IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH,
Patent Owner.

U.S. Patent No. 8,853,156 to Dugi *et al.*
Issue Date: Oct. 7, 2014
Title: Treatment for Diabetes in Patients
Inappropriate for Metformin Therapy

Inter Partes Review No.: IPR2016-01565

Petition for *Inter Partes* Review of U.S. Patent No. 8,853,156 Under 35 U.S.C. §§ 311–319 and 37 C.F.R. §§ 42.1–.80, 42.100–.123

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1002	Declaration of Mayer B. Davidson, M.D.
1003	Mikhail, "Incretin mimetics and dipeptidyl peptidase 4 inhibitors in clinical trials for the treatment of type 2 diabetes," Expert Opin. Investig. Drugs, 17(6): 845-853 (2008) ("Mikhail")
1004	Huettner *et. al*., "BI 1356, a novel and selective xanthine based DPP-4 inhibitor demonstrates good safety and tolerability with a wide therapeutic window (Poster No. 0586P)," American Diabetes Association, Chicago IL (June 22-25, 2007) ("Huettner")
1005	Eckhardt *et. al.*, "8-(3-(R)-Aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-diydropurine-2,6-dione (BI 1356), a Highly Potent, Selective, Long-Acting, and Orally Bioavailable DPP-4 Inhibitor for the Treatment of Type 2 Diabetes," J. Med. Chem., 50:6450–6453 (2007) ("Eckhardt 2007")
1006	Januvia (sitagliptin phosphate tablets) Prescribing Information (2006) ("Januvia Label")
1007	Curriculum Vitae of Mayer B. Davidson, M.D.
1008	Glucophage® (metformin hydrochloride tablets) and Glucophage® XR (metformin hydrochloride extended-release tablets) prescribing information (2001) ("Glucophage")
1009	Mathieu *et. al.*, "Antihyperclycaemic therapy in elderly patients with type 2 diabetes: potential role of incretin mimetics and DPP-4 inhibitors," International Journal of Clinical Practice, 61 (Suppl. 154):29–37 (2007) ("Mathieu")
1010	Vincent *et. al.*, "Metabolism and Excretion of the Dipeptidyl Peptidase 4 Inhibitor [^{14}C]Sitagliptin in Humans," Drug Metabolism and Disposition, 35(4):533–538 (2007) ("Vincent")
1011	Flatt *et. al.*, "Dipeptidyl peptidase IV (DPP IV) and related molecules in type 2 diabetes," Frontiers in Bioscience, 13:3648–3660 (2008) ("Flatt")

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1012	Zerilli *et. al.*, "Sitagliptin Phosphate: A DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus," 29(12):2614–34 (2007) ("Zerilli")
1013	He *et. al.*, "The influence of hepatic impairment on the pharmacokinetics of the dipeptidyl peptidase IV (DPP-4) inhibitor vildagliptin," Eur. J. Clin. Pharmacol. 63:677–686 (2007) ("He I")
1014	He *et. al.*, "The Influence of Renal Impairment on the Pharmacokinetics of Vildagliptin," Clinical Pharmacology & Therapeutics, 81 (Suppl. 1):S113 (2007) ("He II")
1015	Himmelsbach *et. al.*, U.S. Patent Publication No. 2004/0097510, "8-[3-amino-piperidin-1-yl]-xanthines, the preparation thereof and their use as pharmaceutical compositions" ("the '510 publication")
1016	Dugi, *et. al*., "Safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 1356, a novel DPP-IV Inhibitor with a wide therapeutic window," *Diabetic Medicine* P821 (2006). ("Dugi 2006")
1017	Dugi *et. al*., U.S. Patent Publication No. 2007/0281940, "Uses of DPP-IV Inhibitors" ("the '940 publication")
1018	Heise T *et. al*., Treatment with BI 1356, a Novel and Potent DPP-IV Inhibitor, Significantly Reduces Glucose Excursions after an oGTT in Patients with Type 2 Diabetes, diabetes, A Journal of the American Diabetes Association®, 56(Suppl. 1) at A156, abstract 588-P and Poster No. 0588P (June 2007) ("Heise")
1019	Thomas, *et. al*., "BI 1356, a novel and selective xanthine based DPP-IV inhibitor, exhibits a superior profile when compared to sitagliptin and vildagliptin," *Diabetologia* 50:[Suppl1]S1–S538, Abstract 0879 (2007). ("Thomas")
1020	Gwaltney *et. al*., "Inhibitors of Dipeptidyl Peptidase 4," Annual Reports in Medicinal Chemistry, 40:149–165 (December 2005) ("Gwaltney")

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42, Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *Inter Partes* Review ("IPR") of claims 1–2, 4–8, 10–18, and 23–25 of U.S. Patent No. 8,853,156 (the "'156 patent," Ex. 1001). Concurrently filed herewith is a Power of Attorney pursuant to 37 C.F.R. § 42.10(b). Also, pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this Petition.

II. OVERVIEW

Claims 1–2, 4–8, 10–18, and 23–25 of the '156 patent (the "Challenged Claims") are generally directed to methods for treating type II diabetes in patients for whom the type II diabetes drug, metformin, is contraindicated due to one or more medical conditions, the most relevant here being renal impairment. For these patients, the claims require administering a well-known class of type II diabetes drugs—dipeptidyl peptidase 4 inhibitors ("DPP-IV Inhibitors"). Other claims require administering the DPP-IV Inhibitor, linagliptin.

There is nothing unique about the subject matter of the Challenged Claims. At the time of the invention, it was well-known that DPP-IV Inhibitors, such as sitagliptin, could be administered as an alternative to metformin therapy to type II diabetes patients with renal impairment. In addition, it was well-known that the DPP-IV Inhibitor, linagliptin, was not excreted renally, and thus standard linagliptin

doses could be safely used in patients with renal impairment. It was further well-known that linagliptin was more potent and long-lasting than the other DPP-IV Inhibitors previously used as alternatives to metformin therapy for renally impaired patients. Thus, the POSA would have readily chosen linagliptin over the other DPP-IV Inhibitors.

Accordingly, a POSA would have understood that DPP-IV Inhibitors, such as sitagliptin and linagliptin, could safely and effectively be given to treat type II diabetes patients with renal impairment for whom metformin is contraindicated. Claims 1–2, 4–8, 10–18, and 23–25 are therefore unpatentable, as discussed more fully below.

