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

GREEN, *Administrative Patent Judge*.

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

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 have jurisdiction under 35 U.S.C. § 314, 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." Upon considering the Petition and the Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–10. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner states that it "is concurrently filing 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.

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,” noting, however, that “each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population.” *Id.* at 2:4–7. 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 developed a series of compounds, including BMS-201038, 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.

Thus, according to the ’135 patent, the “invention is based on the surprising discovery that one may treat an individual who has with 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.

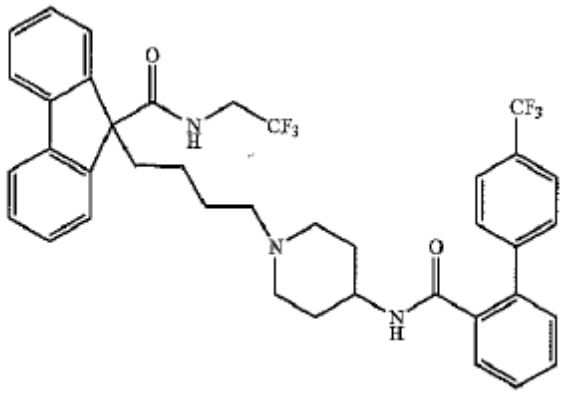
Id. at 11:60–12:3. The ’135 patent teaches further:

> 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.

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 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.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–10 of the '135 patent on the following grounds (Pet. 4):

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), as well as the Declaration of Michael Mayersohn, Ph.D. (Ex. 1003).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable constructions in light of the Specification of the patent in which they appear. *See* 37 C.F.R. §42.100(b); ("Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA," and "the standard was properly adopted by PTO regulation."), *In re Cuozzo Speed Techs., LLC*, 793 F.3d

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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").

1268, 1278–79 (Fed. Cir. 2015), *cert. granted, sub nom. Cuozzo Speed Techs. LLC v. Lee*, 84 U.S.L.W. 3218 (U.S. Jan. 15, 2016) (No. 15-446). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

We determine that, for purposes of this Decision, none of the terms in the challenged claims require express construction at this time. *See, e.g. 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).

B. Real Party in Interest

Patent Owner contends that the Petition should be denied on the basis that Petitioner failed to name all of the real parties in interest. Prelim. Resp. 11–13. Specifically, Patent Owner asserts that Petitioner named nine real parties in interest in its Petition, but failed to name IP Navigation Group, LLC and nXn Partners, LLC, which are listed in other Petitions filed by Coalition for Affordable Drugs ("CFAD"), the Petitioner here. *Id.* at 12. Patent Owner, thus, argues:

> Patent Owner has no ability to determine, in CFAD's intricate web of subsidiary organizations, whether these two firms are real parties in interest to the present matter. However, the fact that they appear as real parties in interest in numerous petitions brought by CFAD, but are absent here, strongly suggests that CFAD has failed to meet its burden to properly name the real parties in interest to this case.

Id. at 13.

The fact that the Coalition for Affordable Drugs may have named IP Navigation Group, LLC and nXn Partners, LLC as real parties in interest in other Petitions, but failed to name them as real parties in interest, is not sufficient, by itself, to demonstrate that Petitioner failed to name all the real parties in interest. Patent Owner points us to no evidence that IP Navigation Group, LLC and nXn Partners, LLC are real parties in interest in the instant proceeding.

C. Effective Filing Date of the '135 Patent

"Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications." *Lucent Technologies, Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008). A patent application is only entitled to the filing date of an earlier filed application "only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112." *In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995); *accord Mendenhall v. Cedarapids Inc.*, 5 F.3d 1557, 1566 (Fed. Cir. 1993) ("A patentee cannot obtain the benefit of the filing date of an earlier application where the claims in issue could not have been made in the earlier application."), *cert. denied*, 511 U.S. 1031 (1994). "[I]t is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, . . . or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010).

Petitioner contends that the '135 patent is not entitled to the filing date of its provisional application, Provisional application No. 60/550,915 ("the

'915 provisional"). Pet. 8–12. Specifically, Petitioner asserts that "[t]he '915 Provisional does not support the claimed dose ranges *or* the piperidine N-oxide derivatives." *Id.* at 8.

