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. 8,673,927 to Dugi *et al.*
Issue Date: Mar. 18, 2014
Title: Uses of DPP-IV Inhibitors

Inter Partes Review No.: IPR2016-01563

Petition for *Inter Partes* Review of U.S. Patent No. 8,673,927 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

Petitioner's Exhibit List

Mylan Exhibit #	***Description***
1001	Dugi *et al.,* U.S. Patent No. 8,673,927, "Uses of DPP-IV Inhibitors"
1002	Declaration of Mayer B. Davidson, M.D.
1003	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")
1004	Glucophage® (metformin hydrochloride tablets) and Glucophage® XR (metformin hydrochloride extended-release tablets) prescribing information (2001) ("Glucophage Label")
1005	Ahrén *et al.,* "Twelve and 52-Week Efficacy of the Dipeptidase IV Inhibitor LAF237 in Metformin-Treated Patients with Type 2 Diabetes," *Diabetes Care* 27:2874–2880 (2004) ("Ahrén")
1006	Hughes, International Patent No. WO 2005/117861, "Use of Organic Compounds" ("Hughes")
1007	Brazg, *et al.*, "Effect of Adding MK-0431 to On-going Metformin Therapy in Type 2 Diabetic Patients Who Have Inadequate Glycemic Control on Metformin," *Diabetes* 54 (Suppl. 1):A3 (2005) ("Brazg")
1008	Curriculum Vitae of Mayer B. Davidson, M.D.
1009	Demuth *et al.*, "Type 2 diabetes—Therapy with dipeptidyl peptidase IV inhibitors," Biochimica et Biophysica Acta 1751:33-44 (2005) ("Demuth")
1010	Deacon *et al.*, "Inhibitors of Dipeptidyl Peptidase IV: a Novel Approach for the Prevention and Treatment of Type 2 Diabetes?" Expert Opin. Investig. Drugs, 13(9):1091-1102 (September 2004) ("Deacon")
1011	Gwaltney *et al*., "Inhibitors of Dipeptidyl Peptidase 4," Annual Reports in Medicinal Chemistry, 40:149-165 (December 2005) ("Gwaltney")

Mylan Exhibit #	***Description***
1012	Chiasson *et al.*, "The Synergistic Effect of Migitol Plus Metformin Combination Therapy in the Treatment of Type 2 Diabetes," Diabetes Care 24:989-994 (2001) ("Chiasson")
1013	Yasuda *et al.*, "Metformin Causes Reduction of Food Intake and Body Weight Gain and Improvement of Glucose Intolerance in Combination with Dipeptidyl Peptidase IV Inhibitor in Zucker fa/fa Rats," The Journal of Pharmacology and Experimental Therapeutics 310:614-619 (2004) ("Yasuda")
1014	Nielson "Incretin mimetics and DPP-IV Inhibitors for the treatment of type 2 diabetes," Drug Discovery Today 10(10):703-710 (2005) ("Nielson")
1015	Kirpichnikov *et al.*, "Metformin: An Update," Ann. Int. Med. 137(1):25-33 (2002) ("Kirpichnikov")
1016	Patent Owner's April 26, 2013 Response to Nonfinal Office Action Dated October 29, 2012 in U.S. Application No. 12/946,193

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 1–26 of U.S. Patent No. 8,673,927 ("the '927 patent," Ex. 1001). Concurrently filed herewith is a Power of Attorney pursuant to 37 C.F.R. § 42.10(b). Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a) accompanies this Petition.

II. OVERVIEW OF GROUNDS FOR UNPATENABILITY

Claims 1–26 of the '927 patent (the "Challenged Claims") are directed to methods for treating type II diabetes by administering a combination of metformin and oral doses of linagliptin—two drugs that, at the time of the alleged invention, were known to treat type II diabetes, but through separate and independent mechanisms of action.

The prior art indisputably demonstrates that the claims of the '927 patent are either anticipated and/or obvious. The '510 Publication specifically teaches the combination of metformin and linagliptin as an effective combination therapy for treating patients with type II diabetes. The '510 Publication also discloses the same oral linagliptin doses recited in the Challenged Claims. While the '510 Publication does not disclose a particular amount of metformin, that reference nonetheless anticipates at least claims 18–26, which are not limited to particular amount of metformin.

The remaining claims would have been obvious in view of the prior art because they require nothing more than using known oral doses of linagliptin as disclosed in the '510 Publication, together with known standard doses for metformin monotherapy—which, at the time of the alleged invention, were the same doses of metformin used in combination with other well-known antidiabetic drugs in the same class and having the same mechanism of action as linagliptin—dipeptidyl peptidase IV Inhibitors (DPP-IV Inhibitors). This class of compounds also includes sitagliptin and vildagliptin.

In sum, the claimed subject matter simply entails using known combinations of two antidiabetic medications—metformin and DPP-IV Inhibitors—in their known effective amounts and for their known purposes to achieve a predictable result, namely, treating type II diabetes. Because the claimed combination "'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int'l Co. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (citation omitted).

As discussed more fully herein, the Challenged Claims of the '927 patent are either anticipated and/or obvious in view of the prior art.

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

Petitioner certifies that (1) the '927 patent is available for IPR; and (2)

Petitioner is not barred or estopped from requesting IPR of any claim of the '927 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 '927 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 herewith, Petitions for *inter partes* review of the following: U.S. Patent Nos. 9,173,859; 8,846,695; and 8,853,156, 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 1–26. Petitioner's full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '927 PATENT

The '927 patent, entitled "Uses of DPP-IV Inhibitors," issued on March 18, 2014. The '927 patent issued from U.S. patent application 12/946,193, which ultimately claims priority to EP 06009203 filed on May 4, 2006. This application is the parent application of 14/161,007, which issued as U.S. Patent No. 9,173,859 and is the subject of co-pending IPR Petition No. IPR2016-01566. According to records at the U.S. Patent and Trademark Office, the '927 patent is assigned to Boehringer

Ingelheim International GmbH.

The Challenged Claims of the '927 patent are directed to methods of treating type II diabetes mellitus[1] by administering 1-[(4-methyl-quinazolin-2-yl)-methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine ("linagliptin") and metformin. (Ex. 1001, '927 Patent, at 23:45–26:18). The '927 patent has five independent claims (claims 1, 10, 18, 19, and 20). Independent claim 1 reads as follows:

> A method of treating type II diabetes mellitus comprising administering to a patient in need thereof a pharmaceutically effective oral amount of 1-[(4-methyl-quinazolin-2-yl)-methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine ["linagliptin"], and a pharmaceutically effective amount of metformin, which is from 300 mg to 1000 mg once or twice a day, or delayed-release metformin in a dose of 500 mg to 1000 mg once or twice a day or 500 mg to 2000 mg once a day.

(*Id.* at 23:46–54). Independent claim 10 is similar to claim 1, but recites a different dosage range of metformin/delayed-release metformin, reciting "500 mg, 850 mg or 1000 mg metformin as a single dose with a total daily dose of metformin of 500–2850 mg, or which is 500 mg, 1000 mg, 1500 mg or 2000 mg metformin in delayed release form." (*Id.* at 24:21–29).

[1] Type II diabetes mellitus is referred to herein as "type II diabetes."

Independent claims 18–20 are also directed to combinations of linagliptin and metformin. These claims, however, require administering a particular oral dose of linagliptin together with an effective amount of metformin. Independent claim 18 recites an oral daily dose of linagliptin from 2.5 mg to 10 mg. (*Id.* at 24:58–64). Independent claim 19 recites an oral daily dose of linagliptin of 5 mg. (*Id.* at 24:65–25:3). Finally, independent claim 20 recites an oral dosage of linagliptin from 0.5 mg to 50 mg. (*Id.* at 25:4–12).