III. STANDING (37 C.F.R. § 42.104(a); PROCEDURAL STATEMENTS)

Petitioner certifies that (1) the '156 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '156 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e). The required fee is paid through Deposit Acct. No. 160605, and the Office is authorized to charge any fee deficiencies and credit overpayments to that account (Customer ID No. 00826).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties in interest for this petition are Mylan Pharmaceuticals Inc., Mylan Laboratories Limited, Mylan Inc., and Mylan N.V.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters

The '156 patent is currently the subject of the following litigation: *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. HEC Pharm Group, et al.*, Civ. Action No. 3:15-cv-05982-PGS-TJB (D.N.J.) (consolidated).

2. Administrative Matters

Petitioner has filed, concurrently with this Petition, Petitions for *inter partes* review of the following U.S. Patents: U.S. Patent Nos. 9,173,859; 8,673,927; and 8,846,695, which are also asserted in *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. HEC Pharm Group, et al.*, Civ. Action No. 3:15-cv-05982-PGS-TJB (D.N.J.) (consolidated).

C. Designation of Lead and Back-Up Counsel and Service (37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), 42.10(a), and 42.10(b))

Lead Counsel: Thomas J. Parker (Registration No. 42,062; thomas.parker@alston.com). Backup Counsel: Christopher L. McArdle (*pro hac vice* application to be filed; chris.mcardle@alston.com); Ellen Y. Cheong (Registration No. 71,852; ellen.cheong@alston.com); and Charles A. Naggar (*pro*

hac vice application to be filed; charles.naggar@alston.com).

Please direct all correspondence to lead counsel at the following address: 90 Park Avenue, Suite 1200, New York, New York 10016; telephone: (212) 210-9400; facsimile: (212) 210-9444. Petitioner consents to email service.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(a))

Petitioner requests IPR and cancellation of claims 1–2, 4–8,10–18, and 23–25. Petitioner's full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '156 PATENT

The '156 patent, entitled "Treatment for Diabetes in Patients Inappropriate for Metformin Therapy." The '156 Patent issued on October 7, 2014. The '156 patent issued from U.S. patent application 13/057,295, and claims priority to provisional applications filed August 6, 2008 and October 16, 2008. According to records at the U.S. Patent and Trademark Office, the '156 patent is assigned to Boehringer Ingelheim International GmbH.

The Challenged Claims of the '156 patent are directed to methods for treating type II diabetes in patients who cannot tolerate the type II diabetes drug, metformin, due to one or more medical conditions, including renal insufficiency. For these patients, the claimed methods require administering other well-known type II diabetes drugs, namely, DPP-IV Inhibitors, including the prior art DPP-IV Inhibitor,

linagliptin.

The ’156 patent has four independent claims (claims 1, 23, 24, and 25). Independent claim 1 is directed to a method of treating or preventing metabolic diseases in a patient who has at least one contraindication against metformin, whereby the method involves orally administering to the patient a DPP-IV Inhibitor. (Ex. 1001, 29:2–11). The contraindication is selected from the following list: renal disease, renal impairment or renal dysfunction, among other medical conditions. (*Id*. at 29:8–11).

Claims 2, 4–8, and 10–18 depend from claim 1. Dependent claim 2 is directed to particular patient contraindications against metformin. (Ex. 1001, 29:12–15). Dependent claim 4 is limited to a particular metabolic disease: type II diabetes. (Ex. 1001, 29:19–20). Dependent claim 5 is directed to particular contraindications against renal disease, impairment, or dysfunction. (Ex. 1001, 29:21–23). Dependent claims 6 through 8 are directed to various DPP-IV Inhibitors, including linagliptin. (Ex. 1001, 29:24–31:55). Dependent claim 10 is directed to the dose of the DPP-IV Inhibitor. (Ex. 1001, 31:56–60). Dependent claims 11 through 17 are directed to characterizations of the metabolites and excretion pathways of the DPP-IV Inhibitors as they are processed by the human body. (Ex. 1001, 31:61–32:12). Dependent claim 18 is directed to the severity of the particular renal contraindication. (Ex. 1001, 32:13–15).

Independent claim 23 is directed to a method of treating type II diabetes in a patient who has at least one contraindication against metformin, whereby the method involves orally administering to the patient a DPP-IV Inhibitor. (Ex. 1001, 32:38–47). The contraindication is selected from the following: renal disease, renal impairment or renal dysfunction, among other medical conditions. (*Id*., 32:44–47). Independent claim 24 is substantively the same as claim 23, except that the treatment involves orally administering linagliptin. (Ex. 1001, 32:47–57).

Like claim 24, independent claim 25 is directed to a method of treating type II diabetes in a patient who has at least one contraindication against metformin, whereby the method involves orally administering linagliptin to the patient. (Ex. 1001, 32:57–65). The contraindication in claim 25, however, is selected from the following: "mild, moderate, or severe renal impairment or end-stage renal disease." (*Id*., 32:64–65).

A. CLAIM CONSTRUCTION

Petitioner believes that no terms or phrases require specific construction for the purpose of this IPR. Therefore, in accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretation in light of the specification of the '156 patent. *Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 1246 (2016).

VII. EXPERT DECLARATION OF MAYER B. DAVIDSON, M.D.

Filed herewith is the supporting declaration of Mayer B. Davidson, M.D. (Ex. 1002). Dr. Davidson is currently a Professor of Medicine at both the David Geffen School of Medicine at UCLA and Charles Drew University. (Ex. 1007 at 2-3). He is board certified in Internal Medicine. He is also board certified in the subspecialty of Diabetes, Endocrinology, and Metabolism. (*Id*. at 2). Dr. Davidson has been practicing in the field of diabetes, endocrinology and metabolism for 50 years. (*See Id*. at 1–2).

During his career, Dr. Davidson focused his practice on the diagnosis and treatment of diabetes. (Ex. 1002 ¶ 8; Ex. 1007). He served as President of the American Diabetes Association from 1997–1998. (Ex. 1007 at 6). He has conducted considerable research on diabetes and spoken on diabetes both nationally and internationally. (*Id.* at 6–40). Dr. Davidson has served on the Editorial Boards of many medical journals, including *Diabetes Care, Diabetes Spectrum, Clinical Diabetes, Geriatrics* and the *Journal of Clinical Endocrinology and Metabolism*. (*Id*. at 3). He was the Founding Editor of *Current Diabetes Reports* and Editor-in-Chief of *Diabetes Care*, the leading diabetes clinical journal in the world, from 2002–2006. (*Id.* at 3–4). He has also written 168 scientific papers, 31 book chapters, and numerous reviews and editorials as well as 3 books on diabetes. (*Id.* at 41–54). In 2016, the American Diabetes Association gave him their *Outstanding Physician*

Clinician Award in Diabetes. (*Id.* at 5–6). Dr. Davidson's declaration explains what the art would have conveyed to a POSA as of August 6, 2008. (Ex. 1002). A current copy of Dr. Davidson's curriculum vitae is submitted herewith as Exhibit 1007.