Petitioner notes that the independent claims of the '135 patent recite using an MTP inhibitor that is the illustrated compound (lomitapide), salts thereof, or "the piperidine N-oxide thereof." Pet. 10. Petitioner contends, however, that "[t]he '915 Provisional nowhere uses the term, or presents by structure, a 'piperidine N-oxide.'" *Id.* According to Petitioner, the "only discussion of 'piperidine' compounds in the '915 Provisional beyond the proffered chemical structures is, '[i]n some embodiments the MTP inhibitors are piperidine, pyrrolidine or azetidine compounds.'" *Id.* at 10–11 (quoting Ex. 1006, 11).

Patent Owner responds that the provisional application discloses a piperidine. Prelim. Resp. 21 (citing Ex. 1006, 11). Patent Owner contends:

> A person of ordinary skill in the art at the time of the invention would have been aware of piperidine N-oxide compound derivatives, and would have understood that the disclosure of the piperidine compounds in the provisional application includes piperidine N-oxides, a sub-class of piperidines.

Id. at 22.

Patent Owner's arguments, however, do not explain why the ordinary artisan would realize, upon reading the provisional application, that the invention relates to a piperidine N-oxide of the illustrated compound, lomitapide.

As to the claimed dose ranges, Petitioner notes that independent claim 1 requires an escalating dose range of from "about 2 to about 13 mg/day," "from about 5 to about 30 mg/day," and "from about 10 to about 50 mg/day," with independent claims 9 and 10 also reciting similar dosing

steps. *Id*. Petitioner argues that the '915 provisional focused on different dose-range combinations, and that the "particular numerical ranges claimed (*e.g.*, about 2–13 mg/day for the first dose) cannot be teased out of the multiplicity of dose ranges listed in the '915 Provisional, either expressly or inherently." *Id.* at 9 (citing Ex. 1002 ¶¶ 83–90).

Patent Owner responds that the "claimed dosage ranges are supported in the provisional application." Prelim. Resp. 17. Specifically, Patent Owner argues:

> For example, the first claimed dosage level "from about 2 to about 13 mg/day," is supported by Paragraph 0047 of the provisional application, which discloses that "[i]n some embodiments, the first dose level is from about 0.02 to about 0.59 mg/kg/day. In some embodiments, [the] second dose level is from about 0.06 to about 0.19 mg/kg/day." Ex. 1006 at 14. The skilled artisan would see that exemplary embodiments reference a 70 kg person, and would use this weight to calculate a range between 1.4 mg/day to 13.3 mg/day, which supports "about 2 to about 13 mg/day." *Id.* at 23.

Id. (footnote omitted). Patent Owner notes that the '915 provisional "discloses that patients weights may vary around the 70 kg mark, and that dosing may be adjusted accordingly." *Id.* at n. 2 (citing Ex. 1006, 22). Patent Owner makes similar arguments for the second and third dose levels (*id.* at 18), and presents a graphic showing the calculations (*id*. at 19).

Again, Patent Owner's arguments do not explain why the ordinary artisan would realize, upon reading the '915 Provisional, that the invention relates to the three dosage ranges required by the challenged claims. The ordinary artisan would have to choose a 70 kg man as the default. And even after the calculations are performed using that assumption, the claimed dosage ranges are not obtained. Thus, even if we were to accept the calculation set forth by Patent Owner, assuming a 70 kg man, a range of 1.4

mg per day to 13.3 mg per day is calculated for the first dose level. *Id.* at 19. The ordinary artisan would then need to envision immediately a dose range of about 2 to about 13 mg/day. *See Purdue Pharma L.P v. Faulding Pharm. Co.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000) (noting that in order to satisfy the written description requirement, "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims").

When we look at the second two calculations for the second two dose levels, the claimed ranges are even more difficult to discern. Thus, again assuming a 70 kg man, a range of 4.2 mg per day to 41.3 mg per day is calculated for the second dose level, whereas the claims require a dose level from about 5 to about 30 mg/day. Prelim. Resp. 19. Finally, making the same assumption as to the patient being treated, a range of 14 mg per day to 41.3 mg per day is calculated for the third dose level, whereas the claims require a dose level from about 10 to about 50 mg/day. *Id.* In the case of that third dose level, the claimed outside dose level of 50 mg/day is higher than the calculated amount of 41.3 mg/day.

Accordingly, based on the record before us at this time, we conclude that Petitioner has reasonably shown that the '135 patent is not entitled to benefit to the '915 provisional, and thus, for purposes of this decision, is only entitled to an effective filing date of March 7, 2005, the filing date of application No. 10/591,923, filed as PCT/US2005/007435 on that date.

