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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VIII, LLC,
Petitioner,

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner.

Case IPR2015-01835
Patent 8,618,135 B2

Before GRACE KARAFFA OBERMANN and MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judges*, LORA M.GREEN, *Administrative Patent Judge*.

GREEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Coalition for Affordable Drugs VIII, LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–10 of U.S. Patent No. 8,618,135 B2 (Ex. 1001, "the '135 patent"). Paper 1 ("Pet."). The Trustees of the University of Pennsylvania ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). We determined that the information presented in the Petition and the Preliminary Response demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–10 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on March 7, 2016, as to the challenged claims of the '135 patent. Paper 7 ("Institution Decision" or "Dec. Inst.").

Patent Owner filed a Response (Paper 16, "PO Resp."), as well as a Corrected Motion to Amend (Paper 24, "Mot. Amend"). Petitioner subsequently filed a redacted copy of its Reply (Paper 30), as well as an unredacted copy of the Reply as Board and parties only (Paper 29). ("Reply"). Petitioner filed also an Opposition to the Motion to Amend. Paper 31 ("Opp. Mot. Amend"). Patent Owner filed a Reply in Support of its Motion to Amend. Paper 35 ("Reply Mot. Amend").

In addition, Patent Owner filed a Motion to Exclude (Paper 38, "Mot. Exclude"), to which Petitioner filed an Opposition (Paper 44, "Opp. Mot. Exclude"), and Patent Owner filed a Reply (Paper 46, "Reply Mot. Exclude"). Patent Owner filed Observations on the Cross-Examination of Petitioner's Reply Witness (Paper 39), to which Petitioner filed a Response (Paper 45). Petitioner filed Observations on the Cross-Examination of Dr. Thomas A. Baille (Paper 41), to which Patent Owner filed a Response

(Paper 43). Oral hearing was held on December 1, 2016, and a transcript of that hearing has been entered into the record. Paper 54 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

Based on the record before us, we conclude that Petitioner has failed to demonstrate by a preponderance of the evidence that claims 1–10 of the '135 patent are unpatentable. Moreover, we *dismiss* Patent Owner's Motion to Amend as moot, and *dismiss* Patent Owner's Motion to Exclude in part and *deny* Patent Owner's Motion to Exclude in part.

A. Related Proceedings

Petitioner concurrently filed a Petition for *Inter Partes* Review of U.S. Patent No. 7,932,268 (IPR2015-01836), which is a member of the same family as the '135 patent. Pet. 3. The final written decision in IPR2015-01836 is being issued concurrently with this Decision.

B. The '135 Patent (Ex. 1001)

The '135 patent issued on December 31, 2013, with Daniel J. Rader as the listed inventor. Ex. 1001. It claims priority to application No. 10/591,923, filed as application No. PCT/US2005/007435 on March 7, 2005, which issued as Patent No. 7,932,268, as well as to Provisional application No. 60/550,915, filed on March 5, 2004. *Id.* The '135 patent

relates to "methods of treating a subject suffering from a disorder associated with hyperlipidemia and/or hypercholesterolemia." *Id.* at 6:38–40.

The '135 patent teaches that "[a] large number of genetic and acquired diseases can result in hyperlipidemia." *Id.* at 1:61–62. Primary hyperlipidemias include "common hypercholesterolemia, familial combined hyperlipidemia, familial hypercholesterolemia, remnant hyperlipidemia, chylomicronemia syndrome and familial hypertriglyceridemia." *Id.* at 1:66–2:3. For example, with homozygous familial hypercholesterolemia ("HoFH"), total plasma cholesterol levels are over 500 mg/dl, and left untreated, patients develop atherosclerosis by age 20 and often do not survive past age 30. *Id.* at 3:46–53. Such patients, however, are often unresponsive to conventional drug therapy. *Id.* at 3:56–58. According to the '135 patent, "[a] number of treatments are currently available for lowering serum cholesterol and triglycerides." *Id.* at 2:4–5. The '135 patent notes, however, that "each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population." *Id.* at 2:5–7. For example, statins may have side effects that include liver and kidney dysfunction. *Id.* at 2:31–40.

The '135 patent teaches that abetalipoproteinemia is a rare genetic disease that is characterized by extremely low cholesterol and triglyceride levels and is caused by mutations in microsomal triglyceride transport protein ("MTP"). *Id.* at 5:1–7. Thus, the '135 patent teaches that the "finding that MTP is the genetic cause of [abetalipoproteinemia] . . . led to the concept that pharmacologic inhibition of MTP might be a successful strategy for reducing atherogenic lipoproteins levels in humans." *Id.* at 5:30–35. Bristol-Myers Squibb ["BMS"] developed a series of compounds,

including BMS-201038 (i.e., lomitapide), which are potent inhibitors of MTP. *Id.* at 5:47–49.

According to the '135 patent, however:

> Clinical development of BMS-201038 as a drug for large scale use in the treatment of hypercholesterolemia has been discontinued, because of significant and serious hepatotoxicities. For example, gastrointestinal side effects, elevation of serum transaminases and hepatic fat accumulation were observed, primarily at 25 mg/day or higher doses.

Id. at 6:20–25. The '135 patent notes that "[c]ombinations using MTP inhibitors and other cholesterol or triglyceride drugs have been previously disclosed . . . but suffer the same drawbacks as described above for MTP inhibitors." *Id.* at 8:30–34.

Thus, according to the '135 patent, the "invention is based on the surprising discovery that one may treat an individual who has hyperlipidemia and/or hypercholesterolemia with an MTP inhibitor in a manner that results in the individual not experiencing side-effects normally associated with the inhibitor, or experiencing side-effects to a lesser degree." *Id.* at 7:11–16.

The '135 patent specifically teaches:

> In some embodiments, the MTP inhibitor is administered at escalating doses. In some embodiments, the escalating doses comprise at least a first dose level and a second dose level. In some embodiments, the escalating doses comprise at least a first dose level, a second dose level, and a third dose level. In some embodiments, the escalating doses further comprise a fourth dose level. In some embodiments, the escalating doses comprise a first dose level, a second dose level, a third dose level, a fourth dose level and a fifth dose level. In some embodiments, six, seven, eight, nine and ten dose levels are contemplated.

Id. at 11:60–12:3.

The ’135 patent teaches further:

> In some embodiments, the first dose level is from about 2 to about 13 mg/day. In some embodiments, the second dose level is from about 5 to about 30 mg/day. In some embodiments, the third dose level is from about 10 to about 50 mg/day. In some embodiments, the fourth dose level is from about 20 to about 60 mg/day. In some embodiments, the fifth dose level is from about 30 to about 75 mg/day.

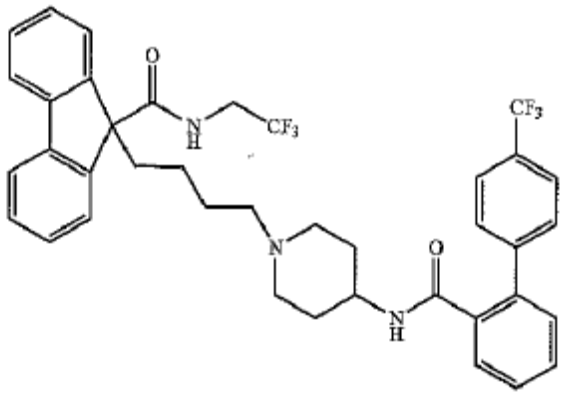
Id. at 12:45–51. In addition, other lipid modifying compounds may be used with the MTP inhibitor. *Id.* at 11:34–41.

The ’135 patent teaches that in phase II studies with BMS-201038 in patients that suffer from primary hypercholesterolemia, “a dosage of 25 mg per day for 4 weeks produced clinically significant gastrointestinal (GI) steatorrhea, abdominal cramping and distention) and statistically significant hepatobiliary (elevated liver function tests and minor fatty liver) symptoms in some patients receiving study drug.” *Id.* at 18:52–56 (Example 8). The ’135 patent teaches that those GI-related symptoms, as well as the hepatic fat, appear to be due to the design of the study, specifically, the dosing regimen. *Id.* at 18:57–59. Six patients with HoFH were given daily doses of BMS-201038 at 4 dosage levels (0.03, 0.1, 0.3, and 1.0 mg/kg) for four weeks at each dose. *Id.* at 19:5–7. According to the ’135 patent, the data provided by the study “indicate that symptoms of steatorrhea and hepatic fat can be significantly reduced by initiating a low dose with a gradual up titration.” *Id.* at 19:28–31.

C. Illustrative Claim

Petitioner challenges claims 1–10 of the ’135 patent. Claims 1, 9, and 10 are independent. Claim 1 is illustrative of the challenged claims and is reproduced below:

1. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three, step-wise, increasing dose levels of the MTP inhibitor wherein a first dose level is from about 2 to about 13 mg/day, a second dose level is from about 5 to about 30 mg/day, and a third dose level is from about 10 to about 50 mg/day, and wherein the MTP inhibitor is represented by:



or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof, and wherein each dose level is administered to the subject for about 1 to about 5 weeks.

Independent claim 9 specifies that the first dose is administered for about 2 weeks, and the second and third doses are administered for about 2 to 4 weeks. Independent claim 10 specifies that the first dose is administered for about 1 to 12 weeks, and the second and third doses are administered for about 4 weeks.

D. Instituted Challenges

We instituted trial based on the following grounds of unpatentability (Dec. Inst. 34):

References	Basis	Claims Challenged
Pink Sheet[1] and Chang[2]	§ 103(a)	1–10
Stein[3] and Chang	§ 103(a)	1–10

Petitioner relies also on the Declaration of Randall M. Zusman, M.D. (Ex. 1002), the Supplemental Declaration of Dr. Zusman (Ex. 1049), as well as the Declaration of Michael Mayersohn, Ph.D. (Ex. 1003).

Patent Owner relies on the Declarations of Frank Sacks, M.D. (Ex. 2023), Thomas A. Baillie, Ph.D., D.Sc. (Ex. 2024), S. David Kimball Ph.D. (Ex. 2025), Richard E. Gregg, M.D. (Ex. 2083), as well as the Declaration of Daniel J. Rader, M.D. (Ex. 2026), the inventor of the '135 patent.

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[1] *Bayer/PPD Implitapide Development Follows Zetia Model as Statin Add-On*, 66 THE PINK SHEET 17 (February 16, 2004) (Ex. 1013) ("Pink Sheet").

[2] George Chang, Roger B'Ruggeri & H James Harwood Jr., *Microsomal Triglyceride Transfer Protein (MTP) Inhibitors: Discovery of Clinically Active Inhibitors Using High-Throughput Screening and Parallel Synthesis Paradigms*, 5 CURRENT OP. DRUG DISCOVERY & DEV. 562–570 (2002) (Ex. 1015) ("Chang").

[3] Evan Stein, CEO & President, MRL Int'l (Division of PPD), Presentation Given at PPD's Analyst Day, *Microsomal Triglygeride [sic] Transfer Protein (MTP) Inhibitor (Implitapide) Program* (Feb. 5, 2004) (Ex. 1014) ("Stein").

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–45 (2016) (upholding the use of the broadest reasonable interpretation standard).[4] Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007), *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

"[T]he specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.'" *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc)). The Court of Appeals for the Federal Circuit has cautioned, however, "[t]here is a fine line between construing the

[4] We note that Patent Owner argues that the "broadest reasonable interpretation" standard is "legally impermissible." PO Resp. 7. We note that Patent Owner filed its Response before *Cuozzo* was decided by the United States Supreme Court.

claims in light of the specification and improperly importing a limitation from the specification into the claims." *Retractable Techs., Inc. v. Becton, Dickinson, and Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011). Thus, "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" *Hill-Rom Services, Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (quoting *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed.Cir.2004)).

In the Institution Decision, we determined that none of the terms in the challenged claims required express construction at that time. Dec. Inst. 7 (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (noting that only claim terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy)).

In its Response, Patent Owner states that it "does not contest any of the specific constructions" proffered by Petitioner. PO Resp. 7. Patent Owner contends, however, that the ordinary artisan

> would have understood that the "method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three, step-wise, increasing dose levels of the MTP inhibitor" means that the claimed method of treating a human patient requires a forced dose titration regimen including, but not limited to, at least three, step-wise, increasing dose levels of lomitapide.

Id. at 8 (citing Ex. 2023 ¶ 44). *But see* Tr. 30 (Counsel for Patent Owner stating "we're not asking you to read in the terms forced titration. We're not saying the claim requires forced titration.").

Petitioner replies that that there is nothing in the claims that limits them to a forced titration method. Reply 4. We agree. All that is required by independent claim 1 are at least three, step-wise doses of the claimed MTP inhibitor at specified dosage ranges. Thus, we decline to limit the challenged claims to a forced dose titration method.

B. Level of Ordinary Skill in the Art

Petitioner contends:

> A person of ordinary skill in the art as relevant to this proceeding would have had a high level of education (graduate and/or post-graduate degrees) in a pertinent discipline such as medicine, medicinal chemistry, pharmacology, pharmacokinetics, or drug development and delivery. Such a person with a medical degree (M.D.) would also have 3-5 years of experience treating patients in the cardiovascular/cardiac field, which would itself provide knowledge of dose-titration; dose-selection as balanced against side effects in individual patients; and developments in the clinical field. (Zusman, ¶¶ 28-29, 32; Mayersohn, ¶ 26). A non-M.D. would have a similarly advanced education, and the experiences and skill sets appropriate to their specialty. (*See* Zusman, ¶¶ 30-32; Mayersohn, ¶ 26).

Pet. 28–29.

Patent Owner responds that that the ordinary artisan "would have had an M.D. and several years of experience in treating patients with lipid disorders, including hyperlipidemia and hypercholesterolemia." PO Resp. 9 (quoting Ex. 2023 ¶ 40). Although acknowledging that the ordinary artisan "would also have had access to and worked with individuals involved in drug discovery and development with degrees in medicinal chemistry, pharmacology, or drug delivery sciences and several years of experience in the development of drugs for the U.S. market," Patent Owner argues that Petitioner's proposed definition adds additional qualifications "that are

unnecessary and erroneous," such as, that the ordinary artisan would consult the Pink Sheet. *Id.* at 9–10 (citing Ex. 1002 ¶ 28).

Petitioner replies that, as acknowledged by Patent Owner's expert, Dr. Kimball, the ordinary artisan "is a person who has the knowledge of an entire drug development team." Reply 3 (quoting Ex. 1056, 19:2–20:3). Such an artisan, Petitioner asserts, would attend investor presentations and read the Pink Sheet. *Id.* (citing Ex. 1002 ¶ 28).

We agree with Petitioner that the ordinary artisan would not be limited to an M.D., but as acknowledged by Patent Owner, would have access to a drug discovery team. Such a team would be aware of the art and the work of other teams, such as that reported by Pink Sheet. Moreover, the level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

C. Obviousness over Stein and Chang

Petitioner contends that claims 1–10 are rendered obvious by the combination of Stein and Chang. Pet. 46–56. Patent Owner disagrees with Petitioner's contentions. PO Resp. 45–56.

i. Overview of Stein (Ex. 1014)

Stein is a slide set prepared by Evan Stein, M.D., Ph.D., for PPD, Inc.. Ex. 1014, 4.[5] According to Stein, the lipid lowering market is one of the largest therapeutic segments, of which statins are the largest component. *Id.*

[5] The page numbers for Stein refer to the page numbers added by Petitioner. We note, however, that unless otherwise noted, our reference to page numbers of an exhibit are to the numbering as set forth in the exhibit itself, and not to the page numbering added by a party.

at 7. Thus, according to Stein, "[n]ew therapeutic agents will be additive or complementary" to statins, or other existing agents. *Id.*

Stein teaches further that there are a growing number of "statin adverse" patients and that 10 to 15% of high risk patients do not meet current goals for LDL cholesterol levels, even at maximum statin doses. *Id.* at 10. Moreover, the number of such patients continues to grow. *Id.*

Stein notes that a number of companies, such as Bayer and BMS, have developed MTP inhibitors, noting further that some of the companies, such as BMS, discontinued their research due to class toxicities. *Id.* at 21. Stein teaches, however, that MTP inhibitors "[m]ay still have [a] role in [homozygous familial hypocholesteremia, heterozygous familial hypocholesteremia, familial combined hyperlipidemia] and hyperchylomicronemia," with the challenge being to find a therapeutic window, that is, where efficacy is obtained without toxicity. *Id.* Stein specifically looks at the MTP inhibitor, implitapide (BAY 13-9952). *Id.* at 22. Thus, Stein proposes a development plan, in which test subjects are started at low doses of 10 mg, and then titrated by 5 mg "based on 'safety' every 5 weeks." *Id.* at 37.

ii. Availability of Stein as Prior Art

Before reaching the merits of Petitioner's obviousness grounds, we must determine whether Stein qualifies as prior art as a printed publication. It is Petitioner's burden to prove that it is, as Petitioner bears the burden of proving unpatentability by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) ("In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is

unpatentable."); *In re Wyer*, 655 F.2d 221, 227 (CCPA 1981) (noting that a party asserting a reference as a prior art printed publication "should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art to which the document relates").