The remaining claims 2–9, 11–17, and 21–26 are dependent from either of the independent claims 1, 10, 18, 19, and 20. These dependent claims recite various amounts of linagliptin.

A. CLAIM CONSTRUCTION

The claim terms in the '927 Patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). Petitioner does not believe that any special meanings apply to the claim terms in the '927 Patent. Petitioner's position regarding the scope of the claims should not be taken as an assertion regarding the appropriate claim scope in other adjudicative forums where a different claim interpretation standard may apply.

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

Filed herewith is the supporting declaration of Mayer B. Davidson, M.D. (Ex.

1002). Also, a current copy of Dr. Davidson's curriculum vitae is submitted with this petition as Ex. 1008. Dr. Davidson is currently a Professor of Medicine at both the David Geffen School of Medicine at UCLA and Charles R. Drew University. (Ex. 1008 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 has focused his practice on the diagnosis and treatment of diabetes. (Ex. 1002 ¶ 8; Ex. 1008). He served as President of the American Diabetes Association from 1997–1998. (Ex. 1008 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, 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,

among other things, what the relevant art would have conveyed to a POSA as of May 4, 2006.

VIII. PERSON OF 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). The 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 relatively 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 POSA would easily have understood the prior art references referred to herein, and would have the capability to draw inferences from them. (Ex. 1002 ¶ 11).

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

IPR of claims 1–26 is respectfully requested on the following grounds of unpatentability:

Ground	Prior Art References	Basis	Claims Challenged
1	'510 Publication	102	18–26
2	'510 Publication in view of the Glucophage Label	103	1–26
3	'510 Publication in view of Ahrén, Hughes, and/or Brazg	103	1–26

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 also filed herewith and 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 person of skill in the art would have a reasonable expectation of success in combining the teachings of the references to arrive at the methods recited in the

Challenged Claims.

A. The Scope and Content of the Prior Art

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)—the body's important source of fuel. (Ex. 1002 ¶ 26). With type II diabetes, the body either resists the effects of insulin—a hormone secreted by the pancreas that regulates the movement of sugar into cells—or does not produce enough insulin to maintain a normal glucose level. (*Id.*). While there is no cure for type II diabetes, it can be managed by eating well, exercising, and maintaining a healthy weight. (*Id.*). If diet and exercise are not enough to adequately manage a diabetic's blood sugar, then he or she will require diabetes medications, insulin therapy, or both. (*Id.*).

1. Metformin

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; Ex. 1006, Hughes at 3; Ex. 1007, Brazg at A3; Ex. 1012, Chiasson at 989). Specifically, metformin is a known biguanide that was first approved by the U.S. Food & Drug Administration for the therapeutic treatment of diabetes in 1994. (Ex 1002 at ¶ 27; *See* Ex. 1004, Glucophage Label).

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 other forms. (Ex. 1002 ¶ 28; *See* Ex. 1004, Glucophage Label). The standard dose of metformin IR was well known to be 500 mg twice a day or 850 mg once a day up to a total of 2,000 mg a day with a maximum of 2,550 mg a day (Ex. 1002 ¶ 27; Ex. 1004 at 6).

Metformin works by decreasing the amount of glucose made by the liver and increasing the amount of glucose absorbed into body tissues. (Ex. 1002 ¶ 27; Ex. 1015, Kirpichnikov at E-26-E-27). As a result, metformin can help the body respond better to its own insulin and decrease blood glucose levels. (Ex. 1002 ¶ 27; Kirpichnikov at E-27). Figure 1 below illustrates generally how metformin reduces blood glucose levels.

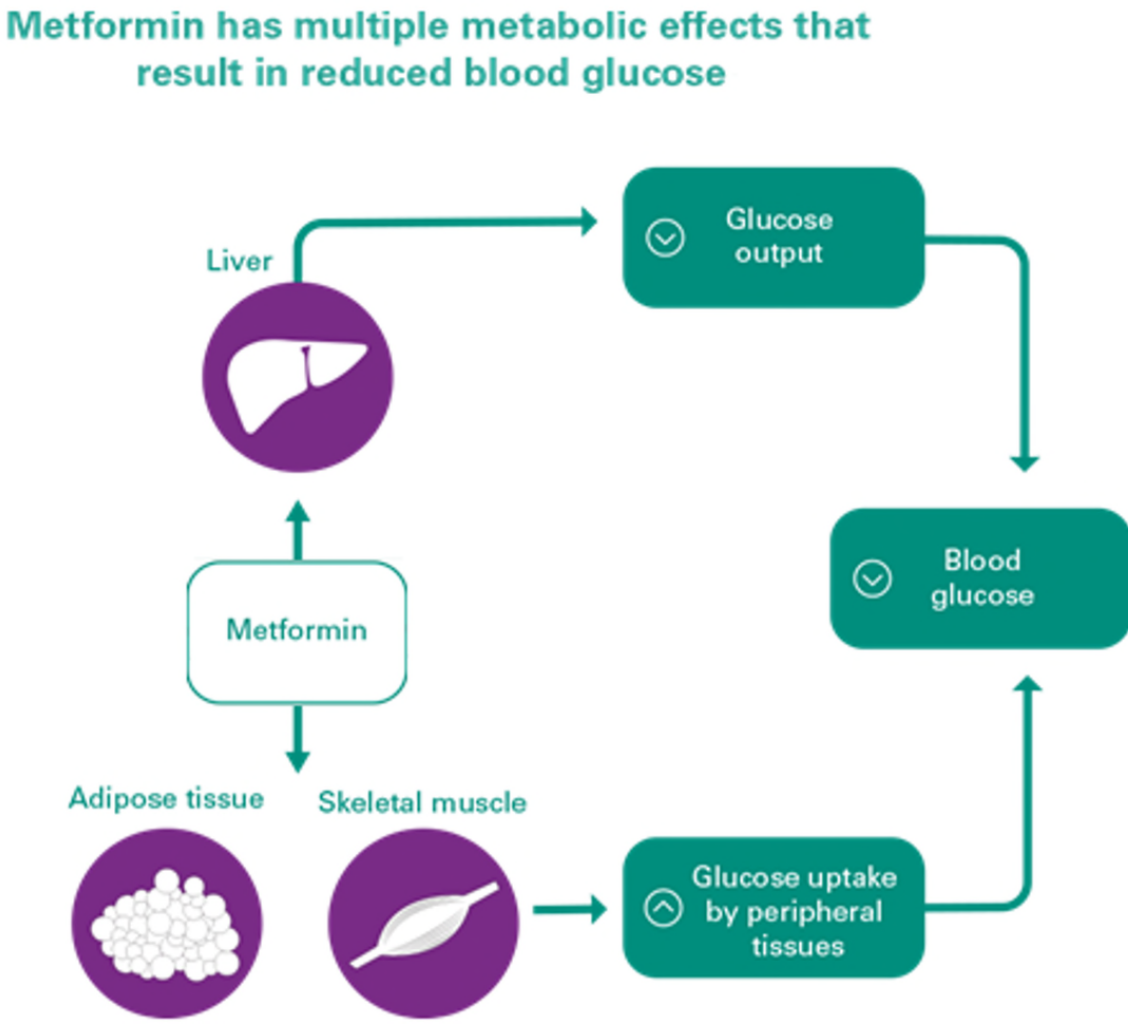


Fig. 1: Metformin's Mechanism of Action.