D. 35 U.S.C. § 325(d)

Patent Owner argues that the art relied upon by Petitioner in challenging the '135 patent, Pink Sheet, Chang, and Stein, were before the Examiner during prosecution, even if they were submitted in a supplemental information disclosure statement that was filed after an allowance. Prelim.

Resp. 14–15. Thus, Patent Owner argues, Petitioner's obviousness arguments, raise issues that were considered, and rejected, by the Examiner. *Id.* at 15. Patent Owner requests that we exercise our discretion under 35 U.S.C. § 325(d) and deny the Petition. *Id*.

Title 35 U.S.C. § 325(d) states, in relevant part (emphasis added), that "[i]n determining whether to institute or order a proceeding under this chapter . . . the Director *may* take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." We have considered the facts and circumstances of the instant proceeding, and we decline to exercise our discretion to deny the Petition under 35 U.S.C. 325(d).

E. Obviousness over Pink Sheet (Ex. 1013) and Chang (Ex. 1015)

Petitioner asserts that claims 1–10 are rendered obvious by the combination of Pink Sheet and Chang. Pet. 31–46. Patent Owner disagrees. Prelim. Resp. 37–47.

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." 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*. 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.

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 notes further that the clinical efficacy of MTP inhibitors, including implitapide (BAY-13-9952) and lomitapide (BMS-201038), has been reported. *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).

iii. Analysis

a. Claims 1, 2, 5–8

Petitioner relies on Chang for teaching "a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia using MTP inhibitors specifically including lomitapide."

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. *Id.* (citing Ex. 1015, 564–65; Ex. 1002 ¶¶ 124, 125, 133, 134). According to Petitioner, the ordinary artisan would understand 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 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. Chang, Petitioner contends, also noted the issues with side-effects associated with MTP inhibitors, and thus could not compete with statins as monotherapy. *Id.* That problem was also addressed by Pink Sheet, which reports a solution to the problem. *Id.* That is, Petitioner asserts,

> follow 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. 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.

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 degree 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).

We conclude that Petitioner has shown a reasonable likelihood that independent claim 1 is rendered obvious by Pink Sheet and Chang. We have carefully considered Patent Owner's arguments to the contrary, but they do not convince us otherwise.

Patent Owner responds that Petitioner asserts that Pink Sheet merely reports on the Stein presentation, making the challenge based on Pink Sheet redundant on the ground based on Stein. Prelim. Resp. 37. Therefore, Patent Owner argues that we should decline to institute trial on the challenge based on Pink Sheet. *Id.* at 38.

We determine that Stein adds additional material that is not disclosed by Pink Sheet. Thus, we do not accept Patent Owner's suggestion to decline to institute trial on the challenge based on Pink Sheet based on the assertion that it is redundant to the challenge based on Stein.

Patent Owner contends further that Pink Sheet "does not disclose a method of step-wise administration of increasing doses of implitapide for the treatment of patients, nor does it suggest that such a regimen could alleviate the known adverse events associated with high dosages of MTP inhibitors." Prelim. Resp. 39–40. According to Patent Owner, the method disclosed by

Pink Sheet was designed to determine a single, low dose of implitapide, and, not an escalating dosing regimen. *Id.* at 40.

The method of challenged claim 1 requires "administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, [and] increasing dose levels of the MTP inhibitor." We agree with Petitioner that Pink Sheet discloses that method, albeit with a different MTP inhibitor than that required by independent claim 1. Patent Owner provides no persuasive evidence on this record that the ordinary artisan would discount that teaching just because it was in the context of a Phase II trial.

Patent Owner argues also that Petitioner has failed to set forth a sufficient reason why the ordinary artisan would have substituted lomitapide for implitapide as taught by Pink Sheet. Prelim. Resp. 41. According to Patent Owner, Petitioner's reasoning is based solely on the fact that both compounds are MTP inhibitors, but offers "nothing to suggest that MTP inhibitors are interchangeable with one another with respect to efficacy at the same dosages or with respect to the anticipated benefit of a dose escalation regime." *Id.* at 42. Moreover, Patent Owner argues, while Petitioner relies on Chang as identifying three MTP inhibitors that have made it to clinical trials, Petitioner does not explain why the ordinary artisan would have chosen lomitapide over the other disclosed MTP inhibitors. *Id.* at 43.