VIII. PERSON OF ORDINARY SKILL IN THE ART ("POSA")

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). A POSA is not an extraordinarily innovative person, but is a person who thinks conventionally in matters affecting the art in which he or she is skilled. *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). "Ordinary skill means at least the ability to understand the technology and make modest adaptations or advances." *In the Matter of Mahurkar Double Lumen Hemodialysis Catheter Patent Litig.*, 831 F. Supp. 1354, 1374 (N.D. Ill. 1993), *aff'd sub nom.*, *In re Mahurkar Double Lumen Hemodialysis Catheter Patent Litig.*, 71 F.3d 1573 (Fed. Cir. 1995). Factors that may be considered for determining the level of a skilled practitioner include: the educational level of the inventor; types of problems encountered in the art; prior art solutions to these problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. *Daiichi Sankyo, Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citations omitted).

Here, a POSA would possess a high level of skill, such as having an advanced degree in the field of medicine, pharmaceuticals, medicinal chemistry, and/or a related discipline. A POSA would also have at least 5 years of clinical experience treating type II diabetes and related disorders as well as experience with the pharmaceutical and clinical properties of DPP-IV Inhibitors. A POSA would also preferably have some experience investigating pharmaceutical compositions for treating diabetes and diabetes-related disorders. A person of ordinary skill in the art would easily have understood the prior art references referred to herein, and would have the capability to draw inferences therefrom. (Ex. 1002 ¶ 13).

IX. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

IPR of claims 1–2, 4–8, 10–18, and 23–25 is respectfully requested on the following grounds of unpatentability:

Ground	References	Basis	Claims Challenged
1	Mikhail	102	1, 2, 4, 5, and 23
2	Januvia Label in View of Huettner together with either the Knowledge of a POSA or Mikhail	103	1–2, 4–8, and 10–18, and 23–25

Pursuant to 37 C.F.R. § 42.6(d), copies of the prior art references supporting each ground are filed herewith. Additional prior art references are discussed herein to provide further background in the art, further motivation to combine the teachings of these references, and/or further support for why a POSA would have a reasonable expectation of success in combining the teachings of the references to arrive at the

methods recited in the Challenged Claims. Copies of these additional references are filed herewith.

A. The Scope and Content of the Prior Art Pertinent to the Claimed Subject Matter of the '156 Patent

As of the earliest claimed priority date (*i.e.*, August 6, 2008), it was known to those skilled in the art that DPP-IV Inhibitors, including sitagliptin and linagliptin, could be used as monotherapy to treat type II diabetes in patients contraindicated against metformin.

Type II diabetes, once known as adult-onset or noninsulin-dependent diabetes, is a chronic condition that affects the way the body metabolizes sugar (glucose). (Ex. 1002 ¶ 27). With type II diabetes, the body both resists the effects of insulin—a hormone secreted by the pancreas that regulates the movement of sugar into cells—and does not produce enough insulin to maintain a normal glucose level. (*Id.*). While there is no cure for type II diabetes, it can initially be managed by eating well, exercising, and maintaining a healthy weight. (*Id.*). When diet and exercise are not enough to adequately manage a diabetic's blood sugar, then he or she may require non-insulin diabetes medications, insulin therapy, or both. (*Id.*).

First discovered in the 1920's, metformin is considered "first line" treatment for type II diabetes and has been used worldwide for many years. (Ex. 1002 ¶ 28). It works mainly by decreasing the amount of glucose made by the liver, and some studies suggest that it also increases the amount of glucose utilized by certain body

tissues. (*Id.*). As a result, metformin can help the body respond better to its own insulin and decrease blood glucose levels. (*Id.*). Metformin has been available in several forms, including an immediate release form (*e.g.*, Glucophage IR in 1994), and long-acting form (*e.g.*, Glucophage XR in 2000), among others. (*Id.*). Figure 1 below illustrates generally how metformin reduces blood glucose levels in type II diabetes patients.