2. DPP-IV Inhibitors

DPP-IV Inhibitors were also known to be beneficial in treating type II diabetes patients. (Ex. 1002 ¶ 28; *See e.g.*, '510 publication ¶¶ [0004], [0297]; Ex. 1010 at 1092). DPP-IV Inhibitors have a completely different mechanism of action as compared to metformin. (Ex. 1002 ¶ 28; Ex. 1009, Demuth at 40; Ex. 1014, Nielson at 707-708; Ex. 1015, Kirpichnikov at E-26-E-27). 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. (Ex. 1002 ¶ 28; *See* Ex. 1014, Nielson at 708; Ex. 1011 at Gwaltney at 149-150). In addition, these drugs help prevent the liver from producing an excess amount of sugar. (Ex. 1002 ¶ 28; *See* Ex. 1014, Nielson at 707–708; Ex. 1011 at Gwaltney at 149–150). Figure 2 below illustrates how DPP-IV Inhibitors reduce blood glucose levels.

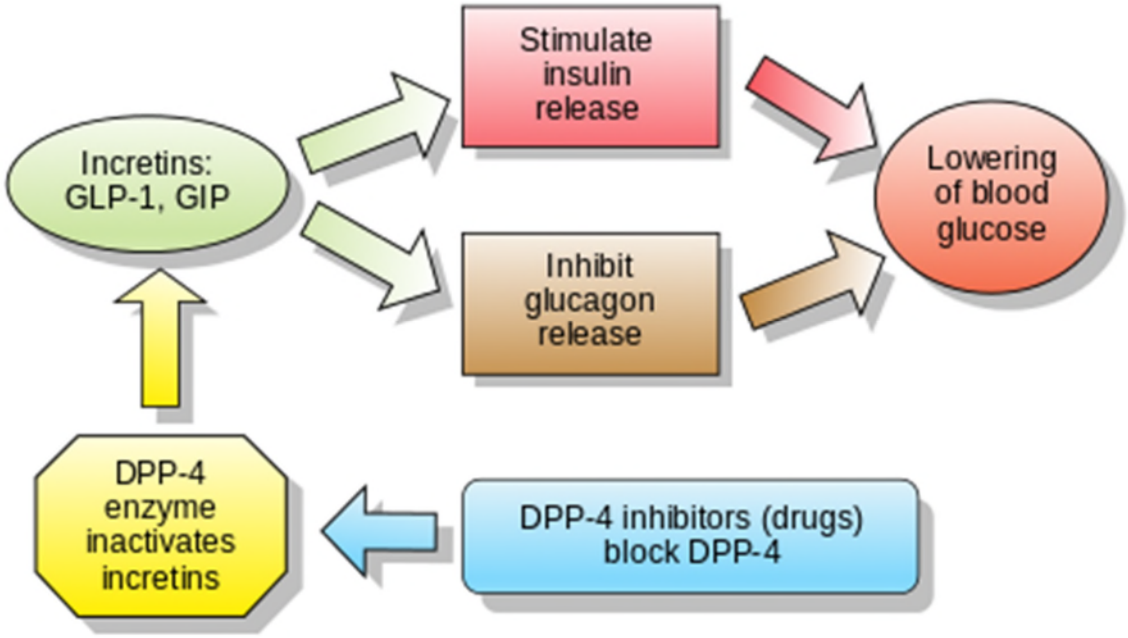


Fig. 2: Mechanism of Action of DPP-IV Inhibitors

As of May 4, 2006, the date of alleged invention, treating type II diabetes with DPP-IV Inhibitors was also well-known. (Ex. 1002 ¶ 29; *See e.g.*, '510 publication ¶ [0004], [0297]). The development of DPP-IV Inhibitors began in the 1970's after

the discovery of DPP IV in the 1960's as an amino peptidase. (Ex. 1002 ¶ 29; Ex. 1009, Demuth at 34). More than a year before the '927 patent's priority date, several DPP-IV Inhibitors, including sitagliptin and vildagliptin, were well-known treatments for type II diabetes. (Ex. 1002 at ¶ 29; *See e.g.*, Ex. 1006, Hughes at 12; Ex. 1005, Ahrén at 2874; Ex. 1007, Brazg at A3; Ex. 1014, Nielson at 708; Ex. 1009, Demuth at 40–41).

Moreover, as of the date of the alleged invention, linagliptin was also a known DPP-IV Inhibitor that was effective in treating type II diabetes. (Ex 1002 at ¶ 29; Ex. 1003, '510 Publication at ¶¶ [0004], [0245], and [0297]). In fact, linagliptin had been reported as more potent than the DPP-IV Inhibitors vildagliptin and sitagliptin. (Ex 1002 ¶ 29). Specifically, Gwaltney disclosed that vildagliptin and sitagliptin had higher IC_{50} values and therefore less potency than linagliptin. (Ex. 1011, Gwaltney at 158); (Ex. 1002 ¶ 29 (*comparing* Ex. 1003, '510 publication at ¶ [0295] *with* Ex. 1011, Gwaltney at 158)).

3. The Benefits of Combining DPP-IV Inhibitors With Metformin Were Well-Known.

Because type II diabetes is a progressive disease, patients who initially respond well to monotherapy often require increased dosages or combination therapy with other antidiabetic agents in order to maintain adequate glycemic control. (Ex. 1002 at ¶ 30; Ex. 1006, Hughes at 2; Ex. 1012, Chiasson at 989). It was well-known in the art that metformin was commonly combined with other

antidiabetic agents having separate and distinct mechanisms of action than metformin's mechanism of action used to treat type II diabetes, including insulin, sulfonylureas, thiazolidinediones, and DPP-IV Inhibitors. (Ex. 1002 at ¶ 30; Ex. 1015, Kirpichnikov at E-25; Ex. 1004, Glucophage Label at 6; Ex. 1006, Hughes at 12–13; Ex. 1005, Ahrén at 2874; Ex. 1007, Brazg at A3). For instance, taking advantage of these different mechanism of action, it had been demonstrated that metformin could be combined with the DPP-IV Inhibitors, vildagliptin and sitagliptin, with such combinations providing a significantly improved patient outcome than use of metformin or either DPP-IV Inhibitor alone. (Ex. 1002 at ¶ 30; Ex. 1006, Hughes at 32; Ex. 1005, Ahrén at 2874; Ex. 1007, Brazg at A3).

Moreover, the interactions between the two drug families—metformin and DPP-IV Inhibitors—were "known to be encouraging and mechanistically predictable." (Ex. 1002 at ¶ 31; Ex. 1010, Deacon at 1096; Ex. 1009, Demuth at 40). In fact, the combination of valine-pyrrolidide, another DPP-IV Inhibitor, and metformin even showed "synergistic" effects compared to either metformin or valine-pyrrolidide alone. (Ex. 1013, Yasuda at 614–15; Ex. 1002 at ¶ 31).

Finally, the specific combination therapy of linagliptin and metformin was taught in the '510 Publication. (Ex. 1002 at ¶ 33; Ex. 1003, '510 Publication at ¶ [0298]).

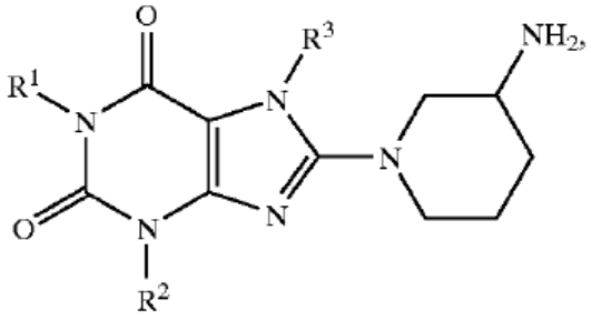
B. Ground 1: Claims 18–26 Are Anticipated Under 35 U.S.C. § 102(b) by the '510 Publication

The ’510 Publication (Ex. 1003) published on May 20, 2004, and is thus prior art to the ’927 patent under 35 U.S.C. § 102(b). This publication discloses each element recited in claims 18–26.