We determine, however, that Petitioner has sufficiently demonstrated that Chang provides a reason to substitute lomitapide for implitapide as taught by Pink Sheet. The fact that Chang discloses MTP inhibitors other than lomitapide, does not, by itself, make the selection of lomitapide any less

obvious. *See, e.g. Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (noting that the prior art's disclosure of a multitude of combinations does not render any particular formulation less obvious).

In addition, Chang notes that the clinical efficacy of MTP inhibitors, including implitapide (BAY-13-9952) and lomitapide (BMS-201038), has been reported. Ex. 1015, 566. 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 used lomitapide as taught by Chang for implitapide in the method of Pink Sheet.

Patent Owner further contends that Chang in general teaches away from the use of MTP inhibitors. Prelim. Resp. 43. In particular, Patent Owner relies on Chang's teaching that "[a]lthough MTP inhibitors have demonstrated impressive lipid lowering efficacy in clinical studies, potentially significant adverse effects surround this mechanism." *Id.* (quoting Ex. 1015, 6). According to Patent Owner, the ordinary artisan would not have combined Pink Sheet with Chang given that "clinical development of lomitapide had been previously halted due to safety concerns." *Id.* at 44. In fact, Patent Owner asserts, Bristol-Meyers Squibb, abandoned lomitapide and donated its rights to the drug. *Id.* (citing Ex. 2001, 30).

Chang was published in 2002, and reflected the understanding of the use of MTP inhibitors as monotherapy at that time. Pink Sheet, which was

published February 16, 2004, acknowledges that MTP inhibitors had been pursued by a number of companies, but that the toxicity seen was most likely related to the high doses used during trials. Ex. 1013. Thus, Pink Sheet, which reflects the state of the art at the time of invention, suggests using the MTP inhibitor as an add-on therapy to statins, in which safety and efficacy would be studied using escalating doses. *Id.* Thus, Pink Sheet was aware of the potential adverse effects associated with MTP inhibitors, but was still pursuing Phase II studies. *Id.*

That is supported by the evidence cited by Patent Owner. In the Technology Donation Agreement ("Agreement," Ex. 2001) cited by Patent Owner, the Agreement notes:

> The parties acknowledge that BMS-201,038, in clinical trials run by BMS prior to 2003, was shown to have significant and serious hepatotoxicities at the dosages used and therefore, while apparently efficacious for the treatment of certain lipid metabolism disorders, could not be developed as a pharmaceutical product of general or wide utility. However, based on certain available clinical data, the parties believed that BMS-201,038 might be useful as a treatment for certain rare and life-threatening disorders or conditions, for which there was no effective medical treatment. While it was not commercially feasible for BMS to develop the compound for such use, University was willing to pursue such development, and BMS was willing to facilitate University's development, with a view to benefiting the public.

Id. at 30.

Thus, Bristol-Meyers Squibb donated its rights to the Trustees of the University of Pennsylvania, Patent Owner in this proceeding, based on clinical data obtained prior to 2003. The Agreement notes, however, similarly to Pink Sheet, that it may be efficacious in certain groups of patients. *See, e.g.* Ex. 1013 (noting that the Phase II study hopes to

"demonstrate implitapide's safety and efficacy in homozygous and severe heterozygous familial hypercholesterolemia 'where even high-dose statins are ineffective or inadequate'").

Patent Owner contends also that Petitioner failed to articulate a reasonable expectation of success of combining Pink Sheet with Chang to arrive at the method of challenged claim 1. Prelim. Resp. 44. Patent Owner argues that the results of the study disclosed by Pink Sheet have not been reported in the prior art, and thus the "work could not have contributed to a reasonable expectation of success for lomitapide." *Id.* Patent Owner argues further that Petitioner and its experts "offer nothing to suggest that MTP inhibitors are interchangeable with one another with respect to the anticipated benefit of a dose escalation regime." *Id.* at 45.

According to Patent Owner, Petitioner relies too heavily on the statement in Chang that lomitapide showed similar efficacy in phase I and phase II clinical trial to establish a reasonable expectation of success. *Id.* at 46 (citing Ex. 1015, 5). Specifically, Patent Owner contends, it is unclear to what parameters Chang is referring, and "[r]ead in context, it is unclear whