead compound) as taught by Hanessian (Ex. 1010) would have led to a compound within the scope of claim 1 of the ’186 patent. Ex. 1003, ¶150; Ex. 1028, ¶150.

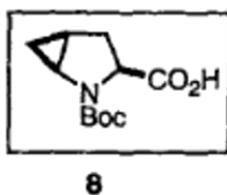
Claim 1 also covers pharmaceutically acceptable salts of the compound, while claim 11 covers a composition with a compound of claim 1 with a pharmaceutically acceptable carrier. As discussed above, Villhauer taught the use of conventional salts and carriers with these kinds of compounds. Ex. 1008, pp. 3, 20, respectively; Ex. 1003, ¶76; Ex. 1028, ¶7.

Claim 2 of the '186 patent is directed to a genus of compounds that encompass the compound of claim 25. Ex. 1003, ¶14; Ex. 1028, ¶14. As noted above, the compound of claim 25 is encompassed within claim 1 with the following R-group elections:  $x = 0$ ,  $y = 1$ ,  $n$  is 0,  $X$  is CN,  $R^1$  is hydroxytricycloalkyl,  $R^2$  is hydrogen and  $R^3$  is hydrogen. As would be appreciated by one of ordinary skill in the art, hydroxy adamantane is a type of hydroxytricycloalkyl. Ex. 1003, ¶151; Ex. 1028, ¶151. Because it would have been obvious to one of ordinary skill in the art to modify the Ashworth lead compound **25**, as described above, the structure of claim 2 of the '186 patent would have been obvious for at least the reasons set forth above with respect to claim 25. Ex. 1003, ¶152; Ex. 1028, ¶152. Thus, as claim 2 encompasses the compound of claim 25, it is also obvious. *Soverain Software LLC*, 778 F.3d at 1315; *Muchmore*, 433 F.2d at 681.

Moreover, mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound 25 (the lead compound) as taught by

Hanessian (Ex. 1010) would have led to a compound within the scope of claim 2 of the '186 patent. Ex. 1003, ¶1512; Ex. 1028, ¶152. Because this modification would have been obvious to one of ordinary skill in the art, for at least the reasons explained above in this context of claim 25, claim 2 is obvious.

Claim 4 of the '186 patent recites a genus of compounds encompassing the compound of claim 25. For example, that compound is encompassed within claim 4 with the following R-group elections: n is 0, R<sup>1</sup> is hydroxytricycloalkyl and R<sup>3</sup> is hydrogen. Ex. 1003, ¶14; Ex. 1028, ¶14. As would be appreciated by one of ordinary skill in the art, hydroxy adamantane is a type of hydroxytricycloalkyl. Ex. 1003, ¶151; Ex. 1028, ¶141. Thus, claim 4 is obvious as comprising a genus that encompasses the obvious species compound of claim 25. *Soverain Software LLC*, 778 F.3d at 1315; *Muchmore*, 433 F.2d at 681. Hanessian discloses the following compound 8:



Ex. 1010, p. 1882. As seen above, the orientation of substituents on the pyrrolidine ring of compound 8 is the same as recited in claim 4. Thus Hanessian (Ex. 1010) provides motivation for the pyrrolidine and cyano orientations of claim 4. The nitrile orientation is also the same as in Ashworth Ex. 1007. In conjunction with

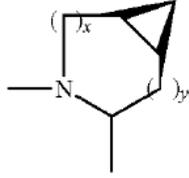
these teachings, one of ordinary skill in the art would have found it routine to optimize the orientation of the R<sup>1</sup> group, especially considering the small number of possible orientations available. Ex. 1003, ¶154; Ex. 1028, ¶154.

Because it would have been obvious to one of ordinary skill in the art to modify lead compound **25** of Ashworth, as described above, the structures of claim 4 of the '186 patent would have been obvious for at least the reasons set forth above with respect to claim 25. Ex. 1003, ¶155; Ex. 1028, ¶155.

Moreover, mere formation of the cyclopropyl group at the 4,5-position of the proline moiety of Ashworth compound 25 (the lead compound) would have produced a compound within the scope of claim 4 of the '186 patent. Ex. 1003, ¶156; Ex. 1028, ¶156. Because this modification would have been obvious to one of ordinary skill, for at least the reasons set forth above, claim 4 would have been obvious as well. Ex. 1003, ¶156; Ex. 1028, ¶156.

Claim 6 limits the compound of claim 1 by restricting R<sup>3</sup> to hydrogen, n to 0 and X to nitrile, while R<sup>2</sup> may be hydrogen and R<sup>1</sup> may be hydroxytricycloalkyl (e.g., hydroxyadamantyl). With these restrictions and selections, claim 6 encompasses the species compound of claim 25. Ex. 1003, ¶14; Ex. 1028, ¶14. Claim 6 is obvious as encompassing an obvious species, *Soverain Software LLC*, 778 F.3d at 1315; *Muchmore*, 433 F.2d at 681.