1. The ’510 Publication (Ex. 1003) Anticipates Independent Claims 18, 19, and 20

Independent claims 18–20 of the ’927 patent each contain four elements: (i) a method of treatment for type II diabetes comprising; (ii) administering to a patient in need thereof a pharmaceutically effective oral dose of linagliptin; (iii) a specific dose of linagliptin; and (iv) a pharmaceutically effective amount of metformin. (Ex. 1001, 24:58–64; Ex. 1002 at ¶ 13).

The ’510 Publication discloses orally administering a combination of metformin and the DDP-IV Inhibitor, linagliptin, as an effective combination therapy for treating type II diabetes, and thus anticipates independent claims 18–20. (Ex. 1003 at ¶ [0004], [0297], and [0298]; Ex. 1002 at ¶ 35). Table 1 below identifies for representative claim 18 where each respective element (*i.e.*, elements i–iv) for this claim is disclosed in the ’510 Publication.

Table 1	
Claim 18 of the '927 Patent	**The '510 Publication**
18[i] A method of treating type II diabetes mellitus comprising	Compounds with "an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV)" are useful "for the prevention or treatment of … type II diabetes mellitus." (Ex. 1003 at ¶ [0004]; Ex. 1002 at ¶ 35; *See also* Ex. 1003 at ¶ [0297] (explaining that the compounds disclosed therein can treat type II diabetes)).
[ii] administering to a patient in need thereof a pharmaceutically effective oral amount of 1-[(4-methyl-quinazolin-2-yl)-methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine ("linagliptin")	"The present invention relates to new substituted xanthines of general formula I:"  (Ex. 1002 ¶ 35; Ex. 1003 at ¶ [0003]). "Most particularly preferred are the following compounds of general formula I: "…1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-y1)-8-(3-(R)-amino-piperidin-1-y1)-xanthine" ("linagliptin"). (*Id*. at ¶ [0245]).

	The ’510 Publication discloses linagliptin, whose activity is also specified in Example 2(142). (Ex. 1003 at ¶ [0245], [0295]; Ex. 1002 at ¶ 35). The compounds of this publication are described as suitable for a medical use, namely, for the prevention and treatment of type II diabetes. Therefore, the ’510 Publication also discloses pharmaceutically effective oral doses of linagliptin. (Ex. 1002 ¶ 35; *see* Ex. 1003 at ¶ [0297] (“In view of their ability to inhibit DPP-IV activity, . . . [i]t is therefore expected that the compounds according to the invention … will be suitable for the prevention or treatment of diseases . . . such as . . . type 2 diabetes mellitus); ¶ [0300] (The dosage required to achieve such an effect […] by oral route [is][*sic*] 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day”); ¶ [0296] (“The compounds prepared according to the invention are well-tolerated. . ..”).
[iii] which is an oral daily dose of from 2.5 mg to 10 mg,	“The dosage required to achieve such an effect [. . .] by oral route [is][*sic*] 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day.” (Ex. 1003 at ¶ [0300]; Ex. 1002 at ¶ 35).

	As seen from this passage, the most preferable oral dosage range for linagliptin encompasses and thus anticipates the claimed dose recited in claim 18. *See Perricone v. Medicis Pharma. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005).
[iv] and a pharmaceutically effective amount of metformin.	"The compounds according to the invention may also be used in conjunction with other active substances. Therapeutic agents which are suitable for such combinations include, for example, antidiabetics, such as me[t]formin. . .." (Ex. 1003 at ¶ [0298]; Ex. 1002 at ¶ 35). A POSA would understand that the '510 Publication's reference to "metformin" refers to a "pharmaceutically" effective amount of metformin because the compound is described as being suitable for a medical use, namely, for combination therapy with DPP-IV inhibitors, including linagliptin, for the prevention and treatment of type II diabetes. (Ex. 1002 ¶ 35; *see* Ex. 1003 at ¶ [0297])

Claims 19 and 20 are similar to claim 18, but respectively limit the linagliptin dose to 5 mg and from 0.5 mg to 50 mg. (Ex. 1001, 24:58–25:3). Those claimed amounts are anticipated for the same reasons set forth in Table 1 above for claim 18(iii). (Ex. 1002 at ¶ 36). Claims 19 and 20 also require administering a

"therapeutically" effective amount of linagliptin and metformin. This limitation is anticipated because the '510 Publication discloses a pharmaceutically effective amount of linagliptin and metformin. (*See* Table 1, claim 18(ii) above). Prior to May 4, 2006, the POSA would have understood that a "therapeutically effective amount" refers to an amount sufficient to produce an intended biological response, and that such amount would include a "pharmaceutically effective amount" because administering an amount suitable for a medical use will elicit a biological response. (Ex. 1002 at ¶ 36).

Accordingly, claims 18–20 are anticipated by the '510 Publication and thus unpatentable under 35 U.S.C. 102(b). *See Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics Inc*., 976 F.2d 1559, 1565 (Fed. Cir.1992) (to establish anticipation a party "must show that each element of the claim in issue is found, either expressly or under principles of inherency, in a single prior art reference").

2. The '510 Publication Anticipates Dependent Claims 21–26

Claims 21–26 depend from claim 20. Each claim recites various oral doses of linagliptin for administering to the patient. (Ex. 1002 at ¶ 37; Ex. 1001, 25:13–26:18). Those amounts are subsets of the amounts recited in claim 20, as shown below in Table 2.

Table 2
Linagliptin Dose Limitation of Claims 21–26 of the '927 Patent
21. ". . . in an oral dosage of from 2.5 mg to 50 mg . . . ."
22. ". . . in an oral dosage of from 2.5 mg to 10 mg . . . ."
23. ". . . in an oral dosage of 0.5 mg, 1 mg, 2.5 mg, 5 mg, or 10 mg . . . ."
24. ". . . in an oral dosage of 1 mg, 2.5 mg, or 5 mg . . . ."
25. ". . . in an oral dosage of 2.5 mg or 5 mg . . . ."
26. ". . . in an oral daily dose of 5 mg . . . ."

The '510 Publication discloses each oral dose of linagliptin recited in claims 21–26. (*see* Ex. 1003 at ¶ [0300]; Ex. 1002 at ¶ 38). Thus, these claims are anticipated for the same reasons as set forth above with respect to claim 20. *See also* Table 1, claim 18(iii). (Ex. 1002 at ¶ 38). Accordingly, claims 21–26 are unpatentable under 35 U.S.C. 102(b).

C. Ground 2: Claims 1–26 Are Unpatentable Under 35 U.S.C. § 103(a) as Obvious over the '510 Publication and the Glucophage Label

1. '510 Publication (Ex. 1003)

Petitioner incorporates herein the discussion on the '510 Publication in support of Ground 1.

2. Glucophage Label (Ex. 1004)

The Final Printed Labeling for Glucophage® ("Glucophage Label") was approved and published by the U.S. Food and Drug Administration ("FDA") for treating type II diabetes in February 2001, and is therefore prior art to the '927 patent

under 35 U.S.C. § 102(b). (Ex. 1002 at ¶ 43).

Glucophage IR is a metformin hydrochloride immediate release tablet. (Ex. 1004, Glucophage Label at 2; Ex. 1002 at ¶ 44). Glucophage Label discloses a dosing schedule for Immediate-Release metformin monotherapy in the "Recommended Dosing Schedule" section:

> The usual starting dose of GLUCOPHAGE (metformin hydrochloride tablets) is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg per day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, GLUCOPHAGE may be given to a maximum daily dose of 2550 mg per day. Doses above 2000 mg may be better tolerated given three times a day with meals.

(Ex. 1004 at 6); Ex. 1002 at ¶ 44).

