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Paper 16
Entered: February 3, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH,
Patent Owner.

Case IPR2016-01563
Patent 8,673,927 B2

Before TONI R. SCHEINER, BRIAN P. MURPHY, and ZHENYU YANG, *Administrative Patent Judges.*

MURPHY, *Administrative Patent Judge*.

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

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–26 of U.S. Patent No. 8,673,927 B2 (Ex. 1001, "the '927 patent"). Paper 2 ("Pet."). Boehringer Ingelheim International GmbH ("Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp."). We have statutory authority under 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Based on the arguments and evidence presented in the Petition and Preliminary Response, we determine there is a reasonable likelihood Petitioner would prevail with respect to claims 1 and 10 of the '927 patent challenged in the Petition. Therefore, we institute an *inter partes* review.

A. Related Proceedings

Petitioner and Patent Owner identify the following as related district court proceedings in the District of New Jersey regarding the '927 patent: *Boehringer Ingelheim Pharmaceuticals Inc. v. HEC Pharm. Group*, Civ. Action No. 3:15-cv-05982-PGS-TJB (consolidated); *Boehringer Ingelheim Pharmaceuticals Inc., v. Accord Healthcare, Inc.*, Case No. 3:16-cv- 00852-PGS-TJB; *Boehringer Ingelheim Pharmaceuticals Inc. v. Dr. Reddy's Laboratories, Ltd.*, Case No. 3:16-cv-02394-PGS-TJB; *Boehringer Ingelheim Pharmaceuticals Inc. v. Prinston Pharmaceutical Inc.*, Case No. 3:16- cv-00851-PGS-TJB; *Boehringer Ingelheim Pharmaceuticals Inc. v. Sun Pharmaceutical Industries Ltd.*, Case No. 3:16-cv-01727-PGS-TJB. Pet. 3; Paper 7, 2–3.

Patent Owner identifies the following inactive district court cases: in the U.S. District Court for the Middle District of North Carolina, *Boehringer Ingelheim Pharmaceuticals Inc. v. Intas Pharmaceuticals Ltd.*, Case No. 1:15-cv-00664-CCE-LPA; in the U.S. District Court for the Northern District of West Virginia, *Boehringer Ingelheim Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1:15-cv-00145-JPB. Paper 7, 3.

Petitioner identifies requests for *inter partes* review of related U.S. Patent Nos. 8,846,695 (IPR2016-01564), 8,853,156 (IPR2016-01565), and 9,173,859 (IPR2016-01566), which also are asserted in *Boehringer Ingelheim Pharmaceuticals Inc. v. HEC Pharm. Group*, Civ. Action No. 3:15-cv-05982-PGS-TJB (D.N.J.) (consolidated). Pet. 3.

B. Proposed Grounds of Unpatentability

Petitioner advances three grounds of unpatentability under 35 U.S.C. §§ 102 and 103 in relation to the challenged claims in the '927 patent:

Reference[s]	Statutory Basis	Challenged Claims
'510 Publication (Ex. 1003)[1]	§ 102	18–26
'510 Publication and Glucophage Label (Ex. 1004)[2]	§ 103	1–26

[1] Himmelsbach et al., U.S. Patent Publication No. 2004/0097510, published May 20, 2004 ("the '510 Publication"). Ex. 1003.

[2] Glucophage® (metformin hydrochloride tablets) and Glucophage® XR (metformin hydrochloride extended-release tablets) prescribing information ("Glucophage Label"). Ex. 1004.

Reference[s]	Statutory Basis	Challenged Claims
'510 Publication, Ahrén (Ex. 1005),[3] Hughes (1006),[4] and/or Brazg (1007)[5]	§ 103	1–26

Pet. 9. Petitioner supports its challenge with a Declaration by Dr. Mayer B. Davidson ("Davidson Declaration"). Ex. 1002.

C. The '927 Patent

The '927 patent, titled "Uses of DPP-IV Inhibitors," issued March 18, 2014, from an application filed November 15, 2010. Ex. 1001. The '927 claims priority, through a continuation application, to EP application 06009203, filed May 4, 2006. *Id.* at (30), 1:3–4. The '927 patent is assigned to Patent Owner. *Id.* at (73).

The Dipeptidyl Peptidase ("DPP")-IV enzyme breaks down bioactive peptides, including the peptide GLP-1. *Id.* at 1:18–23. GLP-1 is a naturally occurring peptide "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 (citing Ex. 1011, 149–150; Ex. 1014, 708); *see also* Prelim. Resp. 10. DPP-IV enzymes deactivate GLP-1 (and related hormones), thereby depressing the level of insulin in the body. *Id.* DPP-IV inhibitors are used to inhibit the DPP-IV enzyme, thereby preventing the breakdown of GLP-1 and helping to regulate blood glucose levels. *Id.* The '927

[3] Ahrén et al., *Twelve and 52-Week Efficacy of the Dipeptidase IV Inhibitor LAF237 in Metformin-Treated Patients with Type 2 Diabetes*, 27 DIABETES CARE 2874–880 (2004) ("Ahrén"). Ex. 1005.
[4] Hughes, International Patent No. WO 2005/117861, published December 15, 2005 ("Hughes"). Ex. 1006.
[5] 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*, 54 DIABETES (Suppl. 1):A3 (2005) ("Brazg"). Ex. 1007.

patent states that DPP-IV inhibitors "are highly promising molecules for the treatment of diabetes mellitus." Ex. 1001, 1:21–23.