Claim 7 requires the following configuration for the pyrrolidine of claim 1:

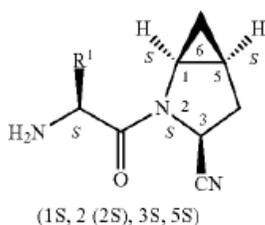


The analysis for claim 7 differs from that of claim 1 (e.g., selecting  $x=0$ ,  $y=1$ ) only in the specified orientation of the cyclopropyl ring. As an initial matter, the cyclopropyl ring would necessarily have one of two orientations (into or out of the plane of the figure) relative to the pyrrolidine. Ex. 1003, ¶¶139-140; Ex. 1028, ¶¶139-140. Moreover, Hanessian taught both the (4S,5S)- and (4R,5R)-cyclopropanations on a proline ring (Ex. 1010, p. 1882, compound 6 and 8) and further taught these cyclopropanations had significant effects on the conformation of the whole molecule and on the bond angle opposite the cyclopropanation (the bond point down in the figure). Ex. 1010, pp. 1882-83 and Table 1. It would have been obvious to try both isomers to determine which had better properties. Ex. 1003, ¶¶139-140; Ex. 1028, ¶¶139-140. The claim chart below identifies where the orientation of the cyclopropyl ring disclosed in claim 7 is found in the teachings of Hanessian.

Claim 8 expressly covers any of eight structures or its pharmaceutically acceptable salt. The second-to-last structure (right before the “or”) is the saxagliptin compound of claim 25. Ex. 1003, ¶99; Ex. 1028, ¶99. Thus, when saxagliptin is chosen, claim 8 is the same as claim 25, which was shown to be obvious and unpatentable above.

Claim 9 depends from claim 8 and requires the salt to be the hydrochloride salt or trifluoroacetic acid salt. Villhauer taught that hydrochloride was a preferred salt for N-glycyl-2cyclopyrrolidine compounds. Ex. 1008, p. 3; Ex. 1003, ¶76; Ex. 1028, ¶76.

The genus of compounds encompassed by claim 10 is extremely large, covering several orders of magnitude more compounds than are described in the '186 patent. Claim 10 depends from claim 1 and defines two alternative structures, one of which is



wherein R<sup>1</sup> may be hydroxytricycloalkyl (e.g., hydroxyadamantyl). The hydroxytricycloalkyl alternative encompasses saxagliptin. Ex. 1003, ¶162; Ex. 1028, ¶162. Thus claim 10 is obvious as encompassing the obvious species compound of claim 25. *Soverain Software LLC*, 778 F.3d at 1315; *Muchmore*, 433 F.2d at 681.

The mere formation of the cyclopropyl group at the 4,5-position of the proline moiety as taught by Hanessian of Ashworth compound **25** (the lead compound) would have also led to a compound within the scope of claim 10 of the '186 patent. Exs. 1007, 1010, 1003, ¶165; Ex. 1028, ¶165. Because this

modification would have been obvious to one of ordinary skill in the art, for at least the reasons set forth above in regard to claim 25, claim 10 is obvious.

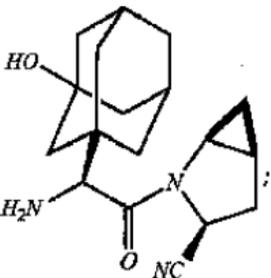
**9. Claims 32-35, 39 and 40: methods of treating type II diabetes mellitus**

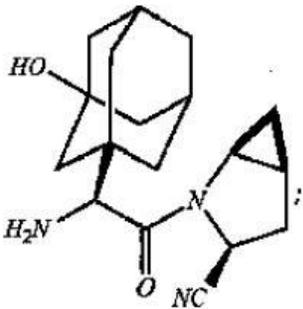
Claim 32 defines a method of treating, diabetes, among other things, using a composition comprising saxagliptin, the compound of claim 25. Claim 39 defines a method of treating type II diabetes mellitus (a type of diabetes) using a composition comprising saxagliptin. Villhauer teaches that DP-IV inhibitors are attractive as therapeutic compounds for treating type II diabetes mellitus. Ex. 1008, p. 1. As explained in section IV.A.6 above, those skilled in the art would have had reason to develop saxagliptin as a DP-IV inhibitor. Hence, those skilled in the art would have expected saxagliptin, as a DP-IV inhibitor, to be useful in treating type II diabetes mellitus. Ex. 1003, ¶172-173; Ex. 1028, ¶172-173. Villhauer also taught that such compounds are conventionally used as compositions with carriers, adjuvants and diluents and in various administration forms. Ex. 1008, p. 20.

Claims 33 and 40 restrict the methods of claims 32 and 39, respectively, to using the hydrochloride salt of saxagliptin. Villhauer taught that the hydrochloride salt was the preferred salt form for N-glycyl-2-cyanpyrrolidine compounds. Ex. 1008, p. 3.

Claims 34 and 35 restrict the methods of claims 32 and 33, respectively, to treating diabetes. As explained above, saxagliptin treats type II diabetes mellitus.

In sum, the method claims use saxagliptin — a DP-IV inhibitor those in the art would have had reason to develop — and its art-preferred salt to treat type II diabetes mellitus. The claim chart below identifies where the specific elements of claims 32-25, 39 and 40 are found in the references.

<b>U.S. Patent No. RE44,186 Challenged Claims 32-35, 39 and 40</b>	<b>Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), Hanessian (Ex. 1010)</b>
<p>32. A method for treating diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, impaired glucose homeostasis, or impaired glucose tolerance in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound that is</p>  <p>or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.</p>	<p>Villhauer discloses DP-IV inhibitors as “useful in the treatment of non-insulin dependent diabetes mellitus” (Ex. 1008, p. 18).</p>
<p>33. The method of claim 32, wherein the pharmaceutically acceptable salt is the hydrochloride salt.</p>	<p>Villhauer discloses DP-IV inhibitors as “useful in the treatment of non-insulin dependent diabetes mellitus” Id.</p>

	Ashworth discloses the “subsequent acid catalyzed deprotection (4N HCl/dioxane) afforded the inhibitor as its hydrochloride salt” (Ex. 1007), p. 1165).
34. The method of claim 32, for treating diabetes.	Villhauer discloses DP-IV inhibitors as “useful in the treatment of non-insulin dependent diabetes mellitus” Id.
35. The method of claim 33, for treating diabetes.	Villhauer discloses DP-IV inhibitors as “useful in the treatment of non-insulindependent diabetes mellitus” (Ex. 1008, p. 18).
39. A method for treating type II diabetes in a mammal comprising administering to the mammal a pharmaceutical composition comprising a compound that is    or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier thereof.	Villhauer discloses DP-IV inhibitors as “useful in the treatment of non-insulindependent diabetes mellitus” Id. Villhauer also discloses “a pharmaceutical composition.” Id., p. 20. The compound is addressed above in the context of claim 25.
40. The method of claim 39, wherein the pharmaceutically acceptable salt is the hydrochloride salt.	Ashworth discloses the “subsequent acid catalyzed deprotection (4N HCl/dioxane) afforded the inhibitor as its hydrochloride salt” (Ex. 1007), p. 1165).

In view of the foregoing, each of claims 1, 2, 4, 6-11, 25-28, 32-35, 39 and 40 is rendered obvious under 35 U.S.C. § 103 based on the combined teachings of Ashworth, Villhauer, Raag and Hanessian. The rationale to combine the teachings, discussed above, with a reasonable expectation of success, provide the basis for finding each of claims 1, 2, 4, 6-11, 25-28, 32-35, 39 and 40 obvious and unpatentable under 35 U.S.C. § 103.

**B. [Ground 2] Claims 12-16, 29, 30, 36, 37, 41 and 42 Are Obvious Under §103 Over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the GLUCOPHAGE Label**

It would have been facially obvious to combine two pharmaceuticals used in treating related symptoms for a variety of reasons, including convenience and marketing considerations such as product line extension. *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 60-61 (1969) (combination of devices a matter of convenience and obvious in the absence of synergy); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1484 (Fed. Cir. 1997) (noting line extension as a motivation to combine pharmaceuticals).

Bachovchin explained that diabetes, including noninsulin-dependent (or type II) diabetes mellitus, has an effect on fat metabolism. Ex. 1011 at 1:8-2:15. Bachovchin's invention provided improved methods for treating diabetes, obesity and atherosclerosis. *Id.* at 3:27-4:11.

**1. GLUCOPHAGE/ Metformin**

Bachovchin teaches using DP-IV inhibitors with other antidiabetics:

The DP-IV inhibitors may also advantageously be applied in combination with other oral agents such as metformin and related compounds or glucosidase inhibitors as, for example, acarbose.

Ex. 1011 at 46:29-31.

Claim 12 defines a pharmaceutical combination comprising a compound of claim 1 with an anti-diabetic agent that is not a DP-IV inhibitor, with an antiobesity agent or with a lipid-modulating agent. Claim 13 depends from claim 12 and limits the invention to a combination with just the non-DP-IV inhibitor. Claim 14 depends from claim 13 and limits the agent to a *Markush* group of antidiabetic agent types. Claim 15 depends from claim 14 and identifies metformin and acarbose (among others) as the anti-diabetic agent. As noted above, Bachovchin recommended the use of both with DP-IV inhibitors. The GLUCOPHAGE FOIA response includes a letter indicating that metformin hydrochloride tablets are approved for treating type II diabetes mellitus. Ex. 1012, at 0008.

The DP-IV inhibitor of claim 1 was obvious for the reasons given above. In view of Bachovchin's recommendation to use metformin (or acarbose) with a DP-IV inhibitor, those skilled in the art would have considered combining saxagliptin with metformin or acarbose to be obvious. Ex. 1003, ¶¶177-178; Ex. 1028, ¶¶177-

178. If a dependent claim is obvious, its parent claims (claims 12-14) are obvious as well.

Although claims 29, 30, 36, 37, 41 and 42 are method claims, they 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). These claims are obvious for the same reasons claims 13 (anti-diabetic agent) and 15 (metformin) are obvious. Ex. 1003, ¶¶175-179; Ex. 1028, ¶¶175-179.

## **2. Weight ratios**

Claim 16 depends from claim 13 and specifies a weight ratio of DP-IV inhibitor to non-DP-IV anti-diabetic agent in the range of 0.01 to 100:1. As an initial matter, the patent does not identify any critical considerations or synergies in selecting a dosage ratio. Ex. 1003, ¶¶37, 203; Ex. 1028, ¶¶37, 203. The patent's discussion about weight ratios covers the ratio between any of the compounds having structure I (essentially claim 1) and "the antidiabetic agent *or any other type of therapeutic agent (depending on its mode of operation).*" Ex. 1001 at 4:48-53 (emphasis added). This vagueness is not surprising given the enormous number of possible combinations. Even when the patent discusses ratios for specific agents, it does so without offering data or further guidance to direct those skilled in the art, but instead relies on that skill to determine an appropriate ratio. Ex. 1001

at 15:1-41; Ex. 1003, ¶¶37, 203; Ex. 1028, ¶¶37, 203. Indeed even the preferred dose of structure I compounds for unspecified adult mammals is very broad: 10-1000 milligrams per day. Ex. 1001 at 21:67-22:3; cf. *Muniauction, Inc.*, 532 F.3d at 1327 n.3 (lack of guidance indicates obviousness; otherwise it indicates lack of enablement). Precedent makes clear that dose-response and compatibility procedures are so routine in the pharmaceutical industry that they do not confer patentability absent an unexpected result. *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (considering much narrower ratio ranges); Ex. 1003, ¶202; Ex. 1028, ¶202; see also, e.g., Ex. 1008, p. 20 (“The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.”).

Villhauer states “for most larger primates, a daily dosage of from about 0.1 mg to about 250 mg, preferably from about 1 mg to about 100 mg” for N-glycyl-2-cyanopyrrolidines. Ex. 1008, p. 19. This range overlaps with the ’186 patent’s disclosed adult dosage range of 10-1000 mg. Ex. 1001 at 21:67-22:3. The GLUCOPHAGE Label indicates the dose is 1500-2550 mg/day. Ex. 1012 at 0047 (2550 mg is the maximum recommended daily dose), p. 0048 (1500 mg is lowest effective daily dose). Drs. Rotella and Muthyala explain that the weight ratios of Villhauer’s compound and of the preferred claim 1 compound dose with the label dose of metformin overlap the claimed range. Ex. 1003, ¶200; Ex. 1028, ¶200.

For Villhauer's preferred dosage range, Drs. Rotella and Muthyala calculate that the weight ratio ranges from 0.0004 to 0.07:1 (i.e., from 1:2550 to 100:1500), which overlaps the claimed "from about 0.01 to about 100:1." Ex. 1003, ¶200; Ex. 1028, ¶200. Overlapping ranges are facially obvious. *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Those skilled in the art formulating a composition with an N-glycyl-2-cyanopyrrolidine DP-IV inhibitor and metformin would have had reason to try weight ratios overlapping the claimed range.

In view of the foregoing, each of claims 12-16, 29, 30, 36, 37, 41 and 42 is rendered obvious under 35 U.S.C. § 103 based on the combined teachings of Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the GLUCOPHAGE Label.

**C. [Ground 3] Claims 12, 17, 18 and 22 Are Obvious Under §103 Over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the XENICAL Label**

As noted previously, both Villhauer and Bachovchin identify obesity as a condition associated with type II diabetes mellitus. Ex. 1008, at pp. 1, 18; Ex. 1011, e.g., Abstract. Also as noted previously, Bachovchin contemplates conjoint administration of a DP-IV inhibitor with agents directed to related symptoms, albeit not with a specifically identified anti-obesity agent. Ex. 1011 at 45:23-46:31. Nevertheless, given the association of obesity with type II diabetes mellitus, it would have been obvious to select an anti-obesity agent for conjoint

administration. *Richardson-Vicks Inc.*, 122 F.3d at 1484; Ex. 1003, ¶¶172, 183-185; Ex. 1028, ¶¶172, 183-185.

One anti-obesity agent known in the prior art was orlistat, which Roche sold under the name XENICAL. Ex. 1013, p. 0011. The XENICAL label information notes that XENICAL has been assessed in clinical trials for its effect on comorbidities, including type II diabetes. *Id.* at 0013. The label reports statistically significant improvement in body weight and glycemic control for type II diabetics receiving XENICAL compared to patients receiving placebo. *Id.* at 0017 (Table 4). The label states that XENICAL is indicated for obese patients with other risk factors, including diabetes. *Id.* at 0018.

Claim 17 depends from claim 12 and defines a *Markush* group of anti-obesity agents. Claim 18 depends from claim 17 and lists orlistat (XENICAL) as one of a *Markush* group of specific anti-obesity agents. As explained above, those skilled in the art would have considered it obvious to combine a DP-IV inhibitor of claim 1 with orlistat because they would be expected to be commonly administered together. *Anderson's-Black Rock, Inc.*, 396 U.S. at 60-61; *Richardson-Vicks Inc.*, 122 F.3d at 1484; Ex. 1003, ¶¶182-184; Ex. 1028, ¶¶182-184. Because claim 18 is obvious, its parent claims (17 and 12) are also obvious. *Muchmore*, 433 F.2d at 824-25.

Claim 22 defines a pharmaceutical composition comprising a compound as defined in claim 1 and list of alternative agents, including an anti-obesity agent.

Claim 22 defines the invention (with emphasis added) as:

“22. A pharmaceutical combination comprising *a compound as defined in claim 1 and* an agent for treating infertility, an agent for treating polycystic ovary syndrome, an agent for treating a growth disorder and/or frailty, an anti-arthritis agent, an agent for preventing or inhibiting allograft rejection in transplantation, an agent for treating autoimmune disease, an anti-AIDS agent, an agent for treating inflammatory bowel disease/syndrome, an agent for treating anorexia nervosa, an anti-osteoporosis agent *and/or an anti-obesity agent.*”

While the use of the initial “and” and the final “and/or” is confusing, the “or” only has meaning if each agent is considered optional as long as at least one agent is selected from the list. Hence, the broadest reasonable interpretation of claim 22 would permit each agent to be used with the claim 1 compound either individually or in any combination of the listed agents. *Cf. In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006) (explaining optional elements are not limiting). Specifically, the broadest reasonable construction of claim 22 would include a pharmaceutical combination comprising the claim 1 compound and just one of the listed agents, for example, an anti-obesity agent. Based on this interpretation, claim 22 is obvious for the same reasons given for claim 18.

Ex. 1003, ¶182-184; Ex. 1028, ¶182-184.

In view of the foregoing, each of claims 12, 17, 18, and 22 is rendered obvious under 35 U.S.C. § 103 based on the combined teachings of Ashworth,

Villhauer, Raag, Hanessian, Bachovchin and the XENICAL Label. The claim chart below identifies where the specific elements of the claims are found in the references. The rationale to combine the teachings, to gain the benefits of a therapeutic combination of a DP-IV inhibitor as defined in claim 1 with an antiobesity agent such as XENICAL, provide the basis for finding each of claims 12, 17, 18 and 22 obvious and unpatentable under 35 U.S.C. § 103.

<b>U.S. Patent No. RE44,186 Challenged Claims 12, 17, 18, 22</b>	<b>Ashworth (Ex. 1007), Villhauer (Ex. 1008), Raag (Ex. 1009), Hanessian (Ex. 1010), XENICAL Label (Ex. 1013)</b>
<p>12. A pharmaceutical combination comprising a compound as defined in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an antiobesity agent and/or a lipid-modulating agent.</p>	<p>The Xenical Label discloses the antiobesity agent, Xenical (i.e., orlistat) (Ex. 1013, p. 0011). The Xenical Label discloses “a relationship between obesity . . . [and] type 2 diabetes” (Ex. 1013, p. 0013). The Xenical Label discloses that “XENICAL is indicated for obesity management . . . in the presence of other risk factors (e.g., . . . diabetes)” (Ex. 1013, p. 0018).</p>
<p>17. The combination as defined in claim 12 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a thyroid receptor beta compound, an anorectic agent, and/or a fatty acid oxidation upregulator.</p>	<p>The Xenical Label discloses that orlistat is a “lipase inhibitor” (Ex. 1013, p. 0011).</p>
<p>22. A pharmaceutical combination comprising a compound as defined in claim 1 and an agent for treating infertility, an agent for treating polycystic ovary syndrome, an agent for treating a growth disorder and/or frailty,</p>	<p>Claim 1 in addressed above. The Xenical Label discloses “a relationship between obesity . . . [and] type 2 diabetes” (Ex. 1013, p. 0013). The Xenical Label discloses that “XENICAL is indicated for obesity</p>

an antiarthritis agent, an agent for preventing inhibiting allograft rejection in transplantation, an agent for treating autoimmune disease, an anti-AIDS agent, an agent for treating inflammatory bowel disease/syndrome, an agent for treating anorexia nervosa, an anti-osteoporosis agent and/or an anti-obesity agent.	management . . . in the presence of other risk factors (e.g., . . . diabetes)” (Ex. 1013, p. 0018).
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**D. [Ground 4] Claims 12 and 19-21 Are Obvious Under §103 Over Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the MEVACOR Label**

**1. MEVACOR/Lovastatin**

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. Ex. 1011, at 45:23-33. Merck sold a lipid-modulating agent, lovastatin, under the name MEVACOR. Ex. 1014 at 0007. Lovastatin reduces low-density, lipoprotein (“LDL”) levels and can increase HDL levels. *Id.* The MEVACOR label indicates that prior to using lovastatin, “secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, ...) should be excluded.” *Id.* at 0010. Diabetes is not listed as a contraindication for using lovastatin; rather, the label indicates that diabetes should be brought under control using another therapy in such cases. *Id.* A combination of two compounds that are often administered together would have been obvious. *Anderson’s-Black Rock, Inc.*, 396 U.S. at 60-61; *Richardson-Vicks Inc.*, 122 F.3d

at 1484 (noting product line extension as a motivation); Ex. 1003, ¶¶187-189; Ex. 1028, ¶¶187-189.

Claim 19 depends from claim 12 and requires selection of the lipidmodulating agent from a *Markush* group of lipid-modulating agent types. Claim 20 depends from claim 19 and lists a *Markush* group of specific lipid-modulating agents, including lovastatin. As explained above, the subject matter of claim 20 would have been obvious because combining the DP-IV inhibitor of claim 1 with lovastatin would make sense for convenience and marketing reasons as they would often be co-administered to patients suffering both type II diabetes mellitus and hypercholesterolemia (not caused by poorly controlled diabetes). Ex. 1003, ¶¶187-189; Ex. 1028, ¶¶187-189. Because claim 20 is obvious, its parent claims (12 and 19) are also obvious. *Muchmore*, 433 F.2d at 824-25.

## **2. Weight ratios**

Claim 21 specifies a weight ratio for the claim 1 compound and the lipidmodifying agent in the range of 0.01 to 100:1. As explained above for claim 16, the specification does not identify any criticality, synergy or unexpected result for this range of ratios, nor does it provide specific guidance about how to select the best ratio for any specific lipid-modulating agent, relying instead on the skill in the art to make the choice. Ex. 1003, ¶196; Ex. 1028, ¶196. Determining appropriate drug combination formulations is routine in the art and is obvious

absent an unexpected result. *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (considering much narrower ratio ranges); Ex. 1003, ¶195; Ex. 1028, ¶195.

In any case, Villhauer discloses “for most larger primates, a daily dosage of from about 0.1 mg to about 250 mg, preferably from about 1 mg to about 100 mg” of the disclosed N-glycyl-2-cyanopyrrolidines. Ex. 1008, p. 19. This range overlaps with the patent’s disclosed adult dosage range of 10-1000 mg. Ex. 1001 at 21:67-22:3. Drs. Rotella and Muthyala explain that the weight ratios of both Villhauer’s preferred dosage and the preferred compound dose with the label dose of metformin overlap the claimed range. Ex. 1003, ¶194; Ex. 1028, ¶194. The MEVACOR label indicates the dose is 20-80 mg/day. Ex. 1014 at 0007. For Villhauer’s preferred adult dosage, Drs. Rotella and Muthyala calculate that the weight ratio ranges from 0.00125 to 12.5:1 (i.e., from 1:80 to 250:20), which overlaps the claimed “from about 0.01 to about 100:1.” Ex. 1003, ¶194; Ex. 1028, ¶194. . Those skilled in the art formulating a composition with an N-glycyl-2-cyanopyrrolidine DP-IV inhibitor and lovastatin would have had reason to try weight ratios overlapping the claimed range. Ex. 1003, ¶195; Ex. 1028, ¶195.

In view of the foregoing, each of claims 12, 19, 20, and 21 is rendered obvious under 35 U.S.C. § 103 based on the combined teachings of Ashworth, Villhauer, Raag, Hanessian, Bachovchin and the MEVACOR Label. The claim

chart below identifies where the specific elements of the claims are found in the references. The rationale to combine the teachings, to gain the benefits of a therapeutic combination of a DP-IV inhibitor as defined in claim 1 with a lipidmodulating agent such as MEVACOR, with a reasonable expectation of success, provide the basis for finding each of claims 12, 19, 20 and 21 obvious and unpatentable under 35 U.S.C. § 103.

<b>U.S. Patent No. RE44,186 Challenged Claims 12, 19, 20, 21</b>	<b>Ashworth (Ex. 1007), Villhauer (Ex.1008), Raag (Ex. 1009), Hanessian (Ex. 1010), and MEVACOR Label (Ex. 1014)</b>
12. A pharmaceutical combination comprising a compound as defined in claim 1 and an antidiabetic agent other than a DP4 inhibitor for treating diabetes and related diseases, an antiobesity agent and/or a lipid-modulating agent.	Compounds of claim 1 are addressed above. The Mevacor Label discloses the lipid-modulating agent, Mevacor (i.e., lovastatin) (Ex. 1014, p. 0007). The Mevacor Label discloses that “poorly controlled diabetes mellitus [is] a secondary cause[ ] for hypercholesterolemia” (Ex. 1014, p. 0010).
19. The combination as defined in claim 12 wherein the lipid modulating agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxxygenase inhibitor, an ACAT inhibitor, a cholesteryl ester transfer protein inhibitor, or an ATP citrate lyase inhibitor.	The Mevacor Label discloses the lipid-modulating agent, Mevacor (i.e., lovastatin) (Ex.1014, p. 0007). The Mevacor Label discloses that “poorly controlled diabetes mellitus [is] a secondary cause[ ] for hypercholesterolemia” (Ex. 1014, p. 0010). The Mevacor Label discloses that Mevacor (i.e., lovastatin) “is a specific inhibitor of HMG-CoA reductase” (Ex. 1014, p. 0007).
20. The combination as defined in claim 19 wherein the lipid modulating agent is	The Mevacor Label discloses the lipidmodulating

pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, implitapide, CP-529,414, avasimibe, TS-962, MD-700, and/or LY295427.	agent, Mevacor (i.e., lovastatin) (Ex.1014, p. 0007). The Mevacor Label discloses that “poorly controlled diabetes mellitus [is] a secondary cause[ ] for hypercholesterolemia” (Ex. 1014, p. 0010).
21. The combination as defined in claim 19 wherein the compound as defined in claim 1 is present in a weight ratio to the lipid-modulating agent within the range from about 0.01 to about 100:1.	Villhauer discloses “a daily dosage of from about 0.1 mg to about 250 mg” of N-glycyl-2-cyanopyrrolidines (Ex. 1008, p. 19, ll. 18-19).

## IX. CONCLUSION

For the reasons set forth above, claims 1, 2, 4, 6-22, 25-30, 32-37 and 39-42 are unpatentable. Petitioner requests that *inter partes* review of these claims be instituted and that the claims be canceled.

## X. CERTIFICATION TO WORD COUNT UNDER 37 C.F.R. § 42.24(d)

I certify that the word count of this Petition is 12,878.

Respectfully submitted,

Dated: June 1, 2016

/Gary J. Speier/  
 Gary J. Speier, Lead Counsel  
 Reg. No. 45,458  
 Iain M. McIntyre, Backup Counsel  
 Reg. No. 40,337  
 Carlson, Caspers, Vandenburg,  
 Lindquist & Schuman  
 225 South Sixth Street, Suite 4200  
 Minneapolis, MN 55402

## XI. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 502880.

## XII. APPENDIX – LIST OF EXHIBITS

<b>Exhibit No.</b>	<b>Description</b>
1001	U.S. Reissue Patent 44,186 E to Robl et al. (reissued Apr. 30, 2013)
1002	U.S. Patent No. 6,395,767 to Robl et al. (issued May 28, 2002)
1003	Declaration of David P. Rotella, Ph.D.
1004	<i>Curriculum Vitae</i> of David P. Rotella, Ph.D.
1005	File History of U.S. Patent No. 6,395,767 to Robl et al.
1006	File History of U.S. Reissued Patent 44,186 E to Robl et al.
1007	Doreen M. Ashworth et al., <i>2-cyanopyrrolidides as potent, stable inhibitors of dipeptidyl peptidase IV</i> , 6 BIOORG. & MED. CHEM. LTRS. 1163 (1996)
1008	WO Patent App. Pub. No. 98/19998 to Villhauer (pub'd May 14, 1998)
1009	Reetta Raag & Thomas L. Poulos, <i>Crystal Structure of Cytochrome P-450CAM Complexed with Camphane, Thiocamphor, and Adamantane: Factors Controlling P-450 Substrate Hydroxylation</i> , 30 BIOCHEMISTRY 2674 (1991)
1010	Stephen Hanessian et al., <i>The Synthesis of Enantiopure ω-Methanoprolines and ω-Methanopipecolic Acids by a Novel Cyclopropanation Reaction: The “Flattening” of Proline</i> ,

Exhibit No.	Description
	36 ANGEW. CHEM. ED. ENGL. 1881 (1997)
1011	WO Patent App. Pub. No. 99/38501 to Bachovchin et al. (pub'd Aug. 5, 1999)
1012	GLUCOPHAGE Label (available by FOIA Jan. 8, 1998)
1013	XENICAL Label (available by FOIA Aug. 9, 1999)
1014	MEVACOR Label (available by FOIA Sept. 15, 1994)
1015	Jian Lin et al., <i>Inhibition of dipeptidyl peptidase IV by fluoroolefin containing N-peptidyl-O-hydroxylamine peptidomimetics</i> , 95 PROC. NATL. ACAD. SCI. USA 14020 (1998)
1016	Howard E. Hoffman et al., <i>Pharmacokinetics and Metabolism of Rimantadine Hydrochloride in Mice and Dogs</i> , 32(11) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 1699 (1988)
1017	Christopher A. Lipinski et al., <i>Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings</i> , 23 ADV. DRUG DELIV. REV. 3 (1996)
1018	Hansch et al., <i>Cluster Analysis and the Design of Congener Sets</i> , in SUBSTITUENT CONSTANTS FOR CORRELATION ANALYSIS IN CHEMISTRY AND BIOLOGY 48 (John Wiley & Sons 1979)
1019	Lindley A. Cates, <i>Calculation of Drug Solubilities by Pharmacy Students</i> , 45 Am. J. Pharm. Educ. 11 (1981)
1020	Walter A. Korfmacher et al., <i>HPLC-API/MS/MS: a powerful tool for integrating drug metabolism into the drug discovery process</i> , 2 Drug Disc. Today 532 (1997)
1021	C. Y. Chiou et al., <i>The Cholinergic Effects and Rates of Hydrolysis of Conformationally Rigid Analogs of Acetylcholine</i> , 166 J. Pharm. Exp. Ther. 243 (1969)

Exhibit No.	Description
1022	Daniel E. Koshland, Jr., <i>The Key-Lock Theory and the Induced Fit Theory</i> , 33 ANGEW. CHEM. ED. ENGL. 2375 (1994)
1023	E.J. Ariëns & A. M. Simonis, <i>Optimalization of Pharmacokinetics – An Essential Aspect of Drug Development – by Metabolic Stabilization</i> , <i>Pharmacochem. Lib.</i> , in 4 PHARMACOCHEM. LIB. 165 (1982)
1024	R. Scott Obach, <i>Prediction of Human Clearance of Twenty-nine Drugs from Hepatic Microsomal Intrinsic Clearance Data: An Examination of In Vitro Half-life Approach and Nonspecific Binding to Microsomes</i> , 27 DRUG METAB. DISPOS. 1350 (1999)
1025	Yung-chi Cheng & William H. Prusoff, <i>Relationship Between the Inhibition Constant (KI) and the Concentration of Inhibitor which Causes 50 Per Cent Inhibition (I50) of an Enzymatic Reaction</i> , 22 Biochem. Pharmacol. 3099 (1973)
1026	Debnath Pal & Pinak Chakrabarti, <i>Cis Peptide Bonds in Proteins: Residues Involved, their Conformations, Interactions and Location</i> , 294 J. of Mol. Biol. 271 (1999)
1027	US Provisional Patent Application No. 60/1888,555 to Robl
1028	Declaration of Ramaiah Muthyala, Ph.D.
1029	<i>Curriculum Vitae</i> of Ramaiah Muthyala, Ph.D.

## CERTIFICATE OF SERVICE

Pursuant to §§42.6(e) and 42.105(a), I certify that I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* Review (and accompanying Exhibits 1001-1027) by EXPRESS MAIL, on this 1<sup>st</sup> day of June, 2016, on counsel of record for AstraZeneca AB in IPR2015-10340 for Re44186 at its correspondence address as follows:

Mr. Charles E. Lipsey  
Finnegan, Henderson, Farabow, Garrett and Dunner,  
11955 Freedom Drive  
Reston VA 20190

Respectfully submitted,

Dated: June 1, 2016

/Gary J. Speier/  
Gary J. Speier, Lead Counsel  
Reg. No. 45,458