3. Claims 1–9

Claim 1 is directed to a method of treating type II diabetes by administering a pharmaceutically effective oral dose of linagliptin and a pharmaceutically effective amount of metformin from 300 mg to 1000 mg once or twice a day.[2] The '510

[2] Claims 1-9 also recite various amounts for delayed-release metformin. Those amounts, however, are not relevant to Ground 2.

Publication discloses administering an oral dose of linagliptin in combination with metformin as a treatment for patients with type II diabetes, as recited in claim 1. (Ex. 1002 at ¶ 45; *see supra* Table 1 at 18(i)-(iv)).

The '510 Publication does not disclose the claimed dosages of metformin combined with linagliptin. (Ex. 1002 at ¶ 46).

However, the Glucophage Label discloses the use of metformin in single oral dose of 500 mg to 1500 mg and 850 mg to 2550 mg. (Ex. 1004 at 2, 6; Ex. 1002 at ¶ 47). These standard metformin dosages disclosed in the Glucophage Label encompass the claimed metformin ranges recited in claim 1. (*Id*.).

Moreover, the metformin dosages disclosed in the Glucophage Label are pharmaceutically effective amounts because they are suitable for a medical use, namely to treat type II diabetes. A "therapeutically" effective amount would include a "pharmaceutically" effective amount. (Ex. 1002 at ¶ 48, 36).

A POSA would have been motivated to employ the known standard metformin dosages as taught in the Glucophage Label to the linagliptin/metformin combination discussed in the '510 Publication. (Ex. 1002 at ¶ 49). Indeed, a POSA would have understood that when metformin was used in combination with other known, less potent DPP-IV Inhibitors—sitagliptin and vildagliptin—to treat type II diabetes, the amounts of metformin used were substantially the same as the standard

monotherapy dosage disclosed in the Glucophage Label. (Ex. 1002 ¶ 49; Ex. 1006, Hughes at 24; Ex. 1005, Ahrén at 2874; Ex. 1007, Brazg at A3).

A POSA would have also had a reasonable expectation that administering standard monotherapy doses of metformin with oral doses of linagliptin would have been effective in treating type II diabetes, particularly given the '510 Publication's disclosure that metformin can be combined with DPP-IV Inhibitors, including linagliptin, to treat type II diabetes. (Ex. 1002 ¶ 50; Ex. 1003 at ¶ [0298]). In the end, the alleged invention simply includes use of two well-known drugs—metformin and DPP-IV Inhibitors (linagliptin)—performing the same function they have been known to perform (reducing blood glucose levels) and yielding no more than one would have expected from combining metformin with other, less potent DPP-IV Inhibitors—which were already known as effective combination therapies for treating type II diabetes and have the same mechanism of action as linagliptin. (Ex. 1002 ¶ 50).

Accordingly, the combination of DPP-IV Inhibitors (linagliptin) and metformin recited in claim 1 would have been obvious in view of the '510 Publication and the Glucophage Label. (Ex. 1002 ¶ 51).

Claims 2–9 depend from claim 1 and recite various oral linagliptin doses, as shown in Table 3 below.

Table 3

Linagliptin Dose Limitation of Claims 21–26 of the '927 Patent
2. ". . . in an oral daily dose of from 2.5 mg to 10 mg . . . ."
3. ". . . in an oral dosage of from 0.5 mg to 50 mg . . . ."
4. ". . . in an oral dosage of from 2.5 mg to 10 mg . . . ."
5. ". . . in an oral dosage of 0.5 mg, 1 mg, 2.5 mg, 5 mg or 10 mg . . . ."
6. ". . . in an oral dosage of 1 mg, 2.5 mg or 5 mg . . . ."
7. ". . . in an oral dosage of 2.5 mg or 5 mg . . . ."
8. ". . . in an oral dosage of from 2.5 mg to 50 mg . . . ."
9. ". . . in an oral dosage of 5 mg . . . ."

The '510 Publication specifically teaches: "such an effect . . . by oral route [is][*sic*] 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day." (Ex. 1003, '510 Publication at ¶ [0300]; Ex. 1002 at ¶ 53). In this passage from the '510 Publication, each of the claimed linagliptin dosages recited in claims 2–9 fall within the '510 Publication's most preferable oral dosage range for linagliptin. (Ex. 1002 at ¶ 53); *see Perricone v. Medicis Pharma. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). Thus, for the same reasons discussed for claim 1, claims 2–9 would have been obvious.

4. Claims 10–17

For the reasons claims 1–9 would have been obvious over the '510 Publication and the Glucophage Label, claims 10–17 would have likewise been obvious. (Ex. 1002 ¶ 53). Independent claims 1 and 10 are substantially the same. Both are directed to a method of treating type II diabetes by administering effective oral doses

of both linagliptin and metformin. Neither claim recites a specific linagliptin dose. However, the claims differ in terms of the recited amounts of metformin. Claim 10 recites the following amounts of metformin: "500 mg, 850 mg or 1000 mg metformin as a single dose with a total daily dose of metformin of 500–2850 mg." (Ex. 1001, 24:21–29). Claims 11–17 depend from claim 10, and each recites a particular linagliptin dose as shown in Table 4 below.

Table 4
Linagliptin Dose Limitation of Claims 11–17 of the '927 Patent
11. ". . . in an oral dosage of from 0.5 mg to 50 mg . . . ."
12. ". . . in an oral dosage of from 2.5 mg to 10 mg . . . ."
13. ". . . in an oral dosage of 0.5 mg, 1 mg, 2.5 mg, 5 mg or 10 mg."
14. ". . . in an oral dosage of 1 mg, 2.5 mg or 5 mg."
15. ". . . in an oral dosage of 2.5 mg or 5 mg."
16. ". . . in an oral dosage of from 2.5 mg to 50 mg."
17. ". . . in an oral daily dose of 5 mg."

The '510 Publication discloses a method of treating type II diabetes by administering an effective oral dose of linagliptin in combination with metformin, as recited in claim 10. (*See* Ex. 1003 at ¶ [0004], [0297], and [0298]; Ex. 1002 at ¶ 55). The '510 Publication also discloses the linagliptin oral doses recited in dependent claims 11–17 as follows: "The dosage required to achieve such an effect . . . by oral route [is][*sic*] 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day." (Ex. 1003 at ¶ [0300]; Ex. 1002 at ¶ 55). The '510 Publication's most

preferable oral dosage range for linagliptin encompasses each of the oral linagliptin doses recited in claims 11–17. (Ex. 1002 at ¶ 55).

The Glucophage label discloses the claimed metformin doses recited in claim 10. The Label specifically teaches that the "usual starting dose of [immediate release metformin] is 500 mg twice a day or 850 mg once a day, given with meals." (Ex. 1004, Glucophage Label at 6; Ex. 1002 at ¶ 56). The dose amounts of metformin specified in the Glucophage Label are considered the standard amounts of immediate release metformin for use in monotherapy when used to treat type II diabetes. (Ex. 1002, ¶ 56).

For the same reasons explained above with respect to claims 1–9, a POSA would have been motivated to employ the monotherapy immediate release doses of metformin, as taught in the Glucophage Label (Ex. 1004 at 6), with the linagliptin/metformin combinations disclosed in the '510 Publication, thus resulting in the alleged invention of claims 10–17. (Ex. 1002 at ¶ 57). In doing so, the POSA would have had a reasonable expectation of success in treating type II diabetes for the same reasons discussed above for claims 1–9. (Ex. 1002 at ¶ 57).

Accordingly, for the reasons discussed above for claims 1–9, claims 10–17 would also have been obvious in view of the '910 Publication and the Glucophage Label.

5. Independent Claims 18–20 and Dependent Claims 21–26

As discussed above in Ground 1 at *supra* B(1) and B(2), independent claims 18–20 and dependent claims 21–26 are anticipated by the '510 Publication. Should the Board finds that some or all of these claims are not anticipated, then the claims would have been obvious over the '510 Publication in view of the Glucophage Label for the same reasons discussed for Claim 1.

Claims 18–26 recite various amounts of oral linagliptin doses but do not recite a particular metformin dose. Rather, these claims recite only that "a pharmaceutically effective amount of metformin" or "a therapeutically effective dose of metformin" be administered to treat type II diabetes. (Ex. 1001, '927 Patent, 24:58–25:10).

The '510 Publication discloses the oral doses of linagliptin recited in claims 18–26. *See Table* 1, Claim 18(iii). The '510 Publication also teaches the use of metformin in combination with effective oral doses of DPP-IV Inhibitors, including linagliptin, for the prevention or treatment of type II diabetes. (Ex. 1003 at ¶ [0004], [0245], [0297], and [0300]; Ex. 1002 at ¶ 61). Because these doses are described as suitable for medical use (*i.e.*, treating type II diabetes), the POSA as of the date of the alleged invention would have considered such doses as "pharmaceutically effective" amounts. (Ex. 1002 at ¶ 61). The POSA would have also understood that a "therapeutically effective" amount would include a "pharmaceutically effective" amount, as the former is directed to an amount sufficient to produce an intended biological response. (*Id*. at ¶ 61).

The Glucophage Label similarly discloses a "pharmaceutically effective amount of metformin" because it is suitable for a medical use—treating type II diabetes. Such amount is also a "therapeutically" effective amount of metformin because it also elicits a biological response. (Ex. 1002 ¶ 62). It also discloses that these dosages can be administered as either monotherapy or combination therapy for the treatment of this disease. (*See, e.g.*, 1004 at 6 ("Concomitant GLUCOPHAGE or GLUCOPHAGE XR and Oral Sulfonylurea Therapy in Adult Patients"); Ex. 1002 at ¶ 62).

For the reasons discussed above for claim 1, the POSA would have been motivated to combine the '510 Publication's linagliptin/metformin combination with the known standard metformin doses disclosed in the Glucophage Label, thus arriving at the alleged claimed invention. In doing so, the POSA would have had a reasonable expectation of success in treating type II diabetes, for the same reasons discussed above for claim 1. (Ex. 1002 ¶ 63). Accordingly, claims 18–26 would have been obvious. (*Id.*).

D. Ground 3: Claims 1–26 Are Unpatentable Under 35 U.S.C. § 103(a) over the '510 Publication in view of Ahrén, Hughes, and/or Brazg

1. '510 Publication (Ex. 1003)

Petitioner incorporates herein the discussion on the '510 Publication in support of Ground 1.

2. Ahrén (Ex. 1005)

Ahrén was published in 2004, and is prior art to the '927 patent under 35 U.S.C. § 102(b). Ahrén discloses the effect of LAF237 (*i.e.*, vildagliptin) added to an ongoing stable dosage of metformin in patients with type II diabetes. (Ex. 1005, Ahrén at 2874–2875; Ex. 1002 at ¶ 64). Ahrén discloses a 12-week study result that compares two groups of patients with type II diabetes that were on a stable metformin monotherapy (1500 to 3000 mg per day), or metformin (1,500–3,000 mg per day) and vildagliptin (50 mg once per day) combination therapy. (Ex. 1005, Ahrén at 2874; Ex. 1002 at ¶ 64). Ahrén further discloses a 40-week extension of the 12-week study. (Ex. 1005, Ahrén at 2874; Ex. 1002 at ¶ 64).

The addition of LAG237 (vildagliptin) to an ongoing metformin treatment improved the glycemic control for at least 1 year in patients with type II diabetes and appeared to be well tolerated. (Ex. 1005, Ahrén at 2875–2878; Ex. 1002 at ¶ 65). Following 12 weeks of combination therapy of metformin and vildagliptin, the glycated hemoglobin ("HbA1c")[3] baseline level decreased by -0.6 ±0.1%. (Ex.

[3] The term "HbA1c" refers to glycated haemoglobin. 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.

1005, Ahrén at 2875; Ex. 1002 at ¶ 65). Treatment with metformin alone had no change from the baseline during the same time period. (Ex. 1005, Ahrén at 2875; Ex. 1002 at ¶ 65). In the 40-week extension study, the difference between the combination therapy and therapy with metformin alone in the HbA1c level was 1.1%. (Ex. 1005, Ahrén at 2875–2876; Ex. 1002 at ¶ 65). As shown in Figure 3 below, the metformin and LAF237 (vildagliptin) combination therapy showed a more significant and rapid reduction in the low glycosylated hemoglobin (HbA1c) level, compared to the metformin monotherapy. (Ex. 1005, Ahrén at 2876–2877; Ex. 1002 at ¶ 65).

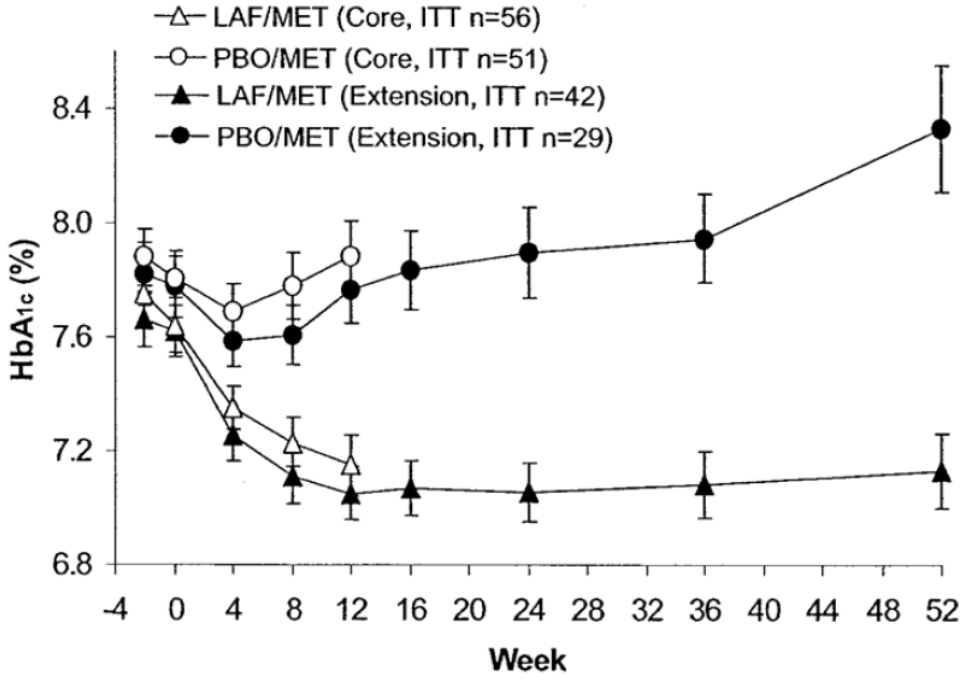


Fig. 3: (Ex. 1005, Ahrén at 2876)

Furthermore, the mean glucose levels were significantly reduced in patients

receiving the LAF237 (vildagliptin) and metformin combination therapy than metformin monotherapy. (Ex. 1005, Ahrén at 2877–2878; Ex. 1002 at ¶ 66). The overall incidence of adverse events was similar in both therapies. (Ex. 1005, Ahrén at 2878; Ex. 1002 at ¶ 66). Thus, Ahrén shows the effectiveness of combining DPP-IV Inhibitors with metformin in treating type II diabetes. (Ex. 1005, Ahrén at 2878; Ex. 1002 at ¶ 66).

3. Hughes (Ex. 1006)

International Patent Application Publication No. WO 2005/117861 to Thomas E. Hughes ("Hughes") (Ex. 1006), entitled "Use of Organic Compounds," published on December 15, 2005 and is prior art to the '927 patent under 35 U.S.C. § 102(a).

Hughes discloses a method of treating patients with type II diabetes using a DPP-IV Inhibitor and metformin over an extended period of time. (Ex. 1006 at 2–3; Ex. 1002 at ¶ 68). Specifically, Hughes teaches the advantages of using the combination of metformin and the DPP-IV Inhibitor vildagliptin for treating diabetes. (Ex. 1006 at 12; Ex. 1002 at ¶ 68). It also teaches that metformin is administered at a daily dosage of from about 50 mg to about 3000 mg, preferably from about 500 mg to about 2000 mg, using 500 mg tablets that are commercially available. (Ex. 1006 at 22; Ex. 1002 at ¶ 68).

Hughes discloses a clinical study with vildagliptin and metformin and reports that the combination of these two diabetes drugs achieved better clinical results

compared to the metformin plus placebo treatment. (Ex. 1006 at 24–32; Ex. 1002 at ¶ 69). It also discloses that this drug combination can effectively maintain low glucose levels or low glycosylated hemoglobin (HbA1c) levels in diabetes patients over an extended period of time. (Ex. 1006 at 2–3; Ex. 1002 at ¶ 69).

4. Brazg (Ex. 1007)

Brazg was published on June 14, 2005 and is therefore prior art to the '927 patent under 35 U.S.C. §§ 102(a). (Ex. 1007). Brazg discloses the efficacy of the combination of DPP-IV Inhibitor, MK-0431 (*i.e.*, sitagliptin) with ongoing metformin therapy in type II diabetes mellitus patients. (Ex. 1007 at A3; Ex. 1002 at ¶ 70). Brazg notes that "[m]etformin is a commonly used first-line antihyperglycemic agent." (Ex. 1007 at A3; Ex. 1002 at ¶ 70). Brazg states that "[c]ombination treatment with MK-0431 [sitagliptin] and metformin may be useful since these agents target different pathophysiologic process leading to hyperglycemia in [type II diabetes]." (Ex. 1007 at A3; Ex. 1002 at ¶ 70).

Brazg discloses the following clinical trial data that compares metformin monotherapy with combining metformin with sitagliptin:

Table 5: Comparison of metformin monotherapy to metformin administered with a DPP-IV Inhibitor.

Parameter	Metformin + Placebo	Metformin + MK-0431 50 mg b.i.d.	Difference in LS means	P value
24-hr WMG* (mg/dl)	157.9	125.0	-32.9	< 0.001
Change in FPG** (mg/dl)	-3.4	-23.8	-20.3	< 0.001

*WMG = weighted mean glucose, **FPG = Fasting Plasma Glucose

(Ex. 1007 at A3; Ex. 1002 at ¶ 71). Patients with inadequate glycemic control on metformin monotherapy were recruited for the testing. (Ex. 1007 at A3; Ex. 1002 at ¶ 72). As shown in Table 5 above, when metformin was administered as a monotherapy, the fasting plasma glucose level was only decreased by 3.4 mg/dL from mean baseline. (Ex. 1007 at A3; Ex. 1002 at ¶ 72). In contrast, when metformin was administered in combination with sitagliptin, the fasting plasma glucose level was decreased by 23.8 mg/dL from mean baseline. (Ex. 1007 at A3; Ex. 1002 at ¶ 72). Thus, the clinical testing result disclosed in Brazg shows greater efficacy with combination therapy over metformin monotherapy. (Ex. 1007 at A3; Ex. 1002 at ¶ 72). Brazg further discloses that "the combination of MK-0431 [sitagliptin] and metformin was efficacious and generally well-tolerated as a treatment regimen for patients with [type II diabetes]." (Ex. 1007 at A3; Ex. 1002 at ¶ 72).

5. Independent Claims 1 and 10

Independent claims 1 and 10 would have been obvious over the '510 Publication in view of Ahrén, Hughes, and/or Brazg. Claim 1 is directed to a method of treating type II diabetes by administering a pharmaceutically effective oral dose of linagliptin and a pharmaceutically effective amount of metformin from 300 mg to 1000 mg once or twice a day. Claim 10 recites the following amounts of metformin: "500 mg, 850 mg or 1000 mg metformin as a single dose with a total daily dose of

metformin of 500–2850 mg." (Ex. 1001, 24:21–29; Ex. 1002 ¶ 73;).

The '510 Publication discloses the combination of metformin and the recited oral doses of a DPP-IV Inhibitor (linagliptin) in claims 1 and 10. And, Ahrén, Hughes, and Brazg each disclose a standard monotherapy dose of a DPP-IV Inhibitor (sitagliptin or vildagliptin) in combination with the metformin dosages recited in claims 1 and 10. (Ex. 1003, '510 Publication ¶ [0298]; Ex 1005, Ahrén at 2874; Ex. 1006, Hughes at 22; Ex. 1002 ¶ 74; Ex. 1007, Brazg at A3). For instance, Ahrén discloses treatment with a standard monotherapy dose of metformin (1,500–3,000 mg per day) in combination with a standard monotherapy dose of vildagliptin (50 mg per day). (Ex. 1002 ¶ 74; Ex 1005, Ahrén at 2874). Hughes discloses administering a standard monotherapy dose of metformin (preferably from about 500 mg to about 2000 mg) in combination with vildagliptin. (Ex. 1002 ¶ 74; Ex. 1006, Hughes at 22). Likewise, Brazg discloses administering a standard monotherapy dose of metformin (≥1500 mg per day) in combination with sitagliptin. (Ex. 1002 ¶ 74; Brazg at A3).

Also, Ahrén, Hughes, and Brazg each meet the recited limitation requiring "a "pharmaceutically effective" amount of metformin because the metformin doses used in these studies were suitable for a medical use, *i.e.*, treating type II diabetes. Likewise with respect to claim 10, Ahrén, Hughes, and Brazg meet the recited limitation of a "therapeutically effective" amount of metformin. (Ex 1005, Ahrén at

2874; Ex. 1006, Hughes at 22). As mentioned, a "therapeutically effective" amount includes a "pharmaceutically effective" amount. (Ex. 1002 ¶ 75).

Ahrén, Hughes, and Brazg also disclose that administering metformin in combination with DPP-IV Inhibitors—vildagliptin and sitagliptin—is more effective in treating type II diabetes than administering metformin alone. (Ex. 1002 at ¶ 76; Ex. 1006, Hughes at 12–13; Ex. 1005, Ahrén at 2874; Ex. 1007, Brazg at A3). Specifically, Ahrén discloses that LAF237 (vildagliptin) and metformin combination therapy showed a more significant and rapid reduction in the HbA1c level (*i.e.*, blood glucose levels) compared to the metformin monotherapy. (Ex. 1005, Ahrén at 2876–2877; Ex. 1002 at ¶ 76). Hughes similarly discloses that the combination of vildagliptin and metformin achieved better clinical results compared to metformin therapy alone. (Ex. 1006, Hughes at 32; Ex. 1002 at ¶ 76). Brazg discloses that combination therapy with MK-0431 (sitagliptin) and metformin provides greater efficacy than metformin monotherapy.[4] (Ex. 1007, Brazg at A3; Ex. 1002 at ¶ 76).

[4] Moreover, Yasuda discloses that the combination of valine-pyrrolidide, a DPP-IV inhibitor, and metformin showed "synergistic" inhibitive effects compared to either metformin or valine-pyrrolidide alone. (Ex. 1013, Yasuda at 614-15; Ex. 1002 at ¶ 77).

The POSA, at the time of the alleged invention, would have been motivated to substitute the linagliptin oral doses disclosed in the '510 Publication for either vildagliptin and/or sitagliptin for use in combination with the metformin doses used in Ahrén, Hughes, and Brazg to treat type II diabetes, thus arriving at the alleged invention of claims 1 and 10. (Ex. 1002 ¶ 78).

The motivation to make this substitution is compelling. (Ex. 1002 ¶ 79). First, combining linagliptin and metformin to treat type II diabetes was disclosed in the '510 Publication. (*Id.*). Second, on May 4, 2006, the '510 Publication reported, among other things, that linagliptin was a potent DPP-IV Inhibitor, which can be combined with metformin for the treatment of type II diabetes. (*Id.*). Third, the '510 Publication reports that linagliptin is more potent than vildagliptin and more potent than sitagliptin. (Ex. 1002 ¶ 33, 79; Ex. 1003, compare '510 Publication at ¶ [0295] (disclosing linagliptin's IC50 value of 1nM) with Ex. 1011 at 158, Gwaltney (disclosing IC50 value 18nM for sitagliptin)). Fourth, Linagliptin's purported higher potency would have potentially allowed for smaller doses of DPP-IV inhibitor to be administered to the patient. (Ex. 1002 ¶ 79, 33).

Fifth, the known combinations of vildagliptin/metformin and sitagliptin/metformin (Ahrén, Hughes, and Brazg) were already known as effective therapies for treating type II diabetes. (*Id.* at ¶ 80). Sixth, the POSA understood that combining metformin with a DPP-IV Inhibitor resulted in higher reduction in blood

glucose level than using metformin alone. (*Id.*). Seventh, this increased efficacy can be attributed to the fact that metformin uses a different mechanism of action than DPP-IV Inhibitors, including linagliptin. (*Id.*).

Therefore, the prior art, discussed above, together with the knowledge of a POSA as of May 4, 2006, would have provided a significant incentive to substitute the oral administrations of linagliptin (the '510 Publication) for vildagliptin or sitagliptin, in combination with the metformin doses used in Ahrén, Hughes, and/or Brazg and thus arrive at the methods of claims 1 and 2. (Ex. 1002 ¶ 81).

The POSA would also have had a reasonable expectation of success; the expectation would have been that a combination of linagliptin and metformin would have been at least as effective as the known combinations disclosed in Ahrén, Hughes, and/or Brazg, particularly given that linagliptin is more potent than vildagliptin and sitagliptin, as reported in the '510 Publication, and coupled with the fact that linagliptin has the same mechanism of action as vildagliptin and sitagliptin. (Ex. 1002 ¶ 82).

Thus, independent claims 1 and 10 would have been obvious over the '510 Publication in view Ahrén, Hughes, and/or Brazg. (*Id*. at ¶ 83).

6. Dependent Claims 2–9 and 11–17

Dependent claims 2–9 depend from claim 1 and present further limitations on the oral dose of linagliptin to be administered to the patient. As discussed above in

each of Grounds 1 and 2, each of the recited doses or dosage ranges are disclosed in the '510 Publication as shown in Table 1, claim 18(iii) *supra*. Thus, claims 2–9 would have been obvious for the same reasons claims 1 and 10 would have been obvious, as discussed above. (Ex. 1002 ¶ 84).

Dependent claims 11–17 depend from claim 10 and present further limitations on the oral dose of linagliptin to be administered to the patient. As discussed above in each of Grounds 1 and 2, each of the recited doses are disclosed in the '510 Publication as show in Table 1, Claim 18(iii) *supra*. (Ex. 1002 ¶ 85). Thus, claims 11–17 would have been obvious for the same reasons claims 1 and 10 are obvious, as discussed above. (*Id*.).

7. Independent Claims 18–20 and Dependent Claims 21–26

Neither independent claims 18–20 nor dependent claims 21–26 recite a particular dosage range for metformin. The claims require only that "a pharmaceutically effective amount of metformin" or "a therapeutically effective dose of metformin" be administered. (Ex. 1001, '927 Patent, 24:58–25:10). Thus, for the reasons discussed above for claim 18, *see* Table 1, 18(ii)–(iii), each element of claims 18–20 and 21–26 are disclosed in the '510 Publication. (Ex. 1002 ¶ 86). Further, the amounts disclosed in the '510 Publication are "pharmaceutically effective." (Ex. 1002 ¶ 86). And, therapeutically effective" amounts include "pharmaceutically effective" amounts. (*Id.*). Thus, claims 18–20 and 21–26 would have been obvious

for the same reasons claims 1 and 10 are obvious, as discussed above. (*Id.*).

E. Objective Indicia of Nonobviousness

Patentee bears the burden of proof in establishing objective indicia of nonobviousness. To date, Patentee has not come forward with any objective indicia of nonobviousness. To the extent Patentee does assert any objective evidence of non-obviousness 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].

Petitioner notes that, during prosecution of the '927 patent, the Patentee, alleged that the claimed dosages of linagliptin in combination with metformin produced unexpected results. (Ex. 1016 at 9). Specifically, Patentee alleged that the combination of 2.5 mg of linagliptin twice daily and either 500 mg or 1000 mg of metformin twice daily yielded a larger reduction in blood glucose levels than metformin or linagliptin alone. (*Id.*). While the claims were allowed for reasons unrelated to Patentee's allegation of unexpected results, Petitioner addresses the allegation as follows.

Patentee is incorrect that it would have been surprising or unexpected that the combination of linagliptin and metformin would be more effective in treating type II diabetes than linagliptin or metformin alone. (Ex. 1002 ¶ 88). Indeed, the benefit

of combining DPP-IV Inhibitors with metformin over DPP-IV Inhibitor or metformin alone was disclosed in the prior art. (*Id.*). For example, Brazg discloses that combination therapy with MK-0431 (sitagliptin) and metformin provides greater efficacy than metformin monotherapy. (Ex. 1007, Brazg at A3; Ex. 1002 ¶ 88). Similarly, Ahrén discloses that LAF237 (vildagliptin) and metformin combination therapy showed a more significant and rapid reduction in the HbA1c level compared to metformin monotherapy. (Ex. 1005, Ahrén at 2876–77; Ex. 1002 ¶ 88). Likewise, Hughes discloses that the combination of vildagliptin and metformin achieved better clinical results compared to metformin therapy alone. (Ex. 1006, Hughes at 32; Ex. 1002 ¶ 88).

Thus, as of the date of the alleged invention, the POSA would have understood that treatment with the combination of a DPP-IV Inhibitor with metformin would yield a larger reduction in blood glucose levels than treatment with metformin or the DPP-IV Inhibitor alone. (Ex. 1002 ¶ 89). This is because, in part, metformin and DPP-IV Inhibitors use different mechanisms of action to lower blood glucose levels. (*Id*.). Given the prior art, a POSA would have expected at least the same reduction in blood glucose levels for linagliptin. (*Id*.). Accordingly, Patentee's argument in the prosecution history concerning unexpected results is wrong. (*Id*.).

X. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that claims

1–26 of the ’927 patent are unpatentable as anticipated and 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

Thomas J. Parker (Reg. No. 42,062)
thomas.parker@alston.com
ALSTON & BIRD LLP
90 Park Avenue, 15th Floor
New York, NY 10016
T: (212) 210-9529
F: (212) 210-9444

Lead Counsel for Petitioner

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. 8,673,927, Power of Attorney, and all supporting exhibits were served via U.S.P.S. Priority Mail Express to the Patent Owner by serving the correspondence address of record for the '927 patent:

Michael P. Morris
Boehringer Ingelheim USA Corporation
900 Ridgebury Road
P. O. Box 368
Ridgefield, CT 06877- 0368

Respectfully submitted,

Thomas J. Parker (Reg. No. 42,062)
thomas.parker@alston.com
ALSTON & BIRD LLP
90 Park Avenue, 15th Floor
New York, NY 10016
T: (212) 210-9529
F: (212) 210-9444

Counsel for Mylan Pharmaceuticals Inc.