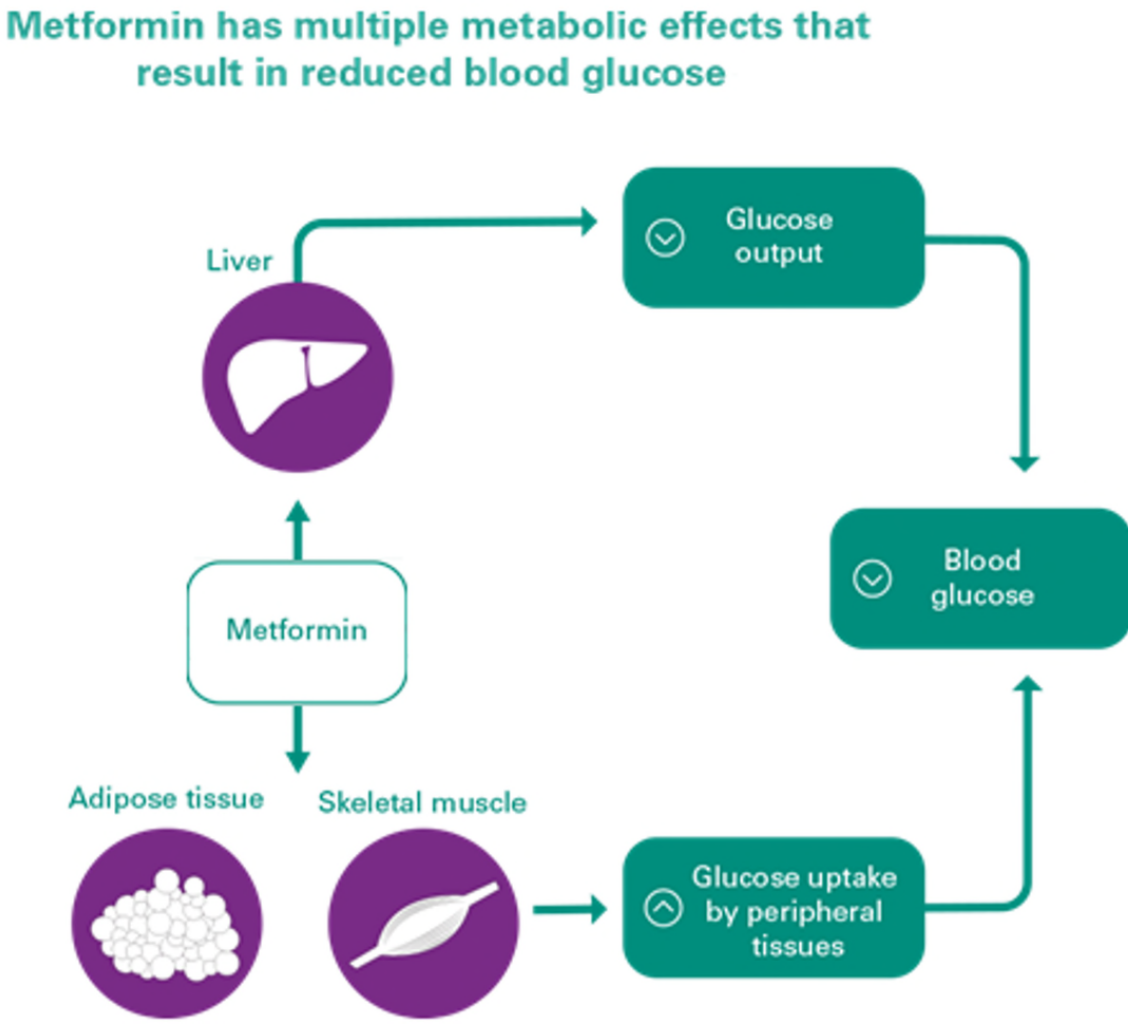

Fig. 1: Metformin's Mechanism of Action.

DPP-IV Inhibitors have also been commonly used to treat type II diabetes patients. (Ex. 1002 ¶ 29). These drugs were first approved for the treatment of type II diabetes in 2006. (Ex. 1002 ¶ 29; Ex. 1006 at 1). DPP-IV Inhibitors have a different mechanism of action as compared to metformin. (Ex. 1002 ¶ 29). DPP-IV Inhibitors work to increase the level of insulin in the body by preventing the breakdown of GLP-1, a naturally occurring substance that helps reduce blood glucose by stimulating the pancreas to produce insulin and by inhibiting the release of glucagon, a substance that causes the liver to release glucose. (*Id.*). As a result, these drugs help prevent the liver from producing an excess amount of glucose. (*Id.*). Figure 2 below illustrates how DPP-IV Inhibitors reduce blood glucose levels in type II diabetes patients.

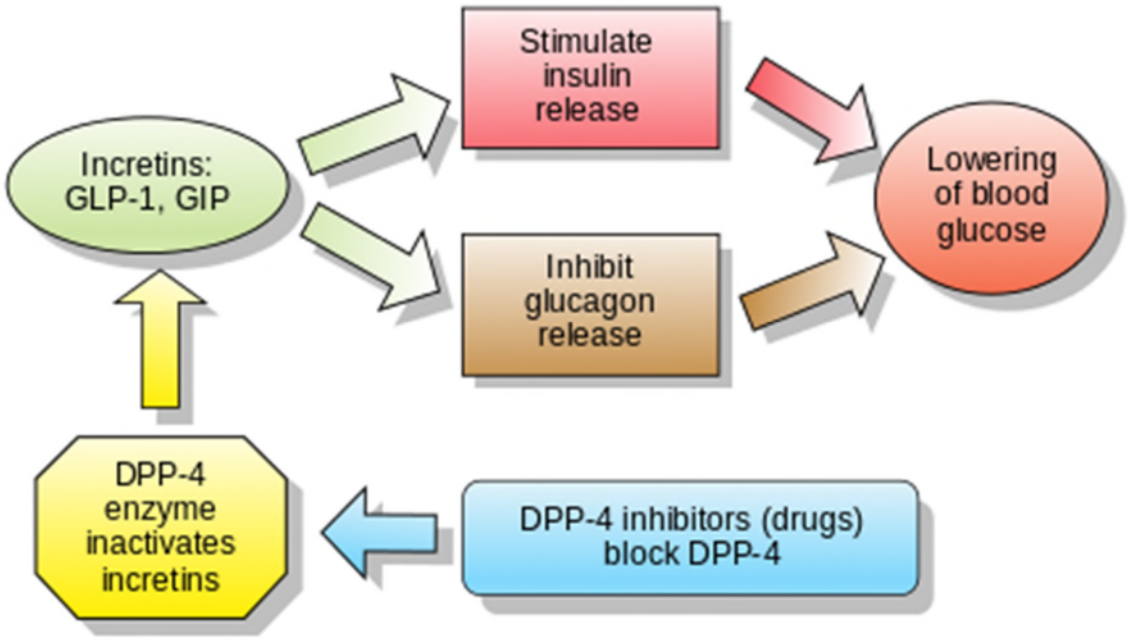

Fig. 2: Mechanism of Action of DPP-IV Inhibitors

DPP-IV Inhibitors were known, and widely used, and many were commercially available, before the alleged earliest priority date of the Challenged Claims (*i.e.*, August 6, 2008). (Ex. 1001, col. 3–9; Ex. 1002 ¶ 30). Prior to that time, DPP-IV Inhibitors were used as monotherapy or in combination with other therapies in treating type II diabetes. (Ex. 1015, '510 Pub. at ¶ [300]; Ex. 1011, Flatt at 3654, Ex. 1002 ¶ 30). For example, the DPP-IV Inhibitors sitagliptin and vildagliptin were used both in monotherapy and in combination therapy with metformin. (Ex. 1011, Flatt at 3654; Ex. 1002 ¶ 30). It was also known that DPP-IV Inhibitors can be used as monotherapy for "[p]atients who cannot take metformin due to adverse effects." (Ex. 1003, Mikhail 2008 at 851; Ex. 1002 ¶ 30).

Metformin is eliminated through the renal excretion pathway. (Ex. 1001, 1:62–65; Ex. 1008, Glucophage at Pharmacokinetics; Ex. 1002 ¶ 31). High blood concentrations of metformin will result if renal excretion of the drug is impaired, which in turn can lead to severe side effects, such as lactic acidosis, a potentially life-threatening condition. (Ex. 1008, Glucophage Label at Warnings; Ex. 1002 ¶ 31). Thus, metformin has been contraindicated for patients with renal disease or renal impairment for years prior to the date of the invention. (Ex. 1002 ¶ 31; *see also* Ex. 1008, Glucophage label (January 2001) at Contraindications ("Glucophage [IR] and Glucophage XR are contraindicated in patients with . . . Renal disease or renal dysfunction . . . .")). Accordingly, it was understood at the time of the alleged

invention that more preferable diabetic medications suitable for patients with renal impairment would need to avoid drugs that are excreted by the kidneys. (*Id.*; Ex. 1002 ¶ 31).

DPP-IV Inhibitors are metabolized differently than metformin, and most DPP-IV Inhibitors, except for linagliptin, are primarily excreted through the kidneys. (Ex. 1003, Mikhail at 851; Ex. 1004, Huettner at Table 2; Ex. 1018, Heise at Results - Pharmacokinetics; Ex. 1002 ¶ 32). However, unlike metformin, high levels of DPP-IV inhibitors will not lead to severe side effects, such as lactic acidosis. For example, the prior art taught that the DPP-IV Inhibitor sitagliptin is excreted mainly unchanged through the kidneys; that metabolism of sitagliptin represents a minor elimination pathway; and that sitagliptin has a safety/tolerability profile that is comparable to placebo. (*See, e.g.*, Ex. 1009, Mathieu at 35; Ex. 1010, Vincent at 537; Ex. 1011, Flatt at 3654; Ex. 1012, Zerilli at 2614–15; Ex. 1002 ¶ 33). For that reason, sitagliptin was recommended as a safe alternative to metformin for patients with mild renal insufficiency. For patients with moderate to severe renal insufficiency, sitagliptin can still be administered by lowering the dose ordinarily taken by patients with normal renal function. (Ex. 1003, Mikhail at 851; Ex. 1006, Januvia Label at 2; Ex. 1002 ¶ 33).

Similarly, prior to the date of invention, it was known that DPP-IV Inhibitor, BI 1356 (linagliptin), was a "potent," "long lasting," and "selective" DPP-IV

Inhibitor that could be used to treat type II diabetes. (Ex. 1018, Heise; Ex. 1019 Thomas; Ex. 1002 ¶ 34). Linagliptin (BI 1356) was characterized as having "the potential to be a *best in class* DPP-IV Inhibitor." (*Id.* (emphasis added); *see also* Ex. 1005, Eckhardt 2007 at 6450 (explaining that BI 1356 is linagliptin)). It was also well-known at the time that linagliptin was an even more potent DPP-IV Inhibitor than sitagliptin. (*See* Ex. 1002 ¶ 34, *comparing* Ex. 1006, '510 publication at ¶ [0295] *with* Ex. 1020, Gwaltney at 158).

Linagliptin was also known to have extremely low (according to one study, less than 1%) renal excretion. (Ex. 1004, Huettner; Ex. 1018, Heise (disclosing approximately 3% renal excretion); Ex. 1016, Dugi 2006 at Abstract P821 ("[r]enal clearance represented a minor elimination pathway"); Ex. 1002 ¶ 36). Because linagliptin had extremely low renal excretion, a POSA would, at the time of the alleged invention, have understood that it could be safely used in patients with renal impairment. (Ex. 1002 ¶ 36).

B. Ground 1: Claims 1, 2, 4, 5, and 23 are Anticipated Under 35 U.S.C. § 102(a) by Mikhail

For Ground 1, Petitioner relies on the teachings of Mikhail (Ex. 1003).

1. Mikhail (Ex. 1003)

Mikhail was published in June 2008 and is § 102(a) prior art to the '156 patent. (Ex. 1003 at Cover). It reports that:

[S]itagliptin was evaluated as monotherapy in several double-blind

> placebo-controlled trials in patients with type II diabetes. Given as a single daily oral dose of 100mg, treatment with sitagliptin was associated with average reduction of HbA1c values of around 0.7%, compared with baseline and placebo values. The average proportions of patients who achieved HbAlc levels < 7% at the trial's end were 44% and 18% in the sitagliptin and placebo groups, respectively.

(*Id*. at 847; Ex. 1002 ¶ 38). Mikhail further reports that similar decreases in HbA1c[1] values were generally observed in trials using vildagliptin. (Ex. 1003 at 847; Ex. 1002 ¶ 39). In these studies, vildagliptin "was given as a 50 mg tablet b.i.d. or 100 mg once daily, with no significant difference in efficacy between the two dosing regimens." (Ex. 1003 at 847; Ex. 1002 ¶ 39). Mikhail found that "in clinical trials lasting ≤ 52 weeks, the use of sitagliptin and vildagliptin was well tolerated. (Ex. 1002 ¶ 39). Withdrawal rates in patients randomized to these two DPP-4 inhibitors were similar to placebo." (Ex. 1003 at 847; Ex. 1002 ¶ 39)

Based on the above results, Mikhail recommended that:

> *DPP-4 inhibitors can be used as monotherapy in the following situations:*

[1] The terms "HbA1c" or "A1c" refer to glycated haemoglobin. (Ex. 1002 ¶ 39). By measuring glycated haemoglobin (HbA1c), clinicians are able to get an overall picture of what an individual's average blood sugar levels have been over a period of weeks and months. (Ex. 1002 ¶ 39).

> • *Patients who cannot take metformin due to adverse effects or renal insufficiency.* In the latter condition, sitagliptin should be used as safety data regarding the use of vildagliptin in renal insufficiency is not yet available.
> • Patients who are not willing to take a [sulfonylurea] because of concerns about hypoglycemia and/or weight gain.

(Ex. 1003 at 851 (emphasis added); Ex. 1002 ¶ 40).

2. Mikhail Anticipates Independent Claims 1 and 23

Independent claim 1 is directed to a method of treating and/or preventing metabolic diseases in a patient for whom metformin therapy is inappropriate due to at least one contraindication against metformin comprising orally administering to the patient a DPP-IV Inhibitor wherein the contraindication is selected from the group consisting of: renal disease, renal impairment, or renal dysfunction, among other medical conditions. (Ex. 1001, 29:2–11).

Claim 23 is nearly identical to claim 1, except that it is limited to a method of treating type II diabetes mellitus.[2] (Ex. 1001, 32:38–47). Claim 23 recites other contraindications not recited in claim 1, but those contraindications are not relevant here. (*Id.*)

Mikhail discloses the use of DPP-IV Inhibitors, specifically sitagliptin and vildagliptin, through a single oral dose, for the treatment of type II diabetes, which

[2] Type II diabetes mellitus is commonly known as type II diabetes (Ex. 1002 ¶ 27).

is a known metabolic disorder. (Ex. 1002 ¶ 43; Ex. 1003 at 847). Mikhail specifically discloses that oral doses of sitagliptin should be used as monotherapy for "patients who cannot take metformin due to adverse effects or renal insufficiency." (Ex. 1003 at 851; Ex. 1002 ¶ 40). Accordingly, Mikhail discloses all of the limitations of independent claims 1 and 23 and thus anticipates those claims. (Ex. 1002 ¶ 43).

3. Mikhail Anticipates Dependent Claims 2, 4, and 5

Claim 2 recites the method according to claim 1, wherein the patient is ineligible for metformin due to a contraindication against metformin. (Ex. 1001, 29:12–14).

Claim 4 recites the method according to claim 1, wherein the metabolic disease is type II diabetes. (Ex. 1001, 29:18–19).

Claim 5 recites the method according to claim 1, wherein the contraindication is renal disease, renal impairment, or renal dysfunction. (Ex. 1001, 29:20–22)

As discussed above, Mikhail discloses each of these further limitations of claims 2, 4, and 5. Specifically, Mikhail discloses the use of a DPP-IV Inhibitor for the treatment of type II diabetes. (Ex. 1003 at 845; Ex. 1002 ¶ 47). Mikhail also discloses that sitagliptin should be used as monotherapy for "patients who cannot take metformin due to adverse effects or renal insufficiency." (Ex. 1003 at 851; Ex. 1002 ¶ 47). Accordingly, Mikhail discloses all of the limitations of dependent claims

2, 4, and 5.

C. Ground 2: Claims 1–2, 4–8, and 10–18, and 23–25 Would Have Been Obvious Under 35 U.S.C. § 103(a) Over the Januvia Label in View of Huettner together with either the Knowledge of a POSA or Mikhail

For Ground 2, Petitioner relies on the teachings of the Januvia in view of the Huettner together with the knowledge of a POSA or Mikhail.

1. Mikhail (1003)

For Ground 2, Petitioner incorporates herein the discussion on Mikhail in support of Ground 1.

2. Januvia Label (Ex. 1006)

Januvia® is a commercially available sitagliptin tablet. (Ex. 1006 at 1). Januvia® (sitagliptin phosphate) tablets were first approved by the FDA on October 16, 2006. (Ex. 1002 ¶ 52). The Januvia Label published in 2006. (Ex. 1006 at 1). Januvia is § 102(b) prior art to the '156 patent.

The Januvia Label describes the use of sitagliptin phosphate tablets as monotherapy and "as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus." (Ex. 1006 at 1; Ex. 1002 ¶ 53). The Januvia Label lists no contraindications for Januvia. (Ex. 1006 at 2; Ex. 1002 ¶ 53). Instead, the Januvia Label provides the following dosage recommendations for patients with renal insufficiency:

For patients with mild renal insufficiency (creatinine clearance [CrCl]

> ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women), no dosage adjustment for JANUVIA is required.
>
> For patients with moderate renal insufficiency (CrCl ≥30 to <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 to ≥3.0 mg/dL in men and >1.5 to ≤2.5 mg/dL in women), the dose of JANUVIA is 50 mg once daily.
>
> For patients with severe renal insufficiency (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of hemodialysis.
>
> Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula.

(Ex. 1003 at 2; Ex. 1002 ¶ 53). Januvia further discloses that "[i]n controlled clinical studies as both monotherapy and combination therapy, the overall incidence of adverse reactions with JANUVIA was similar to that reported with placebo. Discontinuation of therapy due to clinical adverse reactions was . . . similar to placebo. (Ex. 1003 at 3; Ex. 1002 ¶ 54).

Finally, Januvia discloses that "six [sitagliptin] metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin." (Ex. 1003 at 6; Ex. 1002 ¶ 54). In other words, the main metabolites of linagliptin are pharmacologically inactive metabolites. (Ex. 1002 ¶

55).

3. Huettner (Ex. 1004)

Huettner was published in June 2007 and is § 102(b) prior art to the '156 patent (Ex. 1004). This reference discloses that "a novel approach in the treatment of diabetes targets the incretins (*e.g.*, GLP-1), hormones secreted in the intestine in response to food intake." (Ex. 1004 at Introduction; Ex. 1002 ¶ 56). GLP-1 regulates insulin and glucagon secretion. (Ex. 1002 ¶ 56). "DPP-4 inhibitors increase plasma levels of intact GLP-1." (Ex. 1004, Huettner at Introduction; Ex. 1002 ¶ 56).

Huettner conducted "a randomised, double-blind, placebo controlled single rising dose study in healthy male volunteers aged 21–65 years" of BI 1356 (*i.e.*, linagliptin), "a xanthine analogue, which exhibits a high potency for DPP-4 inhibition, increases the half-life of circulating incretin hormones, and improves glucose homeostasis in preclinical studies." (Ex. 1004, at Abstract; Ex. 1002 ¶ 57). Huettner reports that "renal excretion was low and does not constitute the main pathway for elimination of BI 1356." (Ex. 1004, at Abstract; Ex. 1002 ¶ 58). More specifically, Huettner reports that "[r]enal excretion of BI 1356 was below 1% for doses up to 5mg and increased dose dependently." (Ex. 1004, at Table 2; Ex. 1002 ¶ 58). Huettner also discloses that 2.5 mg and 5 mg were common therapeutic dosages for linagliptin. (Ex. 1004, at Abstract (disclosing single doses of 2.5 mg and 5 mg); *see also* Ex. 1016, Dugi 2006 (disclosing 5 mg as a "therapeutic dose"); Ex.

1002 ¶ 59). Huettner concludes that "BI 1356 is a potent DPP-4 inhibitor with a wide therapeutic window of >100-fold based on an expected therapeutic dose of 5 mg." (Ex. 1004, at Conclusions; Ex. 1002 ¶ 59).

4. Eckhardt 2007 (Ex. 1005)

Eckhardt 2007 confirms that the compound designated "BI 1356" in Huettner (Ex. 1004) is linagliptin. (Ex. 1002 ¶ 60). Eckhardt 2007 was published in December 2007 and is prior art to the '156 patent under §102(a). Eckhardt 2007 discloses that BI 1356 corresponds with species 1 (Figure 3 below), which was known at the time to be linagliptin. (Ex. 1005 at 6450; *see also* Ex. 1017 '940 Publication at [0032] (disclosing the above chemical structure as 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-aminopiperidin-1-yl)-xanthine (*i.e.*, linagliptin); Ex. 1002 ¶ 60).

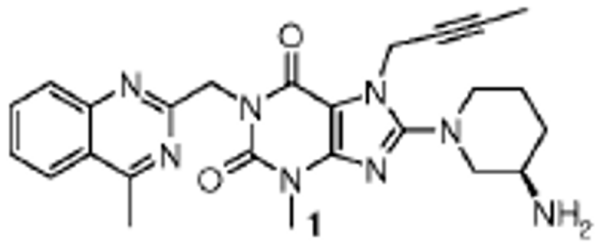

Fig. 3: Chemical Structure for Linagliptin

5. Independent Claims 1 and 23–25 Are Obvious

Claim 1 is directed to a method of (i) treating and/or preventing metabolic diseases; (ii) in a patient for whom metformin therapy is inappropriate due to at least one contraindication against metformin, wherein the contraindication is selected

from the group consisting of: renal disease, renal impairment or renal dysfunction, among other medical conditions; and (iii) comprising orally administering to the patient a DPP-IV Inhibitor. (Ex. 1001, 29:1–12).

The Januvia Label discloses administration of sitagliptin, a DPP-IV Inhibitor, as monotherapy for the treatment of type II diabetes, which is a known metabolic disease. (Ex. 1002 ¶ 62; Ex. 1006 at 1). Thus, the Januvia Label discloses elements (i) and (iii) of claim 1. (*Id.*).

Element (ii) of claim 1 is met by the Januvia Label, coupled with a POSA's knowledge of the limitations in administering metformin to type II diabetes patients, and alternative treatments to metformin therapy. (Ex. 1002 ¶ 63). In particular, at the time of the alleged invention, the POSA would have understood that metformin is contraindicated for patients with renal impairment because metformin is largely eliminated unmetabolized through the kidneys. (*Id.*). Thus, in patients with renal impairment, the potential exists for metformin to build up in the patient's blood, leading to harmful side effects such as lactic acidosis. (*Id.*). The POSA, in view of the Januvia Label, would have also understood that sitagliptin does not cause the same potentially harmful side effects that metformin can cause in patients with renal impairment. (*Id.*). Thus, a POSA would have understood that sitagliptin, as disclosed in the Januvia Label, can be administered to patients for whom metformin is contraindicated due to renal insufficiency. (Ex. 1002 ¶ 64).

Likewise, Mikhail discloses element (ii) as it specifically teaches that sitagliptin can be administered as an alternative treatment for type II diabetes "patients who cannot take metformin due to adverse effects or renal insufficiency." (Ex. 1003 at 851; Ex. 1002 ¶ 65).

The Januvia Label, together with the knowledge of a POSA as of August 6, 2007, or alternatively the Januvia Label combined with Mikhail, disclose all of the limitations of independent claim 1. (Ex. 1002 ¶ 66). Given that the FDA-approved Januvia Label permitted sitagliptin administration to patients with renal insufficiency, a POSA would have a reasonable expectation of success in administering sitagliptin to type II diabetes patients for whom metformin is contraindicated due to renal impairment. (*Id.*). Reasonable expectation of success is also supported by Mikhail's express teaching that sitagliptin can be used to treat type II diabetes "patients who cannot take metformin due to adverse effects or renal insufficiency." (Ex. 1003 at 851; Ex. 1002 ¶ 66).

Accordingly, there is nothing inventive about administering a well-known DPP-IV Inhibitor, sitagliptin, as an alternative therapy for patients with renal disease or renal impairment. (Ex. 1002 ¶ 67). Therefore claim 1 would have been obvious over the Januvia Label in view of Huettner together with either the knowledge of a POSA or Mikhail. (*Id.*)

Claim 23 is nearly identical to claim 1, except that it is limited to a method of

treating type II diabetes mellitus. (Ex. 1001, 32:38–47). Claim 23 recites other contraindications in addition to renal impairment, which are not recited in claim 1, but those contraindications are not relevant here. (*Id.*)

The Januvia Label discloses administration of sitagliptin, a DPP-IV Inhibitor, as monotherapy for the treatment of type II diabetes. (Ex. 1002 ¶ 69). Accordingly, for the same reasons disclosed above for claim 1, claim 23 would have been obvious, and thus unpatentable. (*Id.*).

Claims 24 and 25 are nearly identical to claim 23, except that claims 24 and 25 are limited to orally administering linagliptin to the patient. (Ex. 1001, 32:48–57). The POSA would have been motivated to substitute a long lasting, non-renally excreted DPP-IV Inhibitor disclosed in Huettner—linagliptin—in patients with renal impairment for the well-known DPP-IV Inhibitor disclosed in the Januvia Label—sitagliptin—and would thereby arrive at the alleged invention in claims 24 and 25. (Ex. 1002 ¶ 70). Since linagliptin's renal excretion was extremely low, a POSA would have understood that a standard dose of linagliptin could be given to patients with any degree of renal impairment, an apparent benefit over sitagliptin, which, according to the Januvia Label, requires that the approved dose must be adjusted for patients with moderate or severe renal impairment. (Ex. 1002 ¶ 70; Ex. 1006 at 2; Ex. 1003 at 851). Accordingly, a POSA would have been motivated to substitute the linagliptin disclosed in Huettner for the sitagliptin disclosed in Januvia, thus

arriving at the alleged invention of claims 24 and 25. (*Id.*).

In doing so, a POSA would have a reasonable expectation of success because the POSA would understand that a contraindication against renal impairment can be avoided with a drug that is not excreted by the renal system, and prior to the date of the alleged invention, a POSA was aware that linagliptin was not excreted renally. (Ex. 1004, Huettner; Ex. 1002 ¶ 71). Accordingly, for the same reasons disclosed above for claim 23, claims 24 and 25 would have been obvious, and thus unpatentable. (*Id.*).

6. Dependent Claims 2, 4–8 and 10–18 Are Obvious

Claim 2 recites the method according to claim 1, wherein the patient is ineligible for metformin due to a contraindication against metformin. (Ex. 1001, 29:12–14).

As discussed with claim 1, the Januvia Label in view of either (i) a POSA's knowledge of the limitations of type II diabetes treatments or (ii) Mikhail's disclosure of patients who are ineligible for metformin due to a contraindication against metformin discloses the claimed further limitation that the patient is ineligible for metformin due to a contraindication against metformin. (Ex. 1002 ¶ 73). Accordingly, for the same reasons disclosed above for claim 1, claim 2 would have been obvious, and thus unpatentable. (*Id*.).

Claim 4 recites the method according to claim 1, wherein the metabolic

disease is type II diabetes. (Ex. 1001, 29:18–19). As discussed above for claim 23, the Januvia Label discloses administering sitagliptin, a DPP-IV Inhibitor, as monotherapy for the treatment of type II diabetes. (Ex. 1002 ¶ 74). Accordingly, for the same reasons disclosed above for claim 23, claim 4 would have been obvious, and thus unpatentable. (*Id.*).

Claim 5 recites the method according to claim 1, wherein the contraindication is renal disease, renal impairment, or renal dysfunction. (Ex. 1001, 29:20–22). As discussed above for claim 1, the Januvia Label discloses administration of sitagliptin, a DPP-IV Inhibitor, to patients with renal impairment. (Ex. 1002 ¶ 75). Accordingly, for the same reasons disclosed above for claim 1, claim 5 would have been obvious, and thus unpatentable. (*Id.*).