The '927 patent describes a genus of DPPV-IV inhibitor compounds according to formula I (*id.* at 4:54–5:22), but the claims at issue are directed to methods of treating type II diabetes using one species of DPP-IV inhibitor known as "linagliptin."[6] *Id.* at 5:25–35 ("1-[(4 -methyl-quinazolin-2 -yl)methyl]-3-methy1-7-(2-butyn-1-y1)-8-(3-(R)-amino-piperidin-l-y1)-xanthine (cf. WO2004/018468, Example 2 (142)"). The '927 patent identifies linagliptin as one of twelve "particularly preferred DPP-IV inhibitors" that may "bring about unexpected therapeutic advantages or improvements when combined with other pharmaceutical active substances." *Id.* at 5:23–27, 8:15–17. Metformin is identified as a "particularly preferred example of an antidiabetic combination partner" for the DPP-IV inhibitors. *Id.* at 14:32–33. The '927 patent describes an orally administered dose of "the DPP IV inhibitors" as "0.5 mg to 100 mg, preferably 2.5 mg to 50 mg, in each case 1 to 4 times a day" *(id.* at 8:32–33), and it further describes oral tablet dosage forms containing 0.5, 1.0, 2.5, 5.0, and 10.0 mg of DPP-IV inhibitor (*id.* at 20:4–24).

The '927 patent includes a series of prophetic treatment examples. *Id.* at 16:20–23:44. Prophetic Example 13 describes a "Combined Treatment with DPP IV Inhibitor–Metformin" used for treating type II diabetes or pre-diabetes. *Id.* at 20:52–57. The combined treatment method is described as follows: "a DPP IV inhibitor according to the invention may be combined with the anti-diabetically active substance metformin . . . in a tablet." *Id.* at 20:57–60. The '927 patent further states:

[6] "Type 2 diabetes mellitus . . . manifests itself in a fasting blood sugar level exceeding 125 mg of glucose per dl of plasma." Ex. 1001, 1:30–32.

> 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.

Id. at 20:60–66. Example 13 provides that clinical efficacy can be found if the combination therapy "leads to a significantly greater reduction in the fasting glucose and/or non-fasting glucose and/or the HbAlc value[7] than either the DPP IV inhibitor alone or metformin alone." *Id.* at 21:7–10.

D. Challenged Claims

Petitioner challenges claims 1–26 of the '927 patent. Independent claims 1 and 18 are illustrative and reproduced below:

> 1. 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-y1)- methyl]-3-methy1-7-(2-butyn-l-y1)-8-(3-(R)-amino-piperidin-1-y1)-xanthine, 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.
>
> 18. 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-y1)- methyl] -3-methy1-7-(2-butyn-l-y1)-8-(3-(R)-amino-piperidin-1-y1)-xanthine which is an oral daily dose of from 2.5 mg to 10 mg, and a pharmaceutically effective amount of metformin.

[7] HbA1c value refers to a patient's glycated hemoglobin level, which "reflects the average blood sugar level of the preceding 4-12 weeks." Ex. 1001, 1:59–62; *see also* Ex. 1002 ¶ 65.

II. ANALYSIS

A. Claim Construction

Petitioner relies on the ordinary and customary meaning of the claim terms in the '927 patent. Pet. 6. Patent Owner does not address claim construction in its Preliminary Response. Therefore, we determine that claim construction is not necessary for any of the claim terms at this stage of the proceedings. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (citation omitted).

B. Ground 1: Asserted Anticipation of Claims 18–26

Petitioner asserts that the '510 Publication anticipates claims 18–26. Pet. 16–21. Patent Owner opposes, relying primarily on the assertion that the '510 Publication discloses a much broader dosage range for linagliptin than the broadest dosage range of 0.5 mg to 50 mg recited in independent claim 20. Prelim. Resp. 18–19. We address the evidence and the parties' arguments below.

1. The '510 Publication

The '510 Publication, assigned to Patent Owner, published on May 20, 2004 and is a prior art printed publication under 35 U.S.C. § 102(b). Ex. 1003; Pet. 16. The '510 Publication discloses a genus of substituted xanthine compounds that act as DPP-IV inhibitors, particularly for the prevention and treatment of type II diabetes. *Id.* at Abstract, ¶¶ 3–4. The '510 Publication discloses linagliptin as one in a series of 30 "[m]ost particularly preferred" substituted xanthine compounds. *Id.* ¶¶ 232, 245. The '510 Publication also lists the IC_{50} values of nearly 50 DPP-IV inhibitor compounds, including linagliptin. *Id.* ¶ 295 (linagliptin is Example 2

(142)[8]). Linagliptin is one of six compounds listed as having the highest potency in the group, with the lowest IC_{50} value of 1 nM. *Id.*

The '510 Publication discloses that "the compounds of general formula I according to the invention," due to their "ability to inhibit DPP-IV activity," are "expected . . . [to] be suitable for the prevention or treatment of diseases or conditions such as type 1 and type 2 diabetes mellitus." *Id.* ¶ 297. The '510 Publication discloses that "[t]he compounds according to the invention may also be used in conjunction with other active substances . . ., for example, antidiabetics, such as me[t]formin." *Id.* ¶ 298. The '510 Publication further discloses an oral dosage, delivered by conventional tablet dosage form, of "1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day" for "the compounds of formula I prepared according to the invention, optionally combined with other active substances." *Id.* ¶¶ 300, 2899–2910.

2. Analysis

Independent claims 18 and 19 of the '927 patent each recite "A method of treating type II diabetes mellitus comprising administering to a patient in need thereof a pharmaceutically effective oral amount of [linagliptin] which is an oral daily dose of [specific linagliptin dose or range of doses], and a pharmaceutically effective amount of metformin." Ex. 1001, 24:58–25:3. Claim 18 specifies an oral daily linagliptin dose of "from 2.5 mg to 10 mg." Claim 19 specifies an oral daily linagliptin dose of "5 mg."

Petitioner, in a single sentence of its claim 18 chart that is duplicated in Dr. Davidson's Declaration, argues that the '510 Publication discloses the recited oral

[8] The '510 Publication contains numerous examples for preparing compounds of the general formula, including the preparation of linagliptin in Example 2 (142). Ex. 1003 ¶¶ 1933–37, 2400. The '927 patent also identifies linagliptin as Example 2 (142) from WO 2004/018468. Ex. 1001, 5:27–28.

daily linagliptin dosages because "the most preferable oral dosage range for linagliptin encompasses and thus anticipates the claimed dose recited in claim 18 [and claim 19]." Pet. 18–19 (citing Ex. 1002 ¶ 35; Ex. 1003 ¶ 300). Petitioner also cites *Perricone v. Medicis Pharma. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005). *Id.* at 19. The Petition, however, does not contain any further analysis of the issue. *Id.*

The '510 Publication does not expressly disclose the oral daily linagliptin doses recited in claims 18 and 19. The '510 Publication discloses a preferred oral dose of 1 to 100 mg "1 to 4 times a day . . . [of] the compounds of formula I prepared according to the invention, optionally combined with other active substances." Ex. 1003 ¶ 300. Disclosure of an oral dose of linagliptin in the range of 1 to 100 mg, 1 to 4 times daily, is insufficient to satisfy the test for anticipation. To anticipate a claim, a single prior art reference must disclose all limitations "arranged as in the claim," either expressly or inherently. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983). To be "arranged as in the claim," the anticipatory reference must "show all of the limitations of the claims arranged or combined in the same way as recited in the claims, not merely in a particular order." *NetMoneyIn, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Petitioner's conclusory argument that the '510 Publication discloses an oral daily dosage range that "encompasses" the recited dosages in claims 18 and 19 does not satisfy the standard for anticipation.

The '510 Publication discloses a preferred oral dosage range from 1 to 100 mg, 1 to 4 times daily, for a total range of 1 to 400 mg daily. Prelim. Resp. 16. Although disclosure of such a relatively broad dosage range "encompasses" the specific linagliptin dosages recited in claims 18 (2.5–10 mg) and 19 (5 mg), prior disclosure of such a range of values, without more, is not sufficient to anticipate the specific dosages recited in claims 18 and 19. While Petitioner's assertion is

true, "the inquiry does not end there." *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012). Of "critical importance" in conducting the anticipation analysis is "how one of ordinary skill in the art would understand the relative size of a genus or species in a particular technology." *Id.* Petitioner has not provided evidence to address the critical question of how one of ordinary skill would have understood the dosage range of DPP-IV inhibitors disclosed in the '510 Publication, relative to the claimed linagliptin dosages used in a method for treating type II diabetes. The present case also is distinguishable from *Perricone*, where the prior art disclosure of a composition having an active ingredient concentration of "from 0.01 to 20% by weight" was determined to be sufficient to anticipate claimed ranges "up to 10% by weight" and "from about 0.025% to about 10% by weight." *Perricone*, 432 F.3d at 1377. Unlike Perricone, this is not a case where the prior art range "entirely encompasses, and *does not significantly deviate from*, [the] claimed ranges." *Id.* (emphasis added).

It is "Petitioner's burden to demonstrate that the claimed subject matter was disclosed in the prior art with sufficient specificity to constitute an anticipation of the challenged claims." *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, Case IPR2014-01162, 2015 WL 5578357 at *7 (PTAB Jan. 29, 2015). For example, Petitioner does not address the fact that the '510 Publication's preferred oral daily dosage range is many times broader than the claimed dosage range of 2.5 mg to 10 mg recited in claim 18. Petitioner also does not explain why, based on the disclosure of a genus of dosage ranges for DPP-IV inhibitors, a person of skill in the art would immediately envisage administering linagliptin in the dosage amounts recited in claims 18 and 19 of the '927 patent. *See Dynamic Drinkware,* 2015 WL 5578357, at *7.

Independent claim 20 more broadly recites "an oral dosage of from 0.5 mg to 50 mg." Ex. 1001, 25:11–12. Claims 21–26 depend from claim 20 and recite

progressively narrower dosages. *Id.* at 25:16–26:18. Although a closer question with regard to claim 20, we note Patent Owner's point that the '510 Publication's disclosure of a preferred oral daily dosage range of 1 to 400 mg is still broader than the dosage range claimed in claim 20. We do not consider such a disclosure as falling within the purview of *Perricone*, particularly in the absence of a substantive analysis by Petitioner. Therefore, our analysis above regarding claims 18 and 19 applies equally to claims 20–26.

For the reasons given above, we determine Petitioner has not shown a reasonable likelihood of prevailing in its assertion that claims 18–26 of the '927 patent are anticipated by the '510 Publication.

C. Ground 2: Asserted Obviousness of Claims 1–26 Over the '510 Publication and Glucophage Label

Petitioner asserts that the '510 Publication and the Glucophage Label would have rendered the subject matter of claims 1–26 obvious to a person of ordinary skill in the art ("POSA").[9] Pet. 21–29. Patent Owner opposes, relying on the assertion that Petitioner's evidence is insufficient to establish the Glucophage Label as a "printed publication" under 35 U.S.C. § 102(b). Prelim. Resp. 19–24. We address the evidence and the parties' arguments below.

[9] Petitioner characterizes a POSA as one having an advanced degree in the field of medicine, pharmaceuticals, medicinal chemistry, and/or a related discipline, at least 5 years of clinical experience treating type II diabetes and related disorders, and experience with the pharmaceutical and clinical properties of DPP-IV inhibitors. Pet. 8–9 (citing Ex. 1002 ¶ 11). Preferably, a POSA also would have some experience investigating pharmaceutical compositions for treating diabetes and diabetes-related disorders. *Id.* Patent Owner does not challenge Petitioner's description. Therefore, we adopt and apply Petitioner's definition of a POSA.

1. The Glucophage Label

The Glucophage Label provided by Petitioner as Exhibit 1004 includes a cover page stating it is the "FINAL PRINTED LABELING" for application number 20-357/S019 at the Food and Drug Administration ("FDA") Center for Drug Evaluation and Research. Ex. 1004, 1. Glucophage® is described in the document as metformin hydrochloride tablets and Glucophage® XR is described as metformin hydrochloride extended release tablets, both indicated for the treatment of type II diabetes. *Id.* at 2 (col. 1 ¶ 2). The Glucophage Label identifies Bristol-Myers Squibb as the drug sponsor and contains a date indicated as "Revised January 2001." *Id.* at 7. The Glucophage Label does not contain a copyright date or other indicia of a publication date.

2. Analysis of Glucophage Label as a Printed Publication

Under 35 U.S.C. § 311(b), a petitioner in an *inter partes* review may only challenge the claims of a patent based on "prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). Petitioner has the ultimate burden of persuasion to prove unpatentability by a preponderance of the evidence. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378–79 (Fed. Cir. 2015). Petitioner also bears the initial burden of production to establish the existence of prior art that renders the claims unpatentable. *Id.* To satisfy the initial burden of production, we have often required a petitioner to make a threshold showing that the reference relied upon was publicly accessible as a printed publication prior to the effective filing date of a challenged patent. *See, e.g.*, *Frontier Therapeutics, LLC v. Medac Gesellschaft Für Klinische Spezialpraparate MBH*, Case IPR2016-00649, slip op. at 22 (PTAB September 1, 2016) (Paper 10) (finding that an alleged "printed package insert" was not a printed publication); *Symantec Corp. v. Trs. of Columbia Univ.*, Case IPR2015-00371, slip op. at 5–9 (PTAB June 17, 2015) (Paper 13); *Temporal Power, Ltd. v. Beacon Power, LLC*, Case IPR2015-00146,

slip op. at 8–11 (PTAB Apr. 27, 2015) (Paper 10); *Dell, Inc. v. Selene Comm'n Techs., LLC*, Case IPR2014-01411, slip op. at 21–22 (PTAB Feb. 26, 2015) (Paper 23). "A given reference is "publicly accessible" upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006) (citing *In re Wyer*, 655 F.2d 221, 226 (CCPA 1981)); *see also Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2012). With these principles in mind, we consider the parties' arguments below.

Petitioner relies on Dr. Davidson for the assertion that the Glucophage Label was approved and published by the FDA for the treatment of type II diabetes in February 2001. Pet. 21–22 (citing Ex. 1002 ¶ 43). Dr. Davidson's background indicates he is an expert in the field of diagnosing and treating type II diabetes, having received his medical degree from Harvard Medical School in 1961 and later his board certification in the subspecialty of Diabetes, Endocrinology, and Metabolism. Ex. 1002 ¶¶ 5–8. Dr. Davidson states that metformin "was first approved by the U.S. Food & Drug Administration for the therapeutic treatment of diabetes in 1994," but he cites the January 2001 revision of the Glucophage Label in support. *Id.* at ¶ 27. Dr. Davidson further states that a long-acting extended-release form of metformin, Glucophage XR®, was available in the year 2000, but again cites to the January 2001 revision of the Glucophage Label in support. *Id.* With regard to the Glucophage Label itself, Dr. Davidson's Declaration contains the same conclusory sentence contained in the Petition asserting, without explanation or other supporting evidence, that the Glucophage Label was approved and published by the FDA for treating type II diabetes in February 2001. *Id.* ¶ 43.

We agree with Patent Owner that the Glucophage Label does not contain any source identifying information, e.g. as an FDA-approved label, or other indicia of when the document became publicly available. Prelim. Resp. 22. For example, the Glucophage Label submitted by Petitioner contains no indicia that it (i) is a certified copy of a public record, (ii) is copied from an official 2001 publication such as the United States Pharmacopoeia–National Formulary, (iii) is copied from a recognized periodical published in 2001 such as the Physicians' Desk Reference, or (iv) otherwise bears the hallmarks of a self-authenticating document published in 2001. *See* Fed. R. Evid. 902 (4)–(7), (11). The Glucophage Label indicates Bristol-Myers Squibb is the drug sponsor and the label was revised in January 2001, but it bears no source identifying information from the FDA, copyright notice or publication date. Ex. 1004, 7. Moreover, although Dr. Davidson is an unquestioned expert in the diagnosis and treatment of type 2 diabetes, his Declaration does not provide a sufficient explanation or foundation to establish his personal knowledge of the Glucophage Label's alleged publication in February 2001. Dr. Davidson's statements that Glucophage® was approved by the FDA in 1994 and Glucophage® XR in 2000 are insufficient, by themselves, as a threshold showing that the Glucophage Label was a publicly available printed publication as of February 2001. Earlier FDA approval of the Glucophage® drug products is not co-extensive with a February 2001 publication date of the revised Glucophage Label, on which Petitioner relies for proof of the specific metformin doses recited in claims 1–17 and the "pharmaceutically effective amount" and "therapeutically effective dose" of metformin recited in claims 18–26. Pet. 23–26, 28–29.

For the reasons given above, we determine Petitioner has not satisfied its initial burden of production to show that the Glucophage Label was available as a prior art printed publication. Therefore, we determine Petitioner has not shown a reasonable likelihood of prevailing on its assertion that the subject matter of claims

1–26 of the ’927 patent would have been obvious over the ’510 Publication and the Glucophage Label.

D. Ground 3: Asserted Obviousness of Claims 1–26 Over the ’510 Publication, Ahrén, Hughes, and/or Brazg

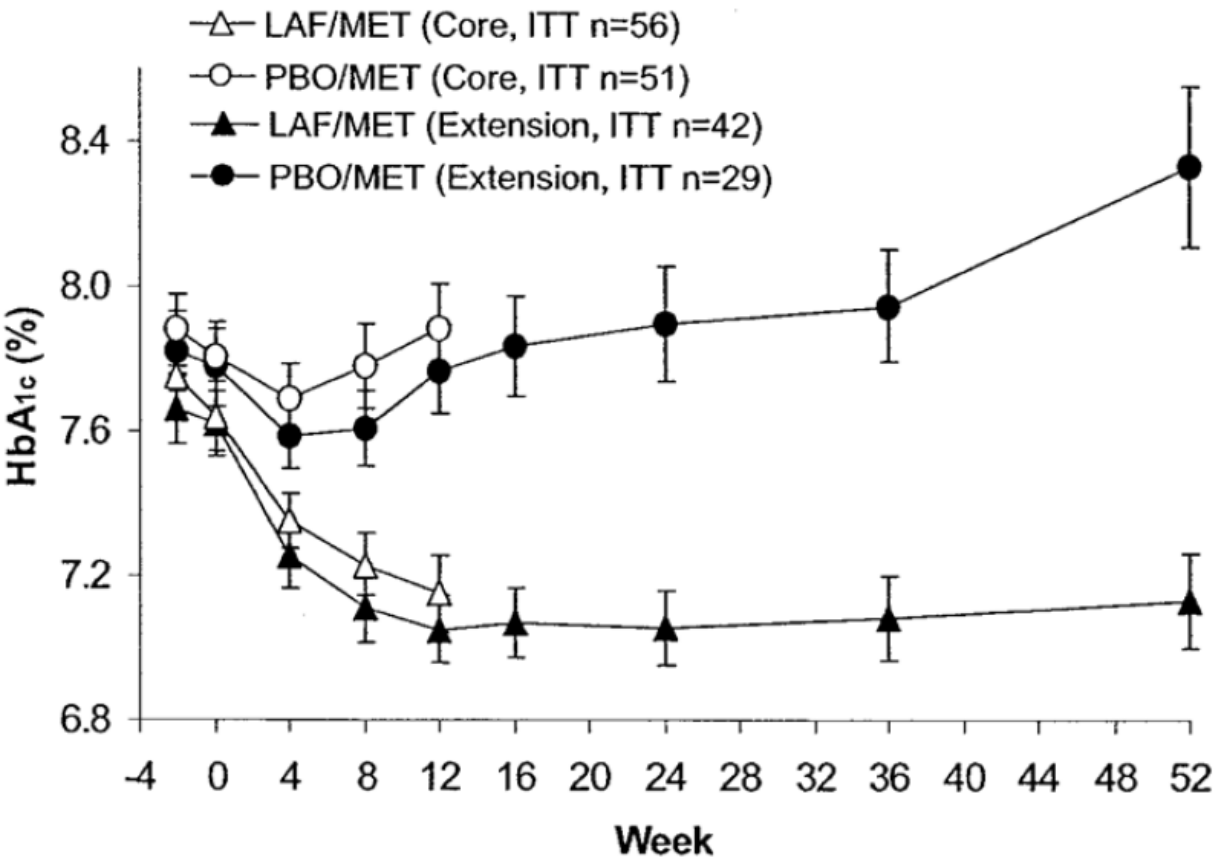
Petitioner asserts that the ’510 Publication, Ahrén, Hughes, and/or Brazg would have rendered the subject matter of claims 1–26 obvious to a POSA. Pet. 29–41. Patent Owner opposes. Prelim. Resp. 24–40. A claimed invention is unpatentable if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. § 103(a). Obviousness under 35 U.S.C. § 103 requires an assessment of (1) the “‘level of ordinary skill in the pertinent art,’” (2) the “‘scope and content of the prior art,’” (3) the “‘differences between the prior art and the claims at issue,’” and (4) “‘secondary considerations’” of nonobviousness such as “‘commercial success, long-felt but unsolved needs, failure of others, etc.’” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)). A party who petitions the Board for a determination of obviousness must show that “‘a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). We assess Petitioner’s evidence and argument according to this standard.

1. Ahrén

Ahrén published in December 2004 and is prior art to the '927 patent under 35 U.S.C. § 102(b) (pre-AIA). Ex. 1005. Ahrén discloses the clinical effect of DPP-IV inhibitor LAF237 (vildagliptin) when combined with metformin to treat patients with type II diabetes. *Id.* at 2874–75[10]. Ahrén discloses a 12-week study that compares two groups of type II diabetes patients treated with either metformin monotherapy (1500 to 3000 mg per day), or metformin (1,500 to 3,000 mg per day) and vildagliptin (50 mg once per day) combination therapy. *Id.* at 2874. In the patients who received metformin and vildagliptin combination therapy for 12 weeks, the glycated hemoglobin (HbA1c) baseline level decreased by -0.6 ±0.1%. *Id.* at 2875 (col. 3 ¶ 4). Treatment with metformin alone showed no change from the baseline during the same time period. *Id.* In a 40-week extension of the 12-week study, the difference in HbA1c level between the combination therapy group and metformin monotherapy group was -1.1 ±0.2%. *Id.* at 2875–76.

The combination therapy group showed a more significant and rapid reduction in HbA1c level when compared to the metformin monotherapy group, as shown in Ahrén Figure 3 below. *Id.* at 2876–77; Ex. 1002 ¶ 65.

[10] Petitioner cites to the internal page numbers of the DIABETES CARE publication, rather than to the pages numbers of Exhibit 1005. For consistency, we do the same.



As shown in Ahrén Figure 3, above, mean glucose levels were significantly reduced in patients who received LAF237 (vildagliptin) and metformin combination therapy, when compared with metformin monotherapy patients. Ex. 1005, 2877–78. The overall incidence of adverse events was similar in both treatment groups. *Id.* at 2878. The authors concluded that "when added to metformin treatment, LAF237 was effective at improving glycemic control for at least 1 year in patients with type 2 diabetes and appeared to be well tolerated." *Id.* (col. 2 ¶ 4).

2. Hughes

Hughes published on December 15, 2005 and is prior art to the '927 patent under 35 U.S.C. § 102(b) (pre-AIA). Ex. 1006. Like Ahrén, Hughes discloses a method of treating patients with type II diabetes using a combination of LAF237

(vildagliptin) and metformin over an extended period of time. *Id.* at Abstract, 3–4, 13[11]. Hughes teaches that vildagliptin may be administered in an oral daily dosage "between 1 and 100 mg; preferably between 10 and 100 mg e.g. 10 mg; most preferably between 25 and 100 mg e.g. 25 mg or 30 or 40 or 50, 61, 70, 90, 100 mg." *Id.* at 23. Metformin is administered at a daily dosage in the range of about 50 mg to about 3000 mg, preferably from about 500 mg to about 2000 mg, using commercially available 500 mg tablets. *Id.* Hughes discloses a clinical study involving the administration of vildagliptin (50 mg once daily) and metformin (1500–3000 mg daily) and reports that the combination therapy achieved better clinical results when compared to metformin plus placebo treatment. *Id.* at 25–33. Hughes further discloses that vildagliptin-metformin combination therapy can effectively maintain low glucose levels or low HbA1c levels in diabetes patients over an extended period of time. *Id.* at 3–4.

3. Brazg

Brazg published in June 2005 and is prior art to the '927 patent under 35 U.S.C. § 102(b) (pre-AIA). Ex. 1007. Brazg discloses the efficacy of combining the DPP-IV inhibitor MK-0431 (sitagliptin) with ongoing metformin therapy in type II diabetes patients. *Id.* at 2 (col. 2). Brazg notes that "[m]etformin is a commonly used first-line antihyperglycemic agent." *Id.* 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]." *Id.* Brazg discloses clinical trial data that compares metformin monotherapy with metformin plus sitagliptin combination

[11] Page references are to the exhibit pages, not the internal document pages.

therapy, represented in the table below as annotated by Petitioner. *Id.*; Pet. 33 (citing Ex. 1002 ¶ 71).[12]

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

As shown in the annotated table above, metformin monotherapy reduced the fasting plasma glucose level by 3.4 mg/dL from mean baseline. Ex. 1007, 2 (col. 2); Ex. 1002 ¶ 72. Metformin plus sitagliptin combination therapy reduced the fasting plasma glucose level by 23.8 mg/dL from mean baseline. *Id.* 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, 2 (col. 2).

4. Evidence Supporting a Reason to Combine the References

Petitioner provides evidence to support its argument that a POSA would have had a reason to substitute the "linagliptin" doses disclosed in the '510 Publication for the DPP-IV inhibitors disclosed in the metformin combination therapies taught by Ahrén, Hughes, and Brazg. Pet. 37–38 (citing Ex.1002 ¶¶ 33, 78–82; Ex. 1003 ¶ 295; Ex. 1011, 158). For example, Petitioner relies on the '510 Publication, the reference to Gwaltney (Ex. 1011, 158), and Dr. Davidson's Declaration testimony for the identification of linagliptin as a particularly preferred DPP-IV inhibitor compound having greater potency than vildagliptin (LAF 237,

[12] The table in Brazg contains additional data not material to this Decision.

Ahrén, Hughes) and sitagliptin (MK-0431, Brazg), as indicated by linagliptin's lower IC_{50} value. *Id.*; *see also* Ex. 1002 ¶¶ 29–32. Petitioner cites to several references, apart from the Glucophage Label, for the proposition that it was well-known in the prior art to combine metformin with other antidiabetic agents "having separate and distinct mechanisms of action . . . including insulin, sulfonylureas, thiazolidinediones, and DPP-IV Inhibitors." Pet. 14–15 (citing Ex. 1002 ¶ 30; Ex. 1005, 2874 (Abstract, col. 3 ¶ 3); Ex. 1006, 13–14; Ex. 1007, 2 (col. 2); Ex. 1015, 1 (col. 2 ¶ 3). Petitioner also supports the assertion that a POSA would have understood that combining metformin with a DPP-IV inhibitor such as linagliptin would result in a higher reduction in blood glucose level than metformin alone, due to their distinct but complementary mechanisms of action. Pet. 37–38 (citing Ex. 1002 ¶ 80); *see Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354–55 (Fed. Cir. 2013) ("Repaglinide and sulfonylureas are both insulin secretagogues, and they therefore have a "similar mechanism of action" in that they both treat diabetes by stimulating the pancreas to release insulin. Metformin is an insulin sensitizer, which treats diabetes patients using a different mechanism, i.e. by reducing their resistance to insulin." (citations omitted)); *see also In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (differentiating between proper and improper applications of "obvious to try" in an obviousness analysis). We further note the '510 Publication expressly teaches that "[i]t is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as . . . type 2 diabetes mellitus," including when "used in conjunction with . . . antidiabetics, such as me[t]formin." Ex. 1003 ¶¶ 297–98.