The determination of whether a document is a "printed publication" under 35 U.S.C. § 102 "involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). "Because there are many ways in which a reference may be disseminated to the interested public, 'public accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016) (citing *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986)).

"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." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

Citing *Klopfenstein*, Petitioner contends that the presentation itself qualifies as a "printed publication." Pet. 17. Specifically, Petitioner asserts that "a skilled artisan could have captured (or recorded), processed and retained the relevant material." *Id.* at 17–18.

As set forth in *Klopfenstein*, the factors to be considered are: (i) the length of time the display was exhibited; (ii) the expertise of the target audience; (iii) the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied; and (iv) the simplicity or ease with which the material displayed could have been copied. *Klopfenstein*, 380 F.3d at 1350. It is only by "considering and balancing these factors can we determine whether or not [a] reference was sufficiently publicly accessible to be a 'printed publication.'" *Id.*

Petitioner asserts that Stein was presented, as well as webcast, on February 5, 2004, at the Analyst Day at PPD, Inc. Pet. 16. The hyperlink was distributed to interested parties and "was targeted to financial analysts, investors, and skilled artisans interested in drug discovery and development." *Id.* (citing Ex. 1005, 4). Moreover, it was reported in Pink Sheet. *Id.* at 16–17 (citing Ex. 1002 ¶¶ 106–110; Ex. 1003 ¶¶ 23–25). Petitioner asserts further that PPD had publicized its investor day for weeks and had provided a hyperlink for interested parties to register for the event or the webcast. *Id.* at 18 (citing Ex. 1005, 4). Petitioner argues that the skilled artisan would have taken great interest in the presentation. *Id.* (citing Ex. 1002 ¶¶ 20–22).

As to the third and fourth factors of *Klopfenstein* of expectation and ease of copying, Petitioner asserts that "[t]here is no evidence Stein or PPD intended to keep Stein's presentation private; no expectation of privacy in a webcast presentation exists absent attempts to keep it private." *Id.* at 19 (citing *Klopfenstein*, 380 F.3d at 1351). Moreover, Petitioner asserts "[i]t would have been simple for the skilled artisan to copy the relevant information from the Stein presentation." *Id.* In fact, Petitioner asserts

"Pink Sheet *did* copy and distribute the step-wise escalating dosing regimen." *Id.*

Petitioner asserts further that the slides themselves, once they were posted online for viewing and download, constituted "a second, re-publication of Stein 2004." Pet. 19. According to Petitioner, "PPD posted the Stein 2004 slides on a clearly marked, tabbed, and indexed page." *Id.* (citing Ex. 1004, 4–5).

Citing *Hall*, 781 F.2d at 899, Petitioner asserts that it "need not prove the specific date Stein 2004 became publicly available, only that in the ordinary course of PPD, Inc.'s business, Stein 2004 would have been accessible by the critical date." Pet. 20. Petitioner contends that a press release issued by PPD announcing the February 5, 2004, Analyst Day, stated that "it would make Stein 2004 available online 'shortly after the call for on-demand replay.'" *Id.* (citing Ex. 1005, 4). Petitioner asserts further that PPD "had an established pattern and practice" in the relevant time period "of uploading presentations to its website for review and download within a few days of their delivery." *Id.* at 20–21. Finally, Petitioner contends "if there were any doubt Stein 2004 was published before March 5, 2004, it was surely available for download no later than April 15, 2004, as captured by the Internet Archive." *Id.* at 22 (citing Ex. 1004, 4–5).

In our Decision on Institution, we determined that, for purposes of institution, Petitioner had "reasonably demonstrated that the Stein presentation was available to the public no later than April 15, 2004, and thus qualifies as prior art under at least 35 U.S.C. § 102(a)." Dec. Inst. 30.

Patent Owner argues that Petitioner has not met its burden of demonstrating that Stein is prior art. PO Resp. 45. First, Patent Owner

argues that Petitioner has not demonstrated by a preponderance of the evidence that the presentation at a PPD investor event on February 5, 2004, qualified as a printed publication. *Id.* at 45–47.

According to Patent Owner, an analysis of the factors set forth in *Klopfenstein* does not support Petitioner's assertion that the presentation qualifies as a printed publication. *Id.* at 46. Patent Owner argues that Petitioner has not provided any evidence that the slides were displayed at all, much less for how long. *Id.* The fact that the slides were purportedly shown at an "Investor Day" suggests that the presentation would have been viewed by business people, and not those of ordinary skill in the art. *Id.* In that regard, Patent Owner cites the deposition testimony of Petitioner's declarants, Drs. Mayersohn and Zusman, who both testified that they did not believe they had ever attended an investor day presentation. *Id.* (citing Ex. 2021, 191:19–21; Ex. 2022, 140:22–141:5). As to the third and fourth *Klopfenstein* factors, Patent Owner asserts "[g]iven the brevity of the Stein Presentation and the fact that it purported to present an extremely dense set of materials in a fleeting timeframe, there would not have been an expectation of copying or ease of copying in real time." *Id.* at 47.

Petitioner responds that Patent Owner's declarant, Dr. Kimball, testified that the ordinary artisan "is an entire drug development team." Reply 15 (citing Ex. 1056, 19:2–20:3). At least one of the members of such a team, Petitioner asserts, would have been aware of the Stein presentation given that PPD publicized the investor day presentation for weeks. *Id.* at 16 (citing Ex. 1005, 4). Moreover, Petitioner relies on Pink Sheet as reporting the presentation, as well as for supporting the ease of copying, as it did in fact "copy and distribute Stein's dosing regimen." *Id.* (citing Ex. 1013).

We conclude that Petitioner has not met its burden of establishing that the Stein presentation itself constitutes a printed publication under *Klopfenstein*. Petitioner asserts that a hyperlink was distributed to interested parties and was targeted to skilled artisans interested in drug development and discovery, citing Exhibit 1005 to support that statement. *See* Pet. 16.

Exhibit 1005[6] at page 4 is a press release advertising that PPD is to hold an analyst day on February 5, 2004. The press release states in full:

> PPD, Inc. (Nasdaq: PPDI) today confirmed that it will hold an analyst day for equity analysts and institutional investors on Thursday, February 5, 2004, at the Plaza Hotel in New York City from approximately 8:00 a.m. to 12:00 p.m. EST. Chief Executive Officer Dr. Fred Eshelman and other PPD senior management will deliver presentations regarding PPD's business strategies. Executives representing some of PPD's strategic partners will also be presenting their business as it relates to PPD.
>
> To attend the presentations, register via the investors section of the PPD Web site, http://www.ppdl.com. Note that space is limited. The event will also be Webcast live, and all interested parties will be able to access the Webcast through the investors section of the PPD Web site. The Webcast will be archived shortly after the call for on-demand replay.
>
> As a leading global provider of discovery and development services and products for pharmaceutical, biotechnology and medical device companies, PPD applies innovative technologies, therapeutic expertise and a commitment to quality to help clients maximize the return on their R&D investments. With proven early discovery through post-market resources, the company also offers unique compound partnering opportunities. PPD has more than 5,700 professionals in 26 countries around the world. For

[6] The page numbers for Exhibit 1005 refer to the page numbers added by Petitioner.

> more information on PPD, visit our Web site at http://www.ppdi.com.

Ex. 1005, 4.

Notably, the press release does not mention hyperlipidemia, hypocholesteremia, MTP inhibitors, or any information relating to the topic of the presentation, other than stating that PPD is a "leading global provider of discovery and development services and products for pharmaceutical, biotechnology and medical device companies." *Id.* The press release does not even mention Dr. Stein. Thus, there is nothing in the press release suggesting that the ordinary artisan in the cardiovascular/cardiac field, or interested in MTP inhibitors, should attend the presentation. We, therefore, decline to credit Dr. Mayersohn's testimony that "[a]person of ordinary skill in the art interested in the development of MTP inhibitors could apparently have attended the meeting or accessed the presentation itself *via* webcast or on the PPD website shortly thereafter" (Ex. 1003 ¶ 25 (citing the PPD Press Release)), as there was nothing in the press release discussing MTP inhibitors.

That finding informs our analysis of the factors set forth in *Klopfenstein*. Thus, although the ordinary artisan may have been able to copy the presentation, and although there may have been an expectation that the materials could be copied, Petitioner does not provide any evidence establishing that the target audience would have been an ordinary artisan in the relevant field.

We acknowledge that Dr. Stein's presentation was reported in Pink Sheet (Ex. 1013), but Pink Sheet was published after the presentation. And Pink Sheet does not provide any evidence that the target audience of Dr. Stein's presentation was an ordinary artisan in the cardiovascular/cardiac

field, as it merely states that Dr. Stein's statements were made during PPD's investor day. Ex. 1013. Moreover, we address the challenge based on Pink Sheet, which Patent Owner does not contest constitutes a printed publication, below.

Second, Patent Owner argues that Petitioner has not demonstrated by a preponderance of the evidence that the Stein slides were posted online "either prior to the March 5, 2004 filing date of the provisional application, or no later than April 15, 2004." PO Resp. 47. Patent Owner notes that Petitioner relies on "Wayback Machine" screenshots to show what may have been posted in April of 2004, but the screenshots do not show the Stein slides, but only a hyperlink. *Id.* (citing Ex. 1004, 4–5). Moreover, Patent Owner contends, there is no evidence as to what was at the hyperlink in 2004, and the hyperlink is defunct. *Id.* at 48 (citing Ex. 1004, 1, 4). If a user attempts to access the hyperlink, the Wayback Machine displays an error message, whereas other hyperlinks still link to a corresponding presentation. *Id.* (citing Exs. 2045, 2046). Thus, Patent Owner contends, that "makes it impossible to test the veracity of [Petitioner's] assertion that the Stein slides marked as Ex. 1014 actually appeared at this link." *Id.*

We again conclude that Petitioner has not met its burden of demonstrating by a preponderance of the evidence that the Stein slides were posted in such a way as to constitute a printed publication.

Petitioner cites Exhibit 1004 at pages 4 to 5 to support its contention that PPD posted the Stein 2004 slides on a clearly marked, tabbed, and indexed page. Pet. 19. Exhibit 1004 is the affidavit of Christopher Butler, the Office Manager at the Internet Archive. Ex. 1004, 1 ¶ 1. Exhibit A to the Affidavit appears to be an archived copy from PPD's website, showing a

link to "PPD Analyst/Investor Day: Microsomal Triglyceride Transfer Protein (MTP) Inhibitor (Implitapide Program), February 2004 (Adobe Acrobat file, 627 Kb)." *Id.* at 4. It also presents purported links to other webcasts. *Id.* at 5. Importantly, the Appendix to Mr. Butler's Affidavit does not show what could be found at those hyperlinks.

As contended by Patent Owner (PO Resp. 48), there is no evidence as to what was at the hyperlink in 2004, and the hyperlink is defunct. Petitioner does not appear to address that statement in its Reply. *See* Reply 15–17. When asked at oral hearing, counsel for Petitioner stated that merely because the hyperlink is now defunct, does not necessarily mean it was defunct five years ago. Tr. 24. Counsel for Petitioner stated further:

> [O]ne of the things is that PPD, Inc.'s January 2004 press release for the February 5, 2004 analyst day stated that it would make Stein 2004 available on line shortly after the call.
>
> So it's indicating that these slides would have been available and then you have the slides themselves. And so when you add up each of the things that we've identified in the petition, I think there is certainly substantial evidence that the Stein slides were available as of that date.

Id. at 25.

We conclude that the preponderance of the evidence does not support Petitioner's argument that Dr. Stein's slides themselves, once they were posted online for viewing and download, constituted a publication of the slides, and, thus, a printed publication for prior art purposes. Although the web page attached to Mr. Butler's affidavit does list a link to "PPD Analyst/Investor Day: Microsomal Triglyceride Transfer Protein (MTP) Inhibitor (Implitapide Program), February 2004 (Adobe Acrobat file, 627 Kb)" (Ex. 1004, 4), Petitioner does not provide any evidence that the hyperlink worked at some point such that the ordinary artisan would have

had access to the Stein slides, except for stating that the Stein slides themselves are evidence that the hyperlink worked. Petitioner, however, provides no evidence that the slides were obtained though that hyperlink, or any evidence at all as to the source of those slides.

We conclude, therefore, that Petitioner has not met its burden of demonstrating by a preponderance of the evidence that the Stein slides constitute a printed publication. Thus, Petitioner cannot demonstrate that the Stein slides in combination with Chang render the challenged claims obvious.

D. Obviousness over Pink Sheet and Chang

Petitioner asserts that claims 1–10 are rendered obvious by the combination of Pink Sheet and Chang. Pet. 31–46. Petitioner also presents a claim chart addressing each of the challenged claims. *Id.* at 32–37. Patent Owner contends that Petitioner has not established the obviousness of the challenged claims by a preponderance of the evidence. PO Resp. 26–44.

i. Overview of Pink Sheet (Ex. 1013)

Pink Sheet is a one page article entitled "Bayer/PPD Implitapide Development Follows *Zetia* Model as Statin Add-On" and reports comments made by PPD subsidiary MRL International CEO Dr. Evan Stein at PPD's investor day on February 5, 2004. Ex. 1013. According to the article, "PPD is conducting *Phase II* proof-of-concept studies on the use of implitapide (BAY-13-9952) as an add-on to statin therapy." *Id*. Pink Sheet teaches that "PPD is hoping to demonstrate implitapide's safety and efficacy in homozygous and severe heterozygous familial hypercholesterolemia 'where even high-dose statins are ineffective or inadequate.'" *Id.*

Specifically, Pink Sheet teaches:

> PPD is conducting three 39-week *Phase II* studies with dose titration occurring every five weeks based on safety and tolerability examined at four weeks. The starting dose will be 10 mg daily, escalating by 5 mg/day every five weeks to a maximum 40 mg/day.

Id.

Pink Sheet notes that Stein "acknowledged that MTP inhibitor projects have been pursued by a number of companies, including Bristol-Myers Squibb, Johnson & Johnson and Pfizer, he argued that the toxicity seen with some of those projects was related to the high doses used during trials." *Id.*

ii. Overview of Chang (Ex. 1015)

Chang teaches that atherosclerosis can cause coronary heart disease, one of the most common causes of cardiovascular morbidity and mortality. Ex. 1015, 562. Elevated levels of total and low density lipoprotein ("LDL") cholesterol are primary risk factors for atherosclerosis. *Id.* According to Chang, statins are effective in lowering LDL cholesterol and somewhat effective in lowering triglycerides, but have minimal effect on high density lipoprotein ("HDL") cholesterol. *Id.* Although reducing LDL cholesterol can reduce the risk of coronary heart disease, patients who have significantly reduced their LDL cholesterol levels may still experience clinical event. *Id.* Thus, inhibitors of MTP are of interest "as a mechanism for reducing not only plasma total and LDL cholesterol, but also plasma very low density lipoprotein (VLDL) cholesterol and triglycerides." *Id.*

Chang discusses studies of implitapide (BAY-13-9952) and lomitapide (BMS-201038) in WHHL rabbits, an animal model for

homozygous familial hypercholesterolemia, in which statins are minimally effective. *Id.* at 565. Chang teaches:

> Studies with BAY-13-9952 administered at 12 mg/kg/day for 4 weeks led to plasma total cholesterol and triglyceride reductions of 70 and 45%, respectively, conditions under which the hepatic VLDL secretion rate was decreased by 80%. BMS-201038 also showed efficacy in the WHHL rabbit, demonstrating an ED_{50} value for total plasma cholesterol and triglyceride lowering of 1.9 mg/kg and a complete normalization of atherogenic apoB-containing lipoprotein particles at a dose of 10 mg/kg.

Id. (references omitted).

Chang further discusses the clinical efficacy of MTP inhibitors, including implitapide (BAY-13-9952) and lomitapide (BMS-201038). *Id.* at 566. Chang discloses:

> CP-346086 showed evidence of activity consistent with its mechanism of action. When administered as a single oral dose to healthy human volunteers, CP-346086 reduced plasma triglycerides and VLDL cholesterol in a dose-dependent manner, with ED_{50} values of 10 and 3 mg, respectively, and maximal inhibition (100 mg) of 66 and 87% when measured 4 h after treatment. In a 2-week, multiple-dose, safety and toleration study in healthy volunteers, CP-346086 (30 mg) administered at bedtime, produced an average decrease in plasma total and LDL cholesterol of 47 and 68%, respectively, relative to either individual baseline values or placebo, with little change in HDL cholesterol. Plasma triglycerides were also decreased by up to 75% immediately after dose administration, but the reduction was transient.
>
> Similar efficacy was reported for BAY-13-9952, which produced a dose-dependent decrease in total cholesterol (45%), LDL cholesterol (55%) and triglycerides (29%) after 4 weeks of treatment at an oral dose of 160 mg/day. BMS-201038 also showed similar efficacy in phase I and phase II clinical trials.

Id. (references omitted).

Chang cites to "Half-year pharma operating highlights - MTP inhibitor research discontinued. *FDC Reports Pink Sheet* (2000) 62:20" in support of its statement that "BMS-201038 also showed similar efficacy in phase I and phase II clinical trials." *Id.* at 566 n.43, *id.* at 569. The report cited in footnote 43 states in full:

> **MTP inhibitor research discontinued**
>
> Development of microsomal transport protein lipid-lowering agent BMS-201038 has been discontinued after Phase II trials showed "adverse events in terms of liver function," Bristol Chief Scientific Officer Peter Ringrose, PhD, said. "We've concluded that this is really a mechanism-related effect rather than a molecule-related effect".

Ex. 2011.

Thus, Chang teaches:

> The impact of fat accumulation in the liver and intestine remains to be evaluated in the clinical setting, particularly in hepato-compromised patients and in patients suffering from diabetes or gastrointestinal abnormalities. In this regard, it is important to note that plasma ALT and AST levels were increased 3-fold above normal in 12 to 27% of patients receiving 80 mg/ day and 160 mg/ day doses of BAY-13-9952. Similar AST and ALT elevations, of a magnitude sufficient to halt the development of BMS-201038, were also reported. Whether these transaminase elevations are a consequence of hepatic lipid accumulation, as had been observed in experimental animals, or are structure-specific remains to be determined experimentally.

Id. at 567 (references omitted) (citing footnote 43 for halting the development of BMS-201038).

iii. Analysis of Combination of Pink Sheet and Chang

Petitioner relies on Pink Sheet for teaching a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, wherein the MPT inhibitor implitapide is administered in at least three step-wise,

increasing doses. Pet. 37 (citing Ex. 1013; Ex. 1002 ¶¶ 110, 123, 126, 127, 129, 130). According to Petitioner, the doses taught by Pink Sheet meet the limitations of claim 1 of "a first dose level is from about 2 to about 13 mg/day, a second dose level is from about 5 to about 30 mg/day, and a third dose level is from about 10 to about 50 mg/day," as well as being administered from about 1 to about 5 weeks. *Id.* at 37–38 (citing Ex. 1013; Ex. 1002 ¶¶ 110, 131–132. 135). Petitioner asserts that the ordinary artisan would have understood that the dosing protocol of Pink Sheet "is a conservative approach in a clinical trial designed to evaluate safety and tolerability." *Id.* at 39 (citing Ex. 1002 ¶¶ 135, 180; Ex. 1003 ¶¶ 66, 71). Petitioner acknowledges that Pink Sheet does not teach the use of the MTP inhibitor represented by the formula of claim 1, lomitapide. *Id.* at 38.

Petitioner relies on Chang for teaching "a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia using MTP inhibitors specifically including lomitapide." *Id.* (citing Ex. 1002 ¶¶ 124–125, 133–134).

Petitioner contends that the ordinary artisan would have combined Chang with Pink Sheet as Chang teaches that lomitapide is one of three discussed MTP inhibitors (another of which is implitapide, the MTP inhibitor used by Pink Sheet) that are furthest along in clinical trials, with each working in humans and being similarly effective. *Id.* at 40 (citing Ex. 1002 ¶¶ 96–99, 136–168; Ex. 1015, 566–567). Chang, Petitioner contends, also noted the issues with side-effects associated with MTP inhibitors, and, thus, MTP inhibitors could not compete with statins as monotherapy. *Id.* (citing Ex. 1015, 566–67; Ex. 1001, 8:27–30). According to Petitioner, that

problem was also addressed by Pink Sheet, which reports a solution to the problem. *Id.* That is, Petitioner asserts, Pink Sheet discloses:

> [F]ollow the clinical model established with ZETIA®, and use MTP inhibitors to target (a) niche conditions like HoFH and (b) levels of clinical improvement acceptable for adjunct therapy (in the ~18-24% range), by using a lower dose starting at 10 mg/day, evaluating the dose every 4 weeks, then escalating stepwise by 5 mg/day every 4-5 weeks to a maximum 40 mg daily dose.

Id. (citing Ex. 1002 ¶¶ 108–110, 139–143; Ex. 1003 ¶¶ 45–46). Because Chang teaches that lomitapide had progressed to clinical trials and was similarly effective to implitapide, Petitioner argues that the ordinary artisan would have had a reason to use lomitapide as taught by Chang as the MTP inhibitor in the method of Pink Sheet. *Id.* at 41 (citing Ex. 1002 ¶¶ 93–95, 97–98, 144; Ex. 1003, ¶¶ 45–56; Ex. 1015, 566–567).

Petitioner argues further that the ordinary artisan would have had a reasonable expectation of success of achieving the invention of claim 1, as implitapide and lomitapide have similar mechanisms and degrees of action, the existing data suggested that they should be dosed similarly, and escalating, step-wise dosing was routine clinical practice. *Id.* at 44–45 (citing Ex. 1002 ¶¶ 43–47, 59–67, 97, 98, 103–105; Ex. 1003 ¶¶ 18, 19, 47–54; Ex. 1015, 562–564).

Patent Owner responds that the protocol reported by Pink Sheet is fundamentally different from that of the claimed invention. PO Resp. 35. That is, Patent Owner asserts, the ordinary artisan would understand that Dr. Stein's protocol reported in Pink Sheet "was a standard dose-ranging study to find a dose of implitapide at which efficacy could be achieved with acceptable side effects." *Id.* (citing Ex. 2021, 211:12–213:9, 214:14–215:19; Ex. 2022, 132:15–133:21, 154:13–156:11; Ex. 2023 ¶¶ 127–129,

Ex. 2024 ¶ 116; Ex. 2025 ¶ 125. In contrast, Patent Owner asserts, the challenged claims are "directed to a forced dose titration regimen, where patients are treated with a regimen of lomitapide that ***requires*** the administration of ***at least three separate doses*** of lomitapide, titrated or escalated in intervals of one to four weeks, in order to ameliorate the tolerability and side effects associated with the compound." *Id.* at 35–36. Patent Owner argues that in the protocol disclosed by Pink Sheet, once a patient takes a dose that is not well tolerated, there is no further dose titration upward, whereas in the instant invention, patients would continue to receive higher doses regardless of the presence of side effects. *Id.* at 35–36.

Petitioner replies that the protocol of Pink Sheet is fundamentally the same as that of the challenged claims, asserting that Patent Owner's argument is not commensurate in scope with the claims. Reply 6. That is, Petitioner asserts, Pink Sheet teaches the claimed dosing schedule. *Id.* at 6–7 (citing Ex. 1058, 136:2–6, 138:11–139:13; Ex. 1048, 96:12–23).

We agree with Petitioner, and find that Pink Sheet teaches a dosing schedule that meets the limitations of independent claim 1, albeit with a different compound, implitapide, than that required by that of the independent challenged claim, that is, lomitapide. The dosing schedule required by the claim, and that taught by Pink Sheet, is shown in the table below.

Claim 1 of the '135 patent-dosing (at least three step-wise, increasing dose levels of MTP inhibitor)	Claim 1 of the '135 patent-period of time receiving dose	Pink Sheet-dosing	Pink Sheet-period of time receiving dose
about 2 to about 13 mg/day	about 1 to about 5 weeks	10 mg/day	5 weeks
about 5 to about 30 mg/day	about 1 to about 5 weeks	15 mg/day	5 weeks
About 10 to about 30 mg.day	about 1 to about 5 weeks	20 mg/day[7]	5 weeks

As can be seen from the above table, we find that the dosing schedule taught by Pink Sheet is encompassed by the dosing schedule of the challenged claims. Thus, the issue becomes whether the ordinary artisan would have substituted the MTP inhibitor lomitapide as required by challenged claim 1 for the MTP inhibitor implitapide taught by Pink Sheet.

Patent Owner responds further that in view of the known side effects of lomitapide, including liver toxicity, the ordinary artisan "would have been dissuaded from developing lomitapide." PO Resp. 26. In fact, Patent Owner asserts that BMS abandoned development of lomitapide. *Id.* at 26–27. Specifically, Patent Owner contends that although implitapide "was still in development as of March 2004, development of lomitapide had been halted nearly four years prior due to toxicity in phase I and II clinical trials." *Id.* at 27 (citing Ex. 2011). Moreover, according to Patent Owner, Chang "states that liver enzyme elevations were 'of a magnitude sufficient to halt

[7] According to Pink Sheet, the increase in 5 mg/day every 5 weeks may increase to a maximum 40 md/day. Ex. 1013.

the development of BMS-201038'" and "reported that lomitapide caused a ***three***-fold liver enzyme increase in animals." *Id.* (citing Ex. 1015, 567).

Patent Owner argues that because of the known liver toxicities of lomitapide, the ordinary artisan would not have looked to that compound. *Id.* Patent Owner relies on the deposition testimony of Petitioner's declarant, Dr. Zusman, who testified that "a compound that caused just a two-fold increase in liver enzymes might have made it '***too hot to handle***,' and that knowing a company had abandoned a compound due to liver toxicity issues would have dissuaded [the ordinary artisan] from pursuing that compound." *Id.* at 27–28 (quoting Ex. 2022, 174:11–175:8). Thus, a three-fold increase in liver enzymes in animal models, Patent Owner asserts, such as that seen for lomitapide, would have further dissuaded the ordinary artisan from pursuing that compound. *Id.* at 28. That, in conjunction with the fact that "there was no publicly-available data reporting the doses used in the clinical trials with lomitapide or the results observed from those clinical trials," would lead the ordinary artisan away from using lomitapide. *Id.* at 28–29 (citing Ex. 2023 ¶ 91; Ex. 2024 ¶¶ 104, 124–125; Ex. 2021, 168:6–173:18; Ex. 2025 ¶¶ 115–116).

Patent Owner contends also that Petitioner and its declarants, Drs. Zusman and Mayersohn, rely heavily on the statement in Chang "that implitapide, lomitapide, and CP-34086 had shown '"similar efficacy" in clinical studies.'" *Id.* (quoting Pet. 14). Patent Owner asserts, however, that Drs. Zusman and Mayersohn testified that Chang does not report any human data to support that statement. *Id.* at 31 (citing Ex. 2021, 168:6–173:18; Ex. 2022, 96:10–99:24). According to Patent Owner, footnote 43 of Chang, which supports the "similar efficacy" statement, "actually refers to a

Pink Sheet article reporting BMS' discontinuation of lomitapide, which contains no human clinical data whatsoever." *Id.* (citing Ex. 2011). Patent Owner further points out in that regard that Dr. Zusman testified that he had never reviewed that Pink Sheet article (i.e., Ex. 2011) in formulating his declaration. *Id.* (citing Ex. 2022, 98:16–22). Thus, Patent Owner asserts that Chang does not provide a reason to select lomitapide, nor does it provide any data suggesting that implitapide and lomitapide should be similarly dosed. *Id.* at 32 (citing Ex. 2022, 125:13–126:9).

Patent Owner argues further that as the clinical data, such as the doses tested, were not publicly available, the ordinary artisan would not have known what dose of lomitapide to start at in substituting lomitapide for implitapide in the method of Pink Sheet. *Id.* at 34. Patent Owner relies on the testimony of Petitioner's declarant, Dr. Zusman, for the proposition that, based on Chang alone, the ordinary artisan would not have known the lower dose of lomitapide that could be used to reduce or eliminate liver toxicities. *Id.* (quoting Ex. 2022, 111:8–112:3).

Petitioner replies that although Patent Owner argues that the ordinary artisan "would have been dissuaded from lomitapide because 'development of lomitapide had been halted [by BMS] … due to toxicity in phase I and II clinical trials,'" the "proper inquiry is whether [the ordinary artisan] would have been motivated to develop lomitapide as of the effective filing date of the '135 patent (*i.e.*, March, 2005), not at the time that *Chang* was published. 35 U.S.C. 103(a)." Reply 9 (alteration in original). As of the time of invention, Petitioner asserts, the ordinary artisan "would have understood in March, 2005 that the toxicity in the clinical trials was due to the high doses, not the lower doses required by the claims." *Id.*

Petitioner relies also on the Technology Donation Agreement (Ex. 2001), which we relied upon in the Institution Decision, arguing that the agreement is evidence that an ordinary artisan would have understood that implitapide and lomitapide could be used to treat certain rare disorders such as homozygous and severe heterozygous familial hypercholesterolemia, and as indicating that BMS abandoned lomitapide for business reasons. *Id.* at 11–12 (citing Inst. Dec. 19; Ex. 1048, 33, 101; Ex. 2001, 30).

Petitioner contends, therefore, the ordinary artisan "would have understood that BMS abandoned lomitapide for business reasons and that the toxicity in the clinical trials was due to the high doses." *Id.* at 12 (citing Ex. 1048, 109:17–22). Petitioner asserts, therefore, that the ordinary artisan would not have been dissuaded from pursuing treatment with lomitapide at lower doses, but would have been motivated to pursue it to treat rare disorders and as an add-on therapy to statins, as taught by Pink Sheet. *Id.* (citing Ex. 1048, 98–99; Ex. 1049 ¶ 124).

In determining whether obviousness is established by combining the teachings of the prior art, "the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). In addition, a reference disclosure is not limited only to its preferred embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art. *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

Although we find this issue to be very close, we find that the Petitioner has established by a preponderance of the evidence that the

ordinary artisan would have looked at other MTP inhibitors, such as lomitapide as taught by Chang, that could be used in the dosing protocol taught by Pink Sheet. Specifically, Pink Sheet teaches a dosing method with the MTP inhibitor, implitamide, wherein, as discussed above, the dosing schedule meets the dosing schedule required by claim 1. Ex. 1013. In addition, Pink Sheet discusses MTP inhibitors generally, and notes that they may have efficacy in situations where high-dose statins are ineffective or inadequate, such as homozygous and severe heterozygous familial hypercholesterolemia. *Id.* Pink Sheet also acknowledges that the toxicity seen with MTP inhibitors may have been due to the high doses used during the clinical trials. *Id.*

Chang discusses the clinical efficacy of MTP inhibitors, including implitapide (BAY-13-9952) and lomitapide (BMS-201038). Ex. 1015, 566. Specifically, Chang discusses the clinical efficacy of CP-346086, and then notes that similar efficacy was reported for implitapide and lomitapide. *Id.* Given that implitapide and lomitapide are from the same class of therapeutics, that is, MTP inhibitors, and that they are known to have similar clinical efficacy, based on the record before us, we determine that Petitioner has demonstrated a reasonable basis as to why the ordinary artisan would have substituted lomitapide as taught by Chang for implitapide in the method of Pink Sheet.

Patent Owner also contends that the ordinary artisan would not have had a reasonable expectation of success of substituting lomitapide for implitapide in the protocol taught by Pink Sheet. PO Resp. 38. According to Patent Owner, the protocol proposed in Pink Sheet is a "'proof-of-concept' study that Dr. Stein 'hoped' would demonstrate implitapide's

safety and efficacy, but the prior art nowhere reports the results of the study." *Id.* (citing Ex. 1013). Thus, the ordinary artisan would not have been able to draw any conclusion regarding that study in the absence of any reported results. *Id.* at 38–39.

Patent Owner asserts that both of Petitioner's declarants agree. *Id.* at 39. That is, Dr. Mayersohn testified "that to reach a conclusion as to whether the implitapide dosing regimen would have similar effects at similar doses in humans when used with lomitapide, results from the studies of both implitapide and lomitapide would be needed." *Id.* at 39–40 (quoting Ex. 2021, 262:24–263:19). Dr. Zusman, Patent Owner asserts, "similarly testified that [an ordinary artisan] would not have been able to reasonably predict whether Pink Sheet 2004's protocol would work for lomitapide without performing a clinical trial and obtaining data." *Id.* at 40 (quoting Ex. 2022, 178:16–179:3). Patent Owner asserts that crucial information for designing a successful dosing regimen, such as the doses that caused toxicity in humans used in BMS' trial, were not known. *Id.* at 41 (citing Ex. 2022, 175:10–17; Ex. 2021, 168:6–173:18).

Moreover, Patent Owner contends that as Dr. Mayersohn conceded, except for WHHL rabbits, the two compounds were not tested in the same animal models. *Id.* at 32 (citing Ex. 1003 ¶ 18; Ex. 2021, 120:24–121:3). And as to the studies in the WHHL rabbits, the data for the two compounds was produced from two unrelated studies, which "[t]he experts agree that because different protocols were used, the comparative value of the data is limited." *Id.* at 32–33 (citing Ex. 1033, 127; Ex. 1018, 753; Ex. 2022, 104:4–10; Ex. 2021; 110:13–19; Ex. 2023 ¶ 99). In addition, Patent Owner argues that as "lomitapide showed greater reductions in cholesterol and

triglycerides than implitapide in the same animal model, [the ordinary artisan] would have understood that lomitapide is potentially more potent and would thus require a different dosing strategy." *Id.* at 33 (citing Ex. 2023 ¶ 100; Ex. 2024 ¶ 105). Patent Owner asserts that result undermines Petitioner's argument that the ordinary artisan "would have reasonably expected lomitapide and implitapide to 'work comparably' and would have been motivated to administer them in the same dosing regimen." *Id.* (citing Pet. 43, Ex. 1003 ¶¶ 18–19).

Patent Owner argues further that Petitioner incorrectly asserts that because lomitapide and implitapide are in the same therapeutic class, that is, MTP inhibitors, an ordinary artisan would have dosed them similarly. *Id.* at 42. For example, Patent Owner asserts that statins may be dosed differently "depending on efficacy, safety, and PK/PD parameters." *Id.* (citing Ex. 2025 ¶¶ 79–80, Ex. 2023 ¶¶ 69-74). In fact, Patent Owner argues, Dr. Stein, in asserting that Dr. Rader's claims in the European application should be limited to lomitapide, "acknowledged that MTP inhibitors are not interchangeable: '. . . [N]ot all of the known MTP inhibitors may have an improved tolerability, safety or even effect if it is administered three-stepwise with increasing dosage of the MTP inhibitor.'" *Id.* at 43–44 (quoting Ex. 1020, 6). Thus, Patent Owner asserts that "the mere fact that lomitapide and implitapide are both MTP inhibitors, without more, would not have indicated to [an ordinary artisan] that the drugs should be dosed the same." *Id.* at 44 (citing Ex. 2024 ¶¶ 126–128; Ex. 2025 ¶ 126; Ex. 2023 ¶¶ 96, 68–74).

Petitioner replies that, as noted in the Institution Decision, there are many reasons why the ordinary artisan would have had a reasonable

expectation of success of achieving the claimed invention. Reply 12–13 (quoting Dec. Inst. 21). In addition, Petitioner asserts that we noted also in the Institution Decision that the prior art indicated that lomitapide and implitapide had similar efficacies. *Id.* at 13–14 (quoting Dec. Inst. 21–22). Moreover, Petitioner asserts that Patent Owner's expert acknowledged that it would be reasonable to look at members of the same therapeutic class of compounds in developing a dosing regimen. *Id.* at 14 (quoting Ex. 1058, 35–36, 175; Ex. 1056, 141).

Petitioner argues also that Patent Owner's arguments are not commensurate in scope with the challenged claims, as the challenged claims recite a broad dosing range. *Id.* at 14. Thus, Petitioner asserts, "as explained by the Board, Petitioner has made this showing: 'Given Chang's teaching that CP-346086, implitapide (BAY-13-9952), and lomitapide (BMS-201038) have similar efficacies, we determine that Petitioner has sufficiently demonstrated a reasonable expectation of success of substituting lomitapide for implitapide and achieve a dosage level that would fall within the claimed ranges.'" *Id.* at 14–15 (quoting Dec. Inst. 21–22).

"The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). As to reasonable expectation of success, we agree with Patent Owner that the ordinary artisan would not have had a reasonable expectation of success of combining Pink Sheet with Chang to arrive at the claimed invention. To the extent that Petitioner relies on our Institution Decision, we note that decision was based on the evidence of record at that time. The evidence advanced by Patent Owner during trial,

discussed herein, however, tips the scale in favor of a finding different from that set forth in our Institution Decision.

As noted by the ’135 patent, BMS abandoned clinical development of lomitapide as a drug for large scale use in the treatment of hypercholesterolemia because of significant and serious hepatotoxicities. Ex. 1001, 6:20–25; *see also* Ex. 2011 (stating that “[d]evelopment of microsomal transport protein lipid-lowering agent BMS-201038 has been discontinued after Phase II trials showed ‘adverse events in terms of liver function’”).

We find also that Petitioner has not provided any evidence showing which dosages of lomitapide demonstrated hepatotoxicities. *See* PO Resp. 41 (noting that “[n]ot even the doses used in BMS’s trials that caused toxicity in humans were known.”). As noted by Patent Owner (PO Resp. 31), footnote 43 of Chang, which supports the “similar efficacy” of implitapide and lomitapide, “actually refers to a Pink Sheet article reporting BMS’ discontinuation of lomitapide.” We also credit the testimony of Dr. Sacks in that regard, who declared:

> No Phase I or Phase II data for lomitapide exists in the prior art. As both Dr. Zusman and Mayersohn acknowledged in their depositions, not even the doses BMS used in the human trials were disclosed. Mayersohn Tr. (Ex. 2021) at 164:7-10; 245:17-22; Zusman Tr. (Ex. 2022) at 96:18-97:12; 99:5-19. Accordingly while the prior art reported that lomitapide had been tested in humans in Phase I and Phase II trials, none of the details or data from those trials were available to [an ordinary artisan]. In fact, the only information known to [an ordinary artisan] about the lomitapide human trials was that they revealed adverse effects to an extent great enough to cause BMS to discontinue its development of the drug. UPenn Ex. 2011. The lack of data, combined with the knowledge that lomitapide showed safety

> issues, would have caused [an ordinary artisan] to avoid further development of this molecule.

Ex. 2023 ¶ 91.

That finding is further supported by the testimony of Dr. Zusman, who stated during cross-examination:

> Q. . . . . Dr. Zusman, the prior art that you're aware of provides no PK or PD data for lomitapide, correct?
>
> A. Not that I'm personally aware of today.
>
> Q. Right. And the prior art provides no dose response in humans for lomitapide, correct?
>
> A. Not that I'm aware of today.

Ex. 2022, 175:9–17.

We find, therefore, that as the prior art did not teach which dosages of lomitapide demonstrated hepatotoxicities, the ordinary artisan would not have had a reasonable expectation of success that using the dosages taught by Pink Sheet for implitapide would reduce and/or avoid the hepatotoxicities seen with lomitapide while still showing a therapeutic effect. *See* PO Resp. 40 (discussing the testimony of Dr. Zusman that the ordinary artisan "would not have been able to reasonably predict whether Pink Sheet 2004's protocol would work for lomitapide without performing a clinical trial and obtaining data" (quoting Ex. 2022, 178:16–179:3)).

We find further that although Pink Sheet teaches that Dr. Stein stated that the toxicities of MTP inhibitors may be due to high doses during trials, he stated that those toxicities were related to only "*some of the projects*" pursued by a number of companies, including BMS, but did not state that BMS was one of those projects in which the toxicity was related to the use of a high dose. Ex. 1013 (emphasis added). Further compounding the

problem, Pink Sheet reports a proposed protocol, but does not report any data for the protocol using Dr. Stein's proposed MTP inhibitor, implitapide. *Id.*

In addition, Patent Owner has provided evidence that the ordinary artisan would not understand that all MTP inhibitors would be expected to act the same. As Patent Owner notes, Dr. Stein, whose protocol for implitapide is reported in Pink Sheet, opposed the European claims that corresponded to those of the '135 patent. Those claims referred to "the use of an MTP inhibitor for treating a subject suffering from a disorder associated with hyperlipidemia and/or hypercholesterolemia, wherein the MTP inhibitor is administered in at least three stepwise, increasing dosages of said MTP inhibitor to said subject." Ex. 1020, 5. Dr. Stein argued that the claims were not enabled for all MTP inhibitors. *Id*. Dr. Stein noted that all of the examples only referred to one MTP inhibitor, BMS-201038. *Id.* Dr. Stein asserted:

> Hence, the opposed patent does not teach the skilled person any other MTP inhibitor, and in which three-stepwise dosages of such MTP inhibitor should be used for the treatment of a human being or an animal. Therefore, it is impossible for the skilled person to rework the present alleged invention over the broad scope of protection claimed. In particular, not all of the known MTP inhibitors may have an improved tolerability, safety or even effect if it is administered three-stepwise with increasing dosage of the MTP inhibitor.

Id. at 6.

Those arguments made in the European Opposition support Patent Owner's argument (PO Resp. 44) that the ordinary artisan would not have understood the dosages reported for implitapide in Pink Sheet to necessarily have the same effect when using lomitapide, such that an acceptable

therapeutic response would be seen without the known unacceptable toxicities. Thus, those arguments further support our finding that the ordinary artisan would not have had a reasonable expectation of success of combining Pink Sheet with Chang to arrive at the challenged claims.

In making our findings as to the "reasonable expectation of success" factor, we keep in mind that absolute predictability is not required. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."). Here, Petitioner has not met its burden to show that a skilled artisan would have reasonably expected or predicted that lomitapide as taught by Change could be substituted for implitapide in the protocol of Pink Sheet with a reasonable expectation of treating hyperlipidemia or hypercholesterolemia, such that the lomitapide would be effective in the claimed method of treatment without unacceptable levels of toxicity. To the extent that this proceeding presents a close call, it is noteworthy that the burden is on Petitioner to demonstrate the patentability of the claims by a preponderance of the evidence. *In re Magnum Oil Tools Int'l, Ltd*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) ("In an *inter partes* review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee." (quoting *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).

In addition, we find that the evidence of secondary considerations is not insubstantial here. Factual inquiries for an obviousness determination include secondary considerations based on objective evidence of

nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The totality of the evidence submitted may show that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Before we make our final obviousness determination, we must consider the evidence of obviousness anew in light of any evidence of secondary considerations of nonobviousness presented by Patent Owner. *See Graham*, 383 U.S. at 17–18 ("Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."); *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) ("This objective evidence must be 'considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.'" (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)). Secondary considerations may include any of the following: long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise. *See Graham*, 383 U.S. at 17; *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Here, we find that commercial success supports the patentability of the challenged claims.

According to Patent Owner, its licensee, Aegerion, "received FDA approval for and launched JUXTAPID®, a lomitapide treatment for HoFH using the claimed dose titration method, in January 2013." PO Resp. 62. Patent Owner contends:

> Within a year of launch, JUXTAPID® sales totaled $48.5 million, and continued to grow each year, with sales of $158.37 million in 2014, $213.51 million in 2015, and $26.2 million for the first quarter of 2016. Aegerion Pharmaceuticals, Inc., U.S. Securities and Exchange Commission, Form 10-K (March 2, 2015) (Ex. 2012, "Aegerion 2014 10-K") at 95; Aegerion Pharmaceuticals, Inc., U.S. Securities and Exchange Commission, Form 10-K (March 15, 2016) (Ex. 2075, "Aegerion 2015 10-K") at 222; Aegerion Pharmaceuticals, Inc., U.S. Securities and Exchange Commission, Form 10-Q (May 16, 2016) (Ex. 2076, "Aegerion 2016 10-Q") at 74. To date, the product has generated over $420 million in revenue. JUXTAPID®'s sales numbers are particularly impressive given its orphan drug status and small patient population. These sales demonstrate that JUXTAPID® is a commercial success.

Id. at 63.

Patent Owner argues that as Juxtapid is a commercial embodiment of the claimed invention, nexus is presumed. *Id.* (citing *PPC Broadband, Inc. v. Corning Optical Comm. RF LLC*, 815 F.3d 734, 747–748 (Fed. Cir. 2016)). Patent Owner asserts further that "the titration method described in the FDA-approved label for JUXTAPID® is featured prominently in Aegerion's marketing materials." *Id.* In addition, Patent Owner argues that on the Juxtapid website, the dosing method is described conspicuously early on the website. *Id.* at 64 (citing Ex. 2301, 1). Moreover, on the site for healthcare providers, "an entire page is dedicated to the titration dosing method." *Id.* (citing Ex. 2302, 1–2).

Petitioner replies that Patent Owner did not establish nexus between the secondary considerations and the challenged claims. Reply 18. But as noted by Patent Owner, nexus is presumed. *PPC Broadband*, 815 F.3d at 747 (noting that in contested proceedings nexus is presumed as petitioner "has the means to rebut the patentee's evidence"). Moreover, Patent Owner

has presented evidence that in marketing Juxtapid, a dosing schedule that is encompassed by the challenged claims is prominently displayed in the marketing and prescribing material.

Petitioner further argues that Patent Owner's purported commercial success is not commensurate in scope with the claims, as "the claims are directed to treating hypercholesterolemia or hyperlipidemia while lomitapide (Juxtapid®) is exclusively approved for HoFH." Reply 23. Petitioner asserts further that Patent Owner has not established that any commercial success is due to the claimed titration method, as the "'Starting Juxtapid' website referenced by [Patent Owner] does not suggest a forced dosage method notwithstanding the presence of side effects; it instead states that the patient should '[s]top taking Juxtapid and tell your doctor if you have severe diarrhea.'" *Id.* at 22–23 (citing Ex. 2301, 3).

Initially, we note that Petitioner does not contest that Juxtapid is a commercial success, and, thus, in view of the unrebutted evidence provided by Patent Owner, we find that Patent Owner has established that Juxtapid is a commercial success.

As to Petitioner's argument that the Juxtapid website does not suggest a forced titration, as set forth in our section on claim construction above, we decline to construe independent challenged claim 1 as requiring a forced titration. Moreover, as shown in the table below, the dosing schedule of independent claim 1 encompasses the dosing method that is given to doctors on the Juxtapid website (Ex. 2301, 1):

Claim 1 of the '135 patent-dosing (at least three step-wise, increasing dose levels of MTP inhibitor)	Claim 1 of the '135 patent-period of time receiving dose	Dosing of Juxtapid	Juxtapid: Period of time receiving dose
about 2 to about 13 mg/day	about 1 to about 5 weeks	5 mg/day	At least 2 weeks
about 5 to about 30 mg/day	about 1 to about 5 weeks	10 mg/day	At least 4 weeks
About 10 to about 30 mg.day	about 1 to about 5 weeks	20 mg/day[8]	At least 4 weeks

We find, therefore, that the challenged claims are commensurate in scope with Patent Owner's evidence of commercial success. Thus, we find the unrebutted evidence of commercial success further supports the patentability of the challenged claims. Looking at the entire record before us, we conclude that Petitioner has not meet its burden to establish unpatentability of challenged claims 1–10 by a preponderance of the evidence over the combination of Pink Sheet and Chang.

E. Motion to Amend

As discussed above, because we conclude that Petitioner has not demonstrated the obviousness of the claims by a preponderance of the evidence, we need not reach the merits of Patent Owner's contingent Motion to Amend (Paper 24). We, thus, *dismiss* the motion a moot.

F. Patent Owner's Motion to Exclude

In its Motion to Exclude, Patent Owner seeks to exclude Petitioner's exhibits 1024, 1025, and 1050–1056. Mot. Exclude 1.

[8] The Juxtapid website contains one more dose of 40mg daily, for at least 4 weeks. Ex. 2301, 1.

First, as to Exhibits 1024, 1025, and 1050–1055, we dismiss the motion as moot as we did not rely on those exhibits in this final written decision.

As to Exhibit 1056, which is the Deposition Transcript of S. David Kimball, and which Patent Owner acknowledges that Petitioner cites in its Reply, Patent Owner argues that it timely objected to the exhibit as an improper duplicate of Exhibit 2304. Mot. Exclude 7.

Petitioner responds that Exhibits 2304 and 1056 are the transcripts of Petitioner's expert. Opp. Mot. Exclude 4. Although acknowledging that the party taking the deposition normally files the transcript, Petitioner asserts that its Reply cites to Ex. 1056, and Patent Owner does not cite to either exhibit. *Id.*

Patent Owner replies that Exhibit 2304 also contains Dr. Kimball's signed errata sheet and is, thus, the more complete of the two documents. Reply Mot. Exclude. 3. Patent Owner asserts that the citations in Petitioner's Reply can be updated to reflect the correct exhibit number, if necessary. *Id.*

Given the posture of this proceeding, that is, it is at final written decision, and as Patent Owner notes, the two documents are not exact duplicates, we decline to exclude Ex. 1056, but will allow both Exhibit 1056 and 2034 to remain in the record.

III. CONCLUSION

After considering Petitioner's and Patent Owner's positions and evidence, we conclude that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–10 of the '135 patent are unpatentable.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner has failed to show by a preponderance of the evidence that claims 1–10 of the '135 patent are unpatentable under 35 U.S.C. § 103(a);

FURTHER ORDERED that Patent Owner's Motion to Amend is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot as to Exhibits 1024, 1025, and 1050–1055, and denied as to Exhibit 1056; and

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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