Claims 6, 7, 8 recite the method of claim 1, wherein the DPP-IV Inhibitor includes linagliptin. (Ex. 1001, 29:23–31:17). As explained above with respect to claims 24 and 25, which require that the DPP-IV Inhibitor is linagliptin, it would have been obvious to substitute the linagliptin of Huettner for the sitagliptin of the Januvia Label. (Ex. 1002 ¶ 76). Accordingly, for the same reasons disclosed above for claims 24 and 25, claims 6–8 would have been obvious, and thus unpatentable. (*Id.*).

Claim 10 depends from claim 1 and is similar to claim 23 except that the DPP-IV Inhibitor is used for said patient in the same dose as for a patient with normal

renal function. (Ex. 1001, 31:56–60). The Januvia Label discloses that for patients with mild renal insufficiency, no dosage adjustment is necessary. (Ex. 1003 at 2; Ex. 1002 ¶ 78). Accordingly, for the same reasons disclosed above for claim 1, claim 10 would have been obvious, and thus unpatentable. (*Id.*).

Moreover, claim 10 would have been obvious for another reason. As described above with respect to claims 24 and 25, the POSA would have been motivated to substitute the linagliptin disclosed by Huettner for the sitagliptin disclosed by the Januvia Label. Because Huettner discloses that renal excretion of linagliptin is extremely low, the POSA would have understood that adjustments to the standard dosage of linagliptin would be unnecessary for patients with renal impairment. (Ex. 1002 ¶ 79). Accordingly, for the reasons described above with respect to claims 24 and 25, claim 10 would have been obvious. (*Id.*).

Claims 11–13 recite various characteristics of the excretion of the DPP-IV Inhibitor of claim 1. Specifically, Claim 11 recites that the DPP-IV Inhibitor and its major active metabolite are primarily eliminated via hepatic metabolism or biliary excretion. (Ex. 1001, 31:61–64). Claim 12 recites that the DPP-IV Inhibitor is excreted mainly via the liver. (*Id*. at 31:65–66). Claim 13 recites that excretion via the kidney represents a minor elimination pathway. (*Id*. at 32:1–2).

As described above with respect to claims 24 and 25, it would have been obvious to substitute the linagliptin disclosed by Huettner for the sitagliptin

disclosed by the Januvia Label. (Ex. 1002 ¶ 81). Huettner further discloses that renal excretion of linagliptin is extremely low. (Ex. 1004, Huettner at Table 2; Ex. 1005 at 6450; Ex. 1002 ¶ 81). A POSA would also have understood that linagliptin was primarily excreted through a pathway other than the kidneys because only 1% of standard linagliptin doses are excreted renally. (Ex. 1002 ¶ 81). In fact, at the time of the alleged invention, a POSA would have known that the primary excretion pathway for linagliptin was via hepatic metabolism (*i.e.*, the liver). (*Id.*). Accordingly, for the reasons described above with respect to claims 24 and 25, claims 11–13 would have been obvious. (*Id.*).

Claims 14–15 recite various characteristics of the excretion of the DPP-IV Inhibitor of claim 1. Claim 14 recites that the DPP-IV Inhibitor is excreted mainly unchanged. (Ex. 1001, 32:3–4). Claim 15 recites that elimination via metabolism represents a minor elimination pathway. (Ex. 1001, 32:5–6).

The Januvia Label discloses that "approximately 79% of sitagliptin is excreted unchanged in the urine, with metabolism being a minor pathway of elimination." (Ex. 1006, Januvia at 6; Ex. 1002 ¶ 83). Accordingly, at the time of the alleged invention, a POSA would reasonably expect that oral administration of sitagliptin would result in the sitagliptin being excreted mainly unchanged (claims 14) with metabolism representing a minor elimination pathway (claim 15). (Ex. 1002 ¶ 83). Accordingly, for the reasons described above with respect to claim 1, claims 14–15

would have been obvious. (*Id.*).

Claim 16 depends from claim 1 and recites that the DPP-IV Inhibitor has placebo-like safety/tolerability and/or is eliminated primarily as the parent drug via the liver. (Ex. 1001, 32:7–9). The Januvia Label discloses that sitagliptin has placebo-like safety and tolerability. (Ex. 1003 at 3; 1002 at ¶ 84). Accordingly, for the reasons described above with respect to claim 1, claim 16 would have been obvious. (*Id.*).

Claim 17 depends from claim 1 and recites that the main metabolite of the DPP-IV Inhibitor is pharmacologically inactive. (Ex. 1001, 32:10–12). The Januvia Label discloses that "six [sitagliptin] metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin." (Ex. 1006 at 6; Ex. 1002 ¶ 85). Thus, at the time of the alleged invention, a POSA would have reasonably expected that the main sitagliptin metabolites would be pharmacologically inactive (claim 17). (Ex. 1002 ¶ 85). Accordingly, for the reasons described above with respect to claim 1, claim 17 would have been obvious. (*Id.*).

Claim 18 recites the method of claim 1 wherein the contraindication is mild, moderate, or severe renal impairment, or end-stage renal disease. As discussed with claim 1, the Januvia Label discloses renal impairment, which is understood to include mild, moderate, and severe renal impairment. (Ex. 1002 ¶ 86). Accordingly,

for the reasons described above with respect to claim 1, claim 18 would have been obvious. (Ex. 1002 ¶ 86).

D. Objective Indicia of Nonobviousness

Patent Owner bears the burden of proof in establishing objective indicia of nonobviousness. To date, Patent Owner has not come forward with any evidence thereof. To the extent Patent Owner does assert any objective indicia in this proceeding, detailed consideration of Patent Owner's evidence should not be undertaken until Petitioner has had an opportunity to respond to it. *Amneal Pharms., LLC v. Supernus Pharms., Inc.,* IPR2013-00368 [Paper 8, pp. 12–13].

X. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that claims 1–8, 10–18, and 23–25 of the '156 patent are unpatentable as obvious over the various prior art references cited herein, and respectfully requests that the Board so finds.

RESPECTFULLY SUBMITTED,
ALSTON & BIRD LLP

Date: August 10, 2016

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CERTIFICATION OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 10th day of August 2016, a complete copy of the foregoing Petitioner's Petition for *Inter Partes* Review of U.S. Patent No. 8,853,156, Power of Attorney, and all supporting exhibits were served *via* Priority Mail Express® to the Patent Owner by serving the correspondence address of record for the '156 patent:

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