Patent Owner argues that Petitioner's evidence is insufficient for several reasons, particularly because the '510 Publication does not provide "any information" suggesting linagliptin would be suitable for combination therapy with

metformin. Prelim. Resp. 25–26. Patent Owner also contests the implications to be drawn from the '510 Publication's disclosure of nearly 50 compounds with varying IC_{50} values. *Id.* at 27–28. Patent Owner makes additional arguments (Prelim. Resp. 28–34) which, on the present record, are not supported by expert declaration testimony. Suffice to say that, at this stage of the proceeding, Petitioner has provided sufficient evidence to support its assertion of a motivation to combine the references. Patent Owner will have the opportunity to cross-examine Dr. Davidson and submit its own expert declaration testimony and evidence regarding motivation to combine during the trial.

5. The Claimed Linagliptin Dosages

The '927 patent claims recite varying dosages of linagliptin in combination with varying dosages of metformin. In view of our analysis in Section II.B., above, we focus on whether the recited linagliptin dosages are disclosed in the '510 Publication, as asserted by Petitioner. We start with the broadest linagliptin dosages recited in claims 1 and 10.

a. claims 1 and 10 – "pharmaceutically effective oral amount" and "therapeutically effective oral dose"

Independent claim 1 recites "a pharmaceutically effective oral amount of [linagliptin]." Independent claim 10 similarly recites "a therapeutically effective oral dose of [linagliptin]." The '510 Publication discloses a preferred oral dose of 1 to 100 mg "1 to 4 times a day . . . [of] the compounds of formula I prepared according to the invention, optionally combined with other active substances." Ex. 1003 ¶ 300. Petitioner relies on this disclosure to satisfy the "pharmaceutically effective" and "therapeutically effective" linagliptin dose limitations in claims 1 and 10. Pet. 37–38; Ex. 1002 ¶¶ 61, 74. The '510 Publication's disclosure of preferred oral doses of DPP-IV inhibitors from "1 to 100 mg, in each case 1 to 4 times a day," is similar to the '927 patent's description of therapeutically effective

oral doses of DPP-IV inhibitors as (i) "0.5 mg to 100 mg, preferably 2.5 mg to 50mg, in each case 1 to 4 times a day" (Ex. 1001, 8:30–33), and (ii) in Example 13 as "[a] therapeutically effective dose of the DPP IV inhibitor (e.g. a dose of between 0.1 and 100 mg)" (Ex. 1001, 20:60–62). Patent Owner does not address the linagliptin dosages recited in claims 1 and 10. Prelim. Resp. 34–39. Therefore, we determine that Petitioner has provided sufficient evidence to support its assertion that the '510 Publication discloses the linagliptin dosages recited in claims 1 and 10.

b. Claims 2–9 and 11–26

Claims 2–9 and 11–26 each recite particular dosages or dosage ranges for linagliptin. Petitioner relies solely on its claim 18 anticipation chart to support its assertion that the recited linagliptin dosages are disclosed in the '510 Publication. Pet. 39. Petitioner does not provide any further analysis or support for its assertion regarding the disclosure of the linagliptin dosages recited in claims 2–9 and 11–26. *Id.*; *see also* Ex. 1002 ¶¶ 35, 38, 53, 55, 61. Petitioner also fails to explain why a POSA would have had a reasonable expectation of successfully determining those dosages from the teachings of the '510 Publication. *Id.* We reiterate our analysis and conclusion with regard to the recited linagliptin dosages in claims 18–26 from Section II.B., above. Petitioner's conclusory argument that the '510 Publication discloses an oral daily dosage range that "encompasses" the recited linagliptin dosages, without more, is not sufficient to support a reasonable expectation of success in determining the linagliptin dosages recited in claims 2–9 and 11–26.

III. CONCLUSION

Petitioner has demonstrated a reasonable likelihood of prevailing with respect to claims 1 and 10 of the '927 patent challenged in the Petition. At this

stage of the proceeding, the Board has not made a final determination as to the patentability of the instituted claims. Our final decision will be based on the full record developed during trial.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review of the '927 patent is instituted on the following grounds:

Claims 1 and 10 as obvious over the '510 Publication, Ahrén, Hughes, and Brazg;

FURTHER ORDERED that *inter partes* review is commenced on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; and

FURTHER ORDERED that the *inter partes* review is limited to the ground of unpatentability listed above, and no other grounds of unpatentability are authorized for *inter partes* review.

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