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. 8,846,695 to Dugi
Issue Date: Sept. 30, 2014
Title: Treatment for Diabetes in Patients
with Inadequate Glycemic Control
Despite Metformin Therapy Comprising a DPP-IV Inhibitor

Inter Partes Review No.: IPR2016-01564

Petition for *Inter Partes* Review of U.S. Patent No. 8,846,695 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. 8,846,695, "Treatment for Diabetes in Patients with Inadequate Glycemic Control Despite Metformin Therapy Comprising a DPP-IV Inhibitor"
1002	Declaration of Mayer B. Davidson, M.D.
1003	Dugi *et al*., U.S. Patent Publication No. 2007/0281940, "Uses of DPP-IV Inhibitors" (the "'940 Publication")
1004	Charbonnel *et al.*, "Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Added to Ongoing Metformin Therapy in Patients With Type 2 Diabetes Inadequately Controlled with Metformin Alone," Diabetes Care, 29:2638-2643 (2006) ("Charbonnel")
1005	Hughes, International Patent No. WO 2005/117861, "Use of Organic Compounds" ("Hughes")
1006	Nauck *et al*., "Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial Diabetes," Obesity and Metabolism, 9:194-205 (2007) ("Nauck")
1007	Janumet® (sitagliptin and metformin HCL tablets) Prescribing Information (rev. 2/2008) ("Janumet")
1008	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 2004")
1009	Curriculum Vitae of Mayer B. Davidson, M.D.
1010	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")
1011	Kohlrausch *et al.*, U.S. Patent Publication No. 2008/0107731, "DPP IV Inhibitor Formulations" (the "'731 Publication")
1012	Himmelsbach *et al.*, U.S. Patent Publication No. 2004/0097510, "8-[3-amino-piperidin-1-yl]-xanthines, the preparation thereof and

Mylan Exhibit #	***Description***
	their use as pharmaceutical compositions" (the "'510 Publication")
1013	EMEA guidelines on Galvus® (2007) ("EMEA Galvus")
1014	Elrishi *et al.*, "The dipeptidyl-peptidase-4 (DPP-4) inhibitors: a new class of oral therapy for patients with type 2 diabetes mellitus," 24 Practical Diabetes Int. 9:474–82 (2007) ("Elrishi")
1015	Pei, "From the bench to the bedside: Dipeptidyl peptidase IV Inhibitors, a new class of oral antihyperglycemic agents," Current 11 Opinion in Drug Discovery & Development 4:512-32 (2008) ("Pei")
1016	EMEA guidelines on Eucreas® (2007) ("EMEA Eucreas")
1017	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")
1018	Gwaltney *et al*., "Inhibitors of Dipeptidyl Peptidase 4," Annual Reports in Medicinal Chemistry, 40:149–165 (December 2005) ("Gwaltney")
1019	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 Diabestes Association, Chicago IL (June 22–25, 2007) ("Huettner")
1020	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")
1021	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")
1022	Ahrén *et al.*, "Novel combination treatment of type 2 diabetes DPP-4 inhibition + metformin," Vascular Health and Risk Management, 4(2):383–394 (2008) ("Ahrén 2008")

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 1–4 of U.S. Patent No. 8,846,695 (the "'695 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

Claims 1–4 of the '695 patent (the "Challenged Claims") are directed to methods for treating type II diabetes in a patient who, despite receiving metformin therapy, has inadequate glycemic control. The methods comprise administering to the patient a combination of linagliptin and metformin. At the time of the alleged invention, both linagliptin and metformin were known to treat type II diabetes, alone or in combination.

Metformin is the most commonly prescribed oral agent for the treatment of type II diabetes. Over time, however, metformin therapy can become less and less effective, leading to progressive loss of glycemic control in a patient, despite continued metformin treatment.

Linagliptin is a dipeptidyl peptidase 4 inhibitor ("DPP-IV Inhibitor"). Like metformin, DPP-IV Inhibitors (*e.g.*, linagliptin, vildagliptin, and sitagliptin) had been shown to be effective in treating type II diabetes, albeit via a separate

mechanism of action.

Because DPP-IV Inhibitors treat type II diabetes through a different mechanism of action than metformin, it was known that DPP-IV Inhibitors were effective in treating type II diabetes even in circumstances when metformin monotherapy was unable to achieve adequate glycemic control.

Indeed, the prior art indisputably establishes the existence, efficacy, and safety of using either of two DPP-IV Inhibitors (vildagliptin and sitagliptin) to treat type II diabetes in those patients who cannot maintain adequate glycemic control despite treatment with metformin alone.

Prior to the alleged invention, the DPP-IV Inhibitor, linagliptin had been shown to be an especially potent and long lasting DPP-IV Inhibitor—more potent and longer-lasting than the other well-known DPP-IV Inhibitors, vildagliptin and sitagliptin. Moreover, linagliptin was also known to be used in conjunction with metformin to treat type II diabetes.

Further, nothing is unique or inventive about the claimed dosages of linagliptin. In the ’695 patent, the claims require that linagliptin be administered in its standard monotherapy dosage—which was well-known and used in the prior art. The same is true of the prior art combinations of other known DPP-IV Inhibitors (vildagliptin and sitagliptin) when combined with metformin. There, both vildagliptin and sitagliptin were each administered in their standard monotherapy

dosages. Accordingly, as of the date of the alleged invention, it would have been obvious to a person of ordinary skill in the art ("POSA") to substitute linagliptin for one of the other two known DPP-IV Inhibitors—vildagliptin and sitagliptin—in combination with metformin to treat type II diabetes patients who cannot maintain adequate glycemic control with metformin alone. Not only would such a POSA have had a reasonable expectation of success, the POSA would have expected that a combination of linagliptin and metformin would have been better than the known combinations of vildagliptin with metformin and sitagliptin with metformin. The superior potency and long-lasting efficacy of linagliptin relative to the other DPP-IV Inhibitors vildagliptin and sitagliptin, both having the same mechanism of action as linagliptin, would have been a significant incentive to make the substitution and arrive at the methods now claimed in the '695 patent.

Accordingly, the Patent Owner in this case has no more right to withdraw from the public domain the claimed use of a combination of linagliptin and metformin than did the patent owner in *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346 (Fed. Cir. 2013). There, as here, "the closest prior art . . . was combination therapy" using a small class of drugs that were "well known in the art to produce beneficial and even synergistic results" when combined with metformin. *Id.* at 1351. There, as here, the patentee merely substituted one of the drugs in the prior art combination—known to have been successfully utilized for the claimed

use—with a newer, more potent, and longer-lasting drug that was "known as . . . having a similar mechanism of action." *Id.* at 1355.

Likewise, in *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476 (Fed. Cir. 1997), the prior art included similar "combinations" of pseudoephedrine with aspirin and pseudoephedrine with acetaminophen, and the patentee had claimed the combination of pseudoephedrine with ibuprofen. There, the Federal Circuit held that even "substantial evidence" of "unexpected results" could "not overcome the . . . evidence that the subject matter sought to be patented is obvious." *Id.* at 1484.

In this case, where the combinations of vildagliptin/metformin and sitagliptin/metformin were well known, substituting linagliptin, which would utilize the same claimed use as vildagliptin or sitagliptin, as the drug to be combined with metformin is not patentable. *See e.g., Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 335 (1945). The claimed invention is simply a combination of known type II diabetes treatments using known ranges, used for their known purpose to achieve a predictable result.

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

Petitioner certifies that (1) the '695 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '695 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 deposit 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 '695 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 have filed concurrently with this Petition, Petitions for *inter partes* review of the following: U.S. Patent Nos. 9,173,859; 8,673,927; 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 1–4. Petitioner's full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '695 PATENT

The '695 patent, entitled "Treatment for diabetes in patients with inadequate glycemic control despite metformin therapy comprising a DPP-IV inhibitor," issued on September 30, 2014. The '695 patent issued from U.S. patent application 13/143,370, which is the national stage application of PCT/EP2010/050103, filed January 7, 2010, and claims priority to EP application 09150159 (filed January 7, 2009). According to records at the U.S. Patent and Trademark Office, the '695 patent is assigned to Boehringer Ingelheim International GmbH.

The Challenged Claims of the '695 patent are directed to methods of treating type II diabetes in a patient with inadequate glycemic control despite therapy with

metformin using a DPP-IV Inhibitor, 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine ("linagliptin"). (Ex. 1001, Abstract, 27:5–25). The '695 patent has two independent claims, claims 1 and 2.

Independent claim 1 is directed to a method for treating type II diabetes in a patient with inadequate glycemic control despite therapy with metformin, comprising orally administering linagliptin to a patient in an amount of 5 mg per day in combination with metformin. (Ex. 1001, 27:5–10).

Independent claim 2 is directed to a method for treating type II diabetes in a patient with inadequate glycemic control despite therapy with metformin, comprising orally administering linagliptin to a patient in an amount of 5 mg per day as add-on combination with metformin. (Ex. 1001, 27:11–17).

Dependent claims 3 and 4 recite different dosing frequencies of linagliptin—5 mg once daily and 2.5 mg twice daily, respectively. (Ex. 1001, 27:18–25)

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 '695 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), and a current copy of Dr. Davidson's curriculum vitae is submitted herewith as Exhibit 1009. Dr. Davidson is currently a Professor of Medicine at both the David Geffen School of Medicine at UCLA and Charles Drew University. (Ex. 1009 at 2–3). He is board certified in Internal Medicine. (*Id*. at 2). He is also board certified in the subspecialty of Diabetes, Endocrinology, and Metabolism. (*Id*.). Dr. Davidson has been practicing in the field of diabetes, endocrinology, and metabolism for 50 years. (*Id*. at 1–2).

During his career, Dr. Davidson focused his practice on the diagnosis and treatment of diabetes. (Ex. 1009). He served as President of the American Diabetes Association from 1997–1998. (*Id*. at 6). He has conducted considerable research on diabetes and spoken on diabetes both nationally and internationally. (Ex. 1009). 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 the Editor-in-Chief of *Diabetes Care,* the leading diabetes clinical journal in the world, from 2002 to 2006. (*Id*.). He has also written 168 scientific papers, 31 book chapters, and numerous reviews and editorials as well as three complete books on diabetes. (Ex. 1009). In 2016, the American Diabetes

Association presented him with their *Outstanding Physician Clinician Award in Diabetes*. Dr. Davidson's declaration explains what the art would have conveyed to a POSA as of January 7, 2009. (Ex. 1002).

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). 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. (Ex. 1002 ¶ 11). 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. (*Id*. at ¶ 11). A person of ordinary skill in the art would also preferably have some experience investigating pharmaceutical compositions for treating diabetes and diabetes-related disorders. (*Id*. at ¶ 11). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and in Dr. Davidson's Declaration, and would have the capability to draw inferences from them. (*Id*. at ¶ 13).

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

IPR of claims 1–4 of the '695 patent is respectfully requested on the specific grounds of unpatentability outlined below. Per 37 C.F.R. § 42.6(c), copies of the references are filed herewith.

Ground	References	Basis	Claims Challenged
1	Charbonnel or Hughes in view of the '940 Publication	103	1–4
2	Janumet, Nauck, or Ahrén 2008 in view of the '940 Publication	103	1–4

Copies of prior art references, in addition to the primary references listed above, are filed herewith 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.

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 ¶ 20). 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

It was well known that metformin, a "first line" treatment for type II diabetes that has been used worldwide for many years, works by decreasing the amount of glucose made by the liver and increasing the amount of glucose absorbed into body tissues. (Ex. 1002 ¶ 21). 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), long-acting form (*e.g.*, Glucophage XR in 2000), among other forms. (*Id.* at ¶ 21). Figure 1 below illustrates generally how metformin reduces blood glucose levels in type II diabetes patients.

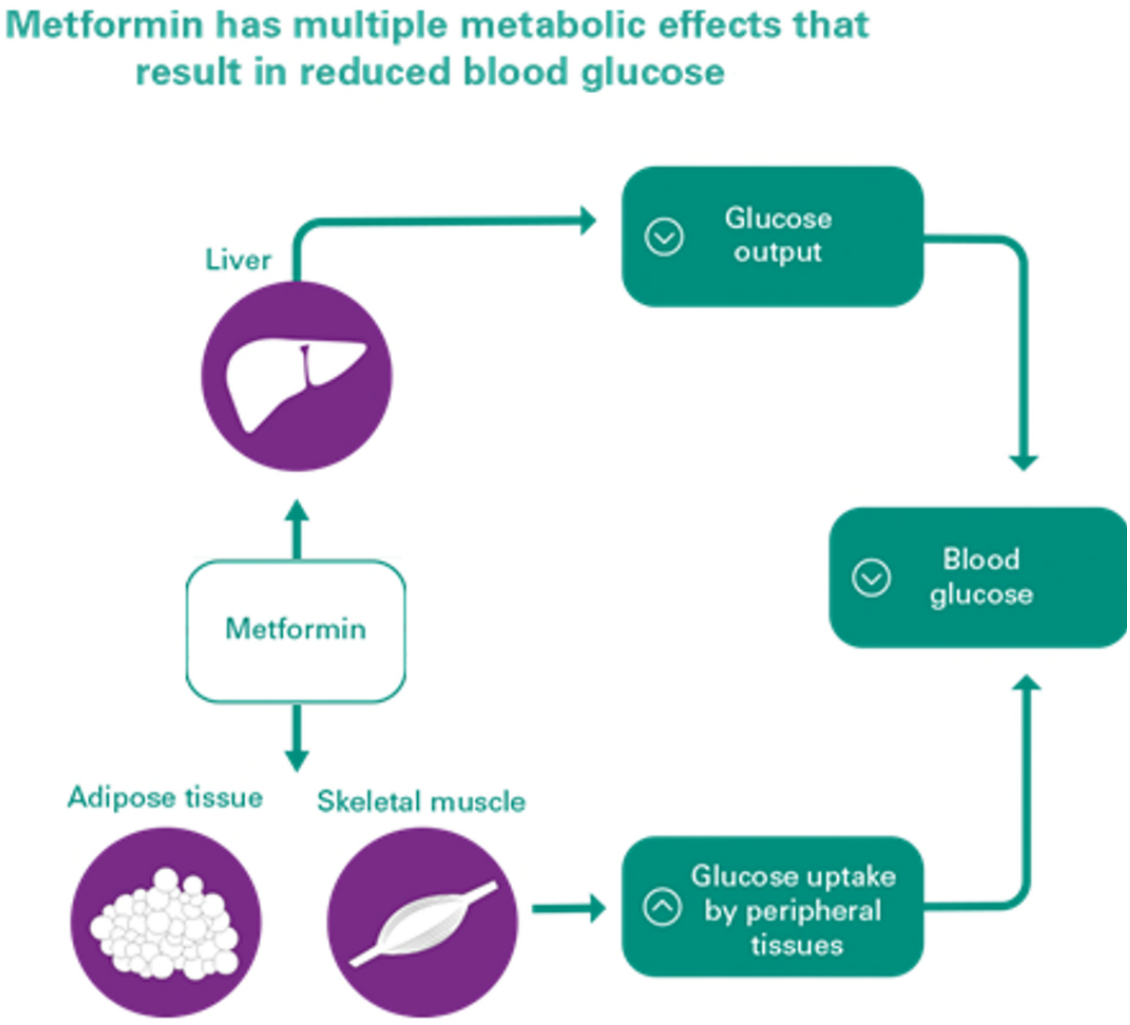

Fig. 1: Metformin's Mechanism of Action. (Ex. 1002 ¶ 21).

2. DPP-IV Inhibitors

DPP-IV Inhibitors have also been commonly used to treat type II diabetes patients. (Ex. 1002 ¶ 22). These drugs were first approved for the treatment of type

II diabetes in 2006. (*Id*.). DPP-IV Inhibitors have a completely different mechanism of action as compared to metformin. (*Id*.). 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.

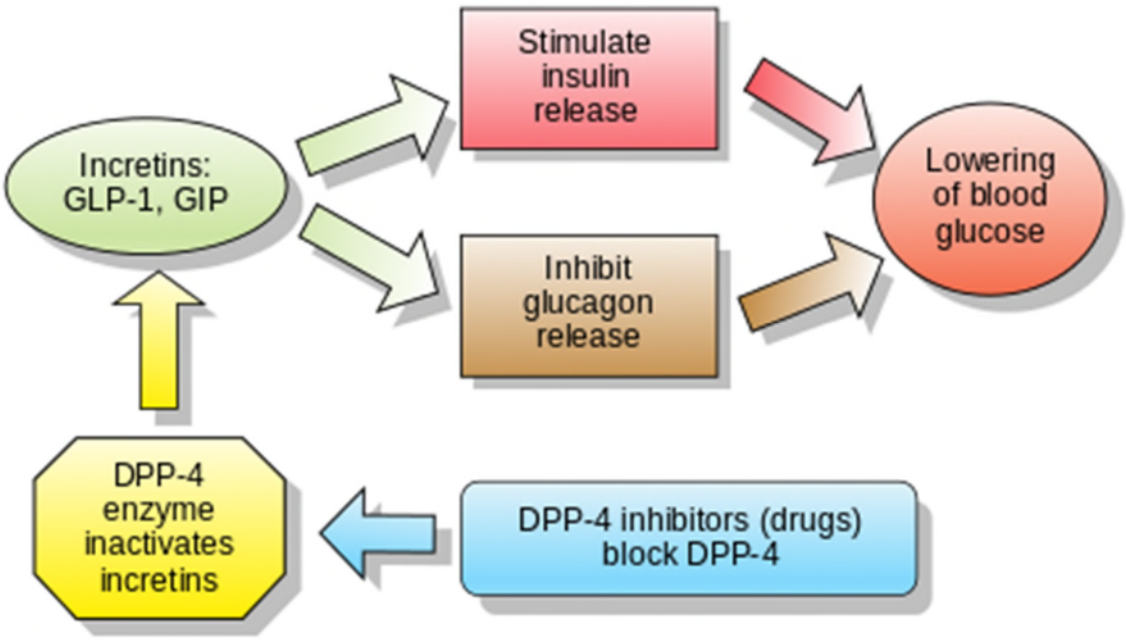

Fig. 2: Mechanism of Action of DPP-IV Inhibitors (Ex. 1002 ¶ 22)

A POSA would have recognized that metformin and linagliptin would work well concomitantly because they accomplish lowering of blood sugar via different physiologic pathways. (Ex. 1002 ¶ 23; Ex. 1010, Brazg at Abstract 11-OR).

3. The Combination of DPP-IV Inhibitors, Specifically Linagliptin, was Known in the Art

The combination of metformin and DPP-IV Inhibitors, such as linagliptin to treat type II diabetes was known in the art. (Ex. 1003, '940 Publication, ¶¶ [0032], [0060]–[0061], [0091]; Ex. 1012, '510 Publication [245], [298]; Ex. 1002 ¶ 24). Selection of linagliptin over other known DPP-IV Inhibitors—vildagliptin and sitagliptin—would have been an obvious choice for the POSA because of linagliptin's superior properties. Specifically, prior to the alleged invention, it was known that linagliptin (also known as BI 1356), was a "longer-lasting," "preferred," "potent," and "selective DPP-IV inhibitor." (Ex. 1002 ¶ 24; '940 Publication, ¶ [0044]; Ex. 1021, Thomas; Ex. 1011, '731 Publication ¶¶ [0021]–[0022]; Ex. 1017, Heise). In fact, linagliptin was known to be an even longer-lasting and potent DPP-IV Inhibitor than sitagliptin and vildagliptin. (Ex. 1021, Thomas ("BI 1356 can be preclinically differentiated from vildagliptin and sitagliptin by a longer-lasting inhibition of plasma DPP-IV activity and a longer lasting improvement of glucose tolerance at the same doses"); Ex. 1003, '940 Publication at [0032], [0044] (showing that linagliptin has "exceptional potency and a long-lasting effect with favourable pharmacological properties, receptor selectivity and a favourable side-effect profile

or bring about unexpected therapeutic advantages or improvements when combined with other pharmaceutical active substances"); Ex. 1002 at 25). In addition, it was known prior to the alleged date of invention that 2.5 mg and 5 mg were effective dosages for linagliptin. (Ex. 1019, Huettner at Abstract; *see also* Ex. 1020, Dugi 2006 (disclosing 5 mg as an effective dose); Ex. 1002 ¶ 26).

It was also well recognized that the combination of a DPP-IV Inhibitor with metformin was especially useful because each drug utilizes a different mechanism of action. (Ex. 1010, Brazg at Abstract 11-OR ("Combination treatment with [sitagliptin] and metformin may be useful since these agents target different pathophysiolic processes leading to hyperglycemia in [type II diabetes]."); Ex. 1008, Ahrén 2004, at 2874, 2878–9 ("LAF237 [vildagliptin] effectively prevents deterioration of glycemic control when added to metformin monotherapy in type 2 diabetes."); *see also* Ex. 1004, Charbonnel at 2638 (DPP-IV Inhibitor "Sitagliptin 100 mg once-daily added to ongoing metformin therapy was efficacious and well-tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone."); Ex. 1002 ¶ 27).

4. The Benefits of Administering DPP-IV Inhibitors with Metformin in Type II Diabetes Patients with Inadequate Glycemic Control Despite Therapy with Metformin Were Well-Known

It was also well known that combinations of metformin with other diabetes drugs, including DPP-IV Inhibitors, such as sitagliptin and vildaglipitin, were used

in addition to metformin when metformin alone provided insufficient glycemic control for a patient. (Ex. 1002 ¶ 28; Ex. 1001, 2:35–40; 2:66–3:7; Ex. 1006, Nauck at 194, 203; Ex. 1013, EMEA Galvus at 1, 33; Ex. 1016, EMEA Eucreas at 1, 26–7; Ex. 1007, Janumet at 1; Ex. 1014, Elrishi at 475–8; Ex. 1015, Pei at 526–8; Ex. 1005, Hughes at 2–3, 13, 22–23). For example, DPP-IV Inhibitor vildaglipitin "prevents deterioration of glycemic control when added to metformin monotherapy in type 2 diabetes." (Ex. 1008, Ahrén 2004, 2874; *see also* Ex. 1002 ¶ 28; Ex. 1005 Hughes at 2–3, 13, 22–23). Likewise, DPP-IV Inhibitor "[s]itagliptin 100mg once-daily added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone." (Ex. 1004, Charbonnel at 2638; *see also* Ex. 1002 ¶ 28; Ex. 1006, Nauck at 194, 203).

B. Ground 1: Claims 1–4 Are Unpatentable Under 35 U.S.C. § 103(a) as Obvious Over Charbonnel or Hughes in View of the '940 Publication

For Ground 1, Petitioner relies on the teachings of Charbonnel (Ex. 1004) or Hughes (Ex. 1005) in view of the '940 Publication (Ex. 1003).

1. Charbonnel (Ex. 1004)

Charbonnel was published in 2006, and is prior art with respect to the '695 patent under 35 U.S.C. § 102(b). Charbonnel discloses the evaluation of the efficacy and safety of the DPP-IV Inhibitor, sitagliptin, added to ongoing metformin therapy

in patients with type II diabetes that suffer from inadequate glycemic control with metformin alone. (Ex. 1004, Charbonnel at 2638; Ex. 1002 ¶ 33). For example, Charbonnel teaches:

> Sitagliptin 100 mg once-daily added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone.

(Ex. 1004, Charbonnel at 2638).

Charbonnel discloses that combining oral doses of sitagliptin with metformin is advantageous "[b]ecause sitagliptin and metformin target potentially complementary pathways." (*Id.*). "[T]he addition of sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin monotherapy may provide improved glycemic control." (*Id.*). Charbonnel further discloses that metformin is often unsuccessful in achieving glycemic control in patients with type II diabetes and many patients require combination therapy. (*Id*. at 2638, 2642–3; Ex. 1002 ¶ 36).

Charbonnel discloses that HbA1C [1] and other relevant responses were sustained during a 24-week treatment period and "[n]early half of the patients

[1] The terms "HbA1c" and "A1c" refer to glycated haemoglobin. By measuring 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/months. (Ex. 1002 ¶ 37).

receiving sitagliptin 100 mg once-daily achieved the current American Diabetes Association glycemic goal of A1C ≤ 7% compared with less than one-fifth of placebo treated patients." (Ex. 1004, Charbonnel at 2642; Ex. 1002 ¶ 36). Charbonnel further discloses that "Sitagliptin 100 mg was well tolerated in this clinical trial" without any "meaningful differences in the overall incidence of clinical adverse experiences." (*Id*. at 2643). "The addition of sitagliptin to ongoing metformin therapy did not lead to an increase in the incidence of gastrointestinal side effects, which are typically associated with metformin treatment alone." (Ex. 1002 ¶ 38).

Charbonnel concludes that "in patients with type 2 diabetes who had inadequate glycemic control with metformin alone, the addition of [oral doses of] sitagliptin 100 mg once-daily was well tolerated and provided effective and sustained improvement" in various measures related to the treatment of type II diabetes (Ex. 1004, Charbonnel at 2643, 2638; Ex. 1002 ¶ 39).

2. Hughes (Ex. 1005)

Hughes published December 15, 2005 and is prior art with respect to the '695 patent under 35 U.S.C. § 102(b).

Hughes teaches that a problem with single-agent therapy for maintaining glycemic control, including metformin, is that it eventually fails to maintain adequate glycemic control over time. (Ex. 1005, Hughes at 2; Ex. 1002 ¶ 41).

Hughes discloses that this limitation may be overcome by combining multiple oral drugs to achieve reductions in blood glucose that cannot be sustained during long-term therapy with single agents. (Ex. 1005, Hughes at 2; Ex. 1002 ¶ 41). Hughes teaches that it was known to add a DPP-IV Inhibitor to the standard diabetes treatment in patients whose disease was not adequately controlled by metformin alone (Ex. 1005 at 2–3, 13; Ex. 1002 ¶ 42). Hughes also teaches that oral doses of DPP-IV Inhibitors such as LAF237 (*i.e.*, vildagliptin) can be administered in doses from about 1 to 100 mg daily. (Ex. 1005 at 22; Ex. 1002 ¶ 42).

3. The '940 Publication (Ex. 1003)

The '940 Publication published December 6, 2007 and is prior art with respect to the '695 patent under 35 U.S.C. § 102(b).

The '940 Publication states that DPP-IV Inhibitors are useful for treating patients diagnosed with disorders including type II diabetes. (*E.g.*, Ex. 1003 ¶¶ [0025]–[0026], [0076]–[0078]; Ex. 1002 ¶ 44). In the '940 Publication linagliptin is listed first among a list of 12 "particularly preferred" DPP-IV Inhibitors. (Ex. 1003 ¶¶ [0031], [0032], and [0046]; Ex. 1002 ¶ 44).

The '940 Publication teaches that the disclosed DPP-IV Inhibitors are especially potent, effective, long-lasting, and bring about "unexpected therapeutic advantages or improvements when combined with other" pharmaceuticals. (Ex. 1003 ¶ [0044]; Ex. 1002 ¶ 45.). Specifically, the '940 Publication discloses DPP-IV

Inhibitors in combination with other active substances including metformin. (Ex. 1003 ¶¶ [0060], [0061], [0068], and [0091]; Ex. 1002 ¶45). In particular, the '940 Publication discloses that a particularly preferred example of an antidiabetic combination partner with DPP-IV Inhibitors is metformin "in doses of about 100 mg to 500 mg or 200 mg to 850 mg (1–3 times a day), or about 300 mg to 1000 mg once or twice a day, or delayed-release metformin in doses of about 100 mg to 1000 mg or preferably 500 mg to 1000 mg once or twice a day or about 500 mg to 2000 mg once a day." (Ex. 1003 ¶ [0068]; Ex. 1002 ¶ 45).

The '940 Publication also teaches that the combination of DPP-IV Inhibitors and metformin is better than administration of metformin alone. (*E.g.*, Ex. 1003 ¶ [0091]; Ex. 1002 ¶ 46). The '940 Publication refers to combinations of DPP-IV Inhibitors with metformin as being "particularly preferred." (Ex. 1003 ¶ [0068]; Ex. 1002 ¶ 46).

The '940 Publication teaches oral administration of the DPP-IV Inhibitor in amounts of 0.5–100 mg, preferably 2.5–50 mg, administered 1–4 times a day. (Ex. 1003 ¶ [0046]; Ex. 1002 ¶ 47). This is more precisely taught in Example 11, which discloses oral tablets comprising DPP-IV Inhibitor dosages of 0.500 mg, 1.000 mg, 2.500 mg, 5.000 mg, and 10.000 mg. (Ex. 1003, Table in paragraph ¶ [0088]; Ex. 1002 ¶ 47).

Example 13 of the '940 Publication is particularly relevant. It is directed to

treating type II diabetes with a DPP-IV Inhibitor and metformin. (Ex. 1003 ¶ [0091]; Ex. 1002 ¶ 48). Example 13 reads in part:

> Combined Treatment with DPP-IV Inhibitor--Metformin
>
> [0091] For treating type 2 diabetes . . . a therapeutically effective dose of the DPP IV inhibitor (e.g. a dose of between 0.1 and 100 mg) may be combined with different doses of metformin, e.g. with 500 mg, 850 mg or 1000 mg metformin as a single dose with a total daily dose of metformin of 500-2850 mg, or with 500 mg, 1000 mg, 1500 mg, or 2000 mg metformin in delayed-release form . . . . Evidence that the combination is appropriate and effective can be found in the fact that the combination of a DPP-IV inhibitor with metformin leads to a significantly greater reduction in the fasting glucose and/or non-fasting glucose and/or the HbA1c value than either the DPP IV inhibitor alone or metformin alone.

(Ex. 1003 ¶ [0091]).

4. Independent Claims 1 and 2

Independent claim 1 of the '695 patent recites the following:

> A method for treating type 2 diabetes mellitus in a patient with inadequate glycemic control despite therapy with metformin, said method comprising orally administering [linagliptin] to said patient in an amount of 5 mg per day in combination with metformin.

(Ex. 1001 at 27:5–10). Independent claim 2 provides:

> A method for treating type 2 diabetes mellitus in a patient with inadequate glycemic control despite therapy with metformin, said

> method comprising orally administering [linagliptin] to said patient in an amount of 5 mg per day as add-on combination with metformin.

(Ex. 1001 at 27:11–17).

Charbonnel discloses that the DPP-IV Inhibitor sitagliptin was effective in treating type II diabetes when added to the ongoing metformin therapy for patients with inadequate glycemic control with metformin alone. (Ex. 1004, Charbonnel at 2638, 2642-3; Ex. 1002 ¶ 51). Likewise, Hughes discloses that the DPP-IV Inhibitor LAF237 (vildagliptin) was effective in treating type II diabetes when added to the ongoing metformin therapy for patients with inadequate glycemic control with metformin alone. (Ex. 1005, Hughes at 2–3, 13; Ex. 1002 ¶ 52).

The ’940 Publication discloses a method for treating type II diabetes by administering an oral dose of a DPP-IV Inhibitor, including linagliptin, and metformin. (Ex. 1003, ¶¶ [0025], [0031], [0032], [0046]; Ex. 1002 ¶ 53). Specifically, the ’940 Publication lists oral administration of linagliptin first among 12 “particularly preferred” DPP IV inhibitors (Ex. 1003 ¶¶ [0031], [0032], [0044], [0046]; Ex. 1002 ¶ 53) in combination with other substances, including metformin (Ex. 1003 ¶¶ [0060], [0061], [0068], and [0091]; Ex. 1002 ¶ 53). The ’940 Publication also teaches that the disclosed DPP-IV Inhibitors are especially potent, effective, long-lasting, and bring about “unexpected therapeutic advantages and improvement when combined with other” pharmaceuticals, including metformin.

(*Id*. at ¶ [0044], [0031], [0032], [0060], [0061], [0068], and [0091]; Ex. 1002 ¶ 53). The '940 Publication further teaches that "the combination of a DPP-IV Inhibitor with metformin leads to a significantly greater reduction in the fasting glucose and/or non-fasting glucose and/or the HbA1c value than either the DPP IV inhibitor alone or metformin alone." (Ex. 1003 ¶ [0091]; Ex. 1002 ¶ 53).

The '940 Publication discloses orally administering 5 mg of a DPP-IV Inhibitor, which includes linagliptin. (*See, e.g.*, Ex. 1003, '940 Publication at [0088]; Ex. 1002 ¶ 54).

Accordingly, a POSA seeking to treat a type II diabetes patient unable to maintain adequate glycemic control, despite treatment with metformin, would have been motivated by the prior art to substitute the oral administration of linagliptin ('940 Publication, Ex. 1003) for the orally administered DPP-IV Inhibitors sitagliptin (Charbonnel, Ex. 1004) or vildagliptin (Hughes, Ex. 1005). (Ex. 1002 ¶ 55).

The motivation to make this substitution is compelling. At the time of the alleged invention, the '940 Publication disclosed, among other things, that linagliptin was a longer-lasting and particularly preferred DPP-IV Inhibitor for combination therapy with metformin. (Ex. 1003 at ¶ [0044]; *see also* Ex. 1021, Thomas). The known combinations of vildagliptin with metformin (Ex. 1004, Charbonnel at 2638, 2642–3) and sitagliptin with metformin (Ex. 1005, Hughes at

2–3, 13) were already well-known to improve glycemic control in a patient with inadequate glycemic control despite metformin therapy. (Ex. 1002 ¶ 56). These teachings, together with the knowledge of a POSA, would have provided a significant incentive to substitute the oral administration of linagliptin for vildagliptin or sitagliptin, in combination with metformin, or as an add-on combination with metformin, and thus arrive at the methods of claims 1 and 2. (Ex. 1002 ¶ 56).

The POSA would also have had a reasonable expectation of success that a combination of linagliptin and metformin would have been at least as effective as the known combination disclosed in Charbonnel or Hughes, particularly in light of the properties of linagliptin, as disclosed in the '940 Publication, and the fact that linagliptin has the same mechanism of action as vildagliptin and sitagliptin. (Ex. 1002 ¶ 57). Moreover, the POSA would have reasonably expected that co-administering 5 mg of linagliptin each day in combination with metformin or as an add-on combination with metformin as taught by the '940 Publication, (Ex. 1003 ¶¶ [0031], [0032], [0046], [0060], [0061], [0068], [0091]; Ex. 1002 ¶ 57) would be an effective method for treating type II diabetes patients for whom metformin therapy alone was inadequate to control their glycemic blood levels, as accomplished with the DPP-IV Inhibitors, vildgliptin and sitagliptin when either drug is combined with metformin. (Ex. 1002 ¶ 57). Therefore, claims 1 and 2 would have been obvious

and are thus unpatentable.

5. Dependent Claims 3 and 4

Claims 3 and 4 depend from claim 1, and further require administering linagliptin, wherein the linagliptin is in an amount of 5 mg once daily or in an amount of 2.5 mg twice daily, respectively. (Ex. 1001 at 27:18–25).

The '940 Publication teaches that one of the recommended oral dosages of linagliptin for the treatment of type II diabetes is 5 mg per day. (Ex. 1003, '940 Publication ¶¶ [0046], [0088]; Ex. 1002 ¶ 58). The '940 Publication also teaches orally administering 2.5 mg of linagliptin twice daily, yielding a total amount of 5 mg per day, for the treatment of type II diabetes. (Ex. 1003, '940 Publication ¶¶ [0046], [0088]; Ex. 1002 ¶ 59).

Moreover, optimizing the dosing amount and frequency of dosing would have been a matter of routine experimentation for a person of ordinary skill in the art. *In re Applied Materials*, 692 F.3d at 1295 (*quoting Application of Aller*, 220 F.2d at 456) ("'[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'"); *see also Hoffmann-La Roche*, 496 F. App'x at 50 (affirming a finding of obvious based, in part, on expert testimony that "once one chooses a particular treatment agent and a particular dosing time interval, determining a dose within the broad therapeutic range is a relatively routine matter").

Accordingly, for the same reasons discussed above for claims 1 and 2, claims 3 and 4 would have been obvious and thus unpatentable. (Ex. 1002 ¶¶ 58–59).

C. Ground 2: Claims 1–4 Are Unpatentable Under 35 U.S.C. § 103(a) Over the Janumet Label, Nauck, or Ahrén 2008 in View of the '940 Publication

For Ground 2, Petitioner relies on the teachings of Janumet, Nauck, and Ahrén 2008 in view of the '940 Publication.

1. The '940 Publication (Ex. 1003)

Petitioner references herein the discussion on the '940 Publication in support of Ground 1.

2. Janumet Label (Ex. 1007)

The label for Janumet® discloses a fixed-dose combination product comprising sitagliptin (another DPP-IV Inhibitor) and metformin. (Ex. 1002 ¶ 60). The Janumet Label published in February 2008, and is prior art with respect to the '695 patent under 35 U.S.C. § 102(a). The Janumet Label states that sitagliptin add-on therapy was efficacious in achieving glycemic control in patients not adequately controlled on metformin alone:

> Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone
>
> A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study to assess the efficacy of sitagliptin in combination with metformin. Patients already

> on metformin . . . In combination with metformin, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG [*i.e.*, blood glucose levels] compared to placebo with metformin.

(Ex. 1007, Janumet Label, at section 14; Ex. 1002 ¶ 61).

3. Nauck (Ex. 1006)

Nauck published in 2007, and is prior art with respect to the '695 patent under, at least, 35 U.S.C. § 102(b). Nauck discloses a clinical study in which patients with type II diabetes with inadequate control despite metformin monotherapy, were randomized to the addition of either sitagliptin or glipizide. (Ex. 1006; Ex. 1002 ¶ 62).

Nauck explains that metformin is the most commonly prescribed oral antihyperglycaemic agent, but that defective β-cell function "continues to deteriorate over time in patients with type 2 diabetes, leading to progressive failure of insulin secretion." (Ex. 1006 at 194-195; Ex. 1002 ¶ 63). According to Nauck, "[t]his progressive loss of β-cell function may explain why many patients who initially achieve glycaemic control [using metformin] fail to maintain control at levels consistent with current guidelines [e.g. haemoglobin A1c (HbA1c) < 7 or <6.5%] and hence require additional therapies" (Ex. 1006 at 195; Ex. 1002 ¶ 63). Nauck states that sulfonylureas are the typical next drug for addition to ongoing metformin therapy. (*Id*.). However, suflonylureas "are associated with hypoglycaemia because of continued stimulation of insulin secretion with falling glucose concentrations."

(*Id.*). According to Nauck, "[a]n agent that can provide efficacy similar to a sulfonylurea but with a better safety profile could provide a useful alternative" for type II diabetes patients incapable of maintaining adequate glycemic control, despite therapy with metformin. (*Id*.).

Nauck describes sitaglipin as a possible additive therapy to ongoing metformin treatment. Nauck states that "[s]itagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a novel treatment for type 2 diabetes that improves glycaemic control through a new mechanism, enhancement of the incretin axis . . . ." (*Id*.). According to Nauck, "[i]n prior clinical studies, sitagliptin added to ongoing metformin monotherapy significantly improved fasting and postprandial glycaemic control and measures of β-cell function in patients with type 2 diabetes." (*Id*.).

Nauck concludes that the DPP-IV Inhibitor sitagliptin is effective and comparable to glipizide when added to the regimen of patients with type II diabetes who have inadequate response to metformin monotherapy. (Ex. 1006 at 201-203; Ex. 1002 ¶ 65).

4. Ahrén 2008 (Ex. 1022)

Ahrén 2008 published in April 2008 and is prior art with respect to the '695 patent under, at least, 35 U.S.C. § 102(a). Ahrén 2008 discloses that metformin is a first line of treatment for diabetes which acts by lowering blood glucose primarily through inhibiting hepatic glucose output. (Ex. 1022, Ahrén 2008 at 383; Ex. 1002

¶ 66). However, Ahrén 2008 discloses that metformin alone is often insufficient, and add-on combination therapy (adding a secondary compound to metformin) is required as the disease progresses. (Ex. 1022 at 384; Ex. 1002 ¶ 66).

Ahrén 2008 discloses that selecting a combination of DPP-IV Inhibitor and metformin is advantageous because the separate components act through complementary mechanisms in treating type II diabetes. (Ex. 1022 at 385; Ex. 1002 ¶ 67). Ahrén 2008 further discloses that "metformin acts primarily by reducing hepatic glucose output and improving insulin sensitivity in liver and muscle whereas DPP-4 inhibitors act by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagon secretion." (*Id*.). "The two strategies therefore have the potential to improve different mechanisms, which are defective in type 2 diabetes and therefore an additive or synergistic action when used in combination is anticipated." (*Id*.).

Ahrén 2008 discloses two studies of add-on therapy with metformin: (i) vildagliptin (50mg daily) or placebo in combination with metformin (1.5 g–3 g daily) for a 52-week trial; and (ii) sitagliptin (100 mg once daily) or placebo in combination with metformin (>1.5 g daily) for 24 weeks. (Ex. 1022 385–388; Ex. 1002 ¶ 68). Ahrén 2008 discloses that the studies conducted suggest the combination of the DPP-IV Inhibitor (*i.e.*, vildagliptin or sitagliptin) along with metformin was more effective than metformin administered alone. (Ex. 1022 at 388; Ex. 1002 ¶ 68).

Ahrén 2008 further discloses that the combination was safe and well tolerated in both instances. (Ex. 1022 at 386-388 Ex. 1002 ¶ 68).

Ahrén 2008 also discloses a study where the combination of sitagliptin (50 mg) and metformin (1000 mg) is given twice daily for over a 24 week period as an initial treatment for diabetes. (*Id*. at 388–9). Ahrén 2008 discloses that the combination therapy produced an additive effect of improved glycemic control, as measured by reduction in fasting glucose and HbA1c level, over metformin monotherapy. (Ex. 1022 at 389; Ex. 1002 ¶ 69). The combination was well tolerated and safe over the 24 week period (Ex. 1022 at 389–390; Ex. 1002 ¶ 69).

Ahrén 2008 concludes that DPP-IV inhibition through monotherapy or combination with metformin is "efficient, highly tolerable and safe with a minimal risk for hypoglycemic events" (Ex. 1022 at 392; Ex. 1002 ¶ 70). "A promising place in therapy for DPP-4 inhibition is in combination with metformin," which "has been demonstrated in large studies with vildagliptin and sitagliptin, since these studies have shown that HbA1c is reduced by 0.65%–1.1% from baseline levels of 7.8%–8.4% in studies up to 52 weeks." (*Id*.). Ahrén 2008 further notes that "[t]his improvement in glycemic control is similar as in studies with sulphonylureas, thiazolidinediones or exenatide when added to metformin treatment," and that "DPP-4 inhibition in combination with metformin is safe and tolerable." (*Id*.). Ahrén 2008 further concludes that it is "a major indication for treatment with DPP-

4 inhibition as add-on to metformin in subjects inadequately controlled with metformin and as first-line treatment in initial combination therapy with metformin." (*Id*.).

5. Independent Claims 1 and 2

Independent claim 1 of the '695 patent recites the following:

> A method for treating type 2 diabetes mellitus in a patient with inadequate glycemic control despite therapy with metformin, said method comprising orally administering [linagliptin] to said patient in an amount of 5 mg per day in combination with metformin.

(Ex. 1001 at 27:5–10). Independent claim 2 provides:

> A method for treating type 2 diabetes mellitus in a patient with inadequate glycemic control despite therapy with metformin, said method comprising orally administering [linagliptin] to said patient in an amount of 5 mg per day as add-on combination with metformin.

(Ex. 1001 at 27:11–17).

The Janumet Label states that sitagliptin add-on therapy was efficacious in achieving glycemic control in patients not adequately controlled on metformin alone. (Ex. 1007, Janumet, Section 14; Ex. 1002 ¶ 71). Likewise, Nauck concludes that the DPP-IV Inhibitor sitagliptin is effective when added to the regimen of patients with type II diabetes who have inadequate response to metformin monotherapy. (Ex. 1006, Nauck at 201–203; Ex. 1002 ¶ 71).

Further, Ahrén 2008 discloses the two studies involving DPP-IV Inhibitors

vildagliptin and sitagliptin: (1) as add-on therapy to metformin; and (2) as initial combination therapy with metformin. (Ex. 1022 at 385–390; Ex. 1002 ¶ 72). Ahrén 2008 further concludes that it is "a major indication for treatment with DPP-4 inhibition as add-on to metformin in subjects inadequately controlled with metformin and as first-line treatment in initial combination therapy with metformin." (*Id*. at 392; Ex. 1002 ¶ 72).

The '940 Publication discloses a method for treating type II diabetes by administering a DPP-IV Inhibitor, including linagliptin, and metformin. (Ex. 1003 ¶¶ [0025], [0031], [0032], [0044], [0046], [0060], [0061], [0068], and [0091]; Ex. 1002 ¶ 73). The '940 Publication reports that the disclosed DPP-IV Inhibitors are especially long-lasting and bring about "unexpected therapeutic advantages and improvements when combined with other" pharmaceuticals, including metformin. (*Id.* at ¶ [0044]; Ex. 1002 ¶ 73). The '940 Publication also discloses that the combination of a DPP-IV Inhibitor with metformin leads to a significantly improved treatment of type II diabetes and greater reduction in blood glucose than either the DPP IV inhibitor alone or metformin alone. (Ex. 1003, '940 Publication ¶ [0091]; Ex. 1002 ¶ 73). In addition, the '940 Publication discloses orally administering 5mg of the DPP-IV Inhibitor, which includes linagliptin. (*See, e.g.*, Ex. 1003, '940 Publication ¶ [0088]; Ex. 1002 ¶ 73).

Accordingly, a POSA seeking to treat a type II diabetes patient who is unable

to maintain adequate glycemic control, despite receiving treatment with metformin would have been motivated by the prior art to substitute the oral administration of linagliptin ('940 Publication) for the orally administered DPP-IV Inhibitors—sitagliptin or vildagliptin—in the Janumet Label, Nauck or Ahrén 2008. (Ex. 1002 ¶ 77). The motivation to make this substitution is compelling. (*See e.g*,, Ex. 1003, '940 Publication ¶ [0044]; Ex. 1002 ¶ 77).

At the time of the alleged invention, the '940 Publication disclosed, among other things, that linagliptin was a longer-lasting and particularly preferred DPP-IV Inhibitor for combination therapy with metformin. (*Id*. at [0025], [0031], [0032], [0044], [0046], [0060], [0061], [0068], and [0091]; Ex. 1002 ¶ 78). The known combinations of vildagliptin with metformin (Charbonnel, Ex. 1004) and sitagliptin with metformin (Hughes, Ex. 1005) were already well-known to improve glycemic control in a patient with inadequate glycemic control despite metformin therapy. (Ex. 1002 ¶ 78). These teachings, together with the knowledge of a POSA, would have provided a significant incentive to substitute the oral administration of linagliptin for vildagliptin or sitagliptin, in combination with metformin, or as an add-on combination with metformin, and thus arrive at the methods of claims 1 and 2. (*Id*.)

The POSA would also have had a reasonable expectation of success that a combination of linagliptin and metformin would have been at least as effective as

the known combination disclosed in Charbonnel or Hughes, particularly in light of the properties of linagliptin, as disclosed in the '940 Publication, and the fact that linagliptin has the same mechanism of action as vildagliptin and sitagliptin. (Ex. 1002 ¶ 79). Moreover, the POSA would have had a reasonable expectation that co-administering 5 mg of linagliptin each day in combination with metformin or as an add-on combination with metformin as taught by the '940 Publication (Ex. 1003 ¶¶ [0060], [0061], [0068], [0046], [0088], and [0091]) would be an effective method for treating type II diabetes patients for whom metformin therapy alone was inadequate to control their glycemic blood levels, as accomplished with the DPP-IV Inhibitors, vildagliptin and sitagliptin when either drug is combined with metformin, particularly in light of the positive attributes of linagliptin, together with the successful vildagliptin and sitagliptin therapies employed by the Janumet Label, Nauck, and Ahrén 2008. (Ex. 1002 ¶ 79). Accordingly, Claims 1 and 2 would have been obvious and thus unpatentable. (*Id*.)

6. Dependent Claims 3 and 4

Claims 3 and 4 depend from claim 1, and further require administering linagliptin, wherein the linagliptin is in an amount of 5 mg once daily or in an amount of 2.5 mg twice daily, respectively. (Ex. 1001 at 27:18–25).

The '940 Publication teaches that one of the recommended oral dosages of linagliptin for the treatment of type II diabetes is 5 mg per day. (Ex. 1003 at ¶ [0046],

[0088]; Ex. 1002 ¶ 80). The prior art '940 Publication also teaches administering about 2.5 mg linagliptin twice daily, yielding a total amount of 5 mg linagliptin per day, for the treatment of type II diabetes. (Ex. 1002 ¶ 81; *See, e.g.*, Ex. 1003, '940 Publication ¶ [0046], [0088]).

Moreover, optimizing the dosing amount and frequency of dosing would have been a matter of routine experimentation for a person of ordinary skill in the art. *In re Applied Materials, Inc*., 692 F.3d 1289, 1295 (Fed. Cir. 2012) (*quoting Application of Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)) ("'[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'"); *see also Hoffmann-La Roche Inc. v. Apotex Inc*., 496 F. App'x 46, 50 (Fed. Cir. 2012) (affirming a finding of obvious based, in part, on expert testimony that "once one chooses a particular treatment agent and a particular dosing time interval, determining a dose within the broad therapeutic range is a relatively routine matter").

Accordingly, for the same reasons discussed above for claims 1 and 2, claims 3 and 4 would have been obvious, and thus unpatentable.

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 such evidence. 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 1–4 of the '695 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

Telephone: 212-210-9400
Fax: 212-210-9444

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. 8,846,695, 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 '695 patent:

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

Respectfully submitted,

ALSTON & BIRD LLP

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 Petitioner, Mylan Pharmaceuticals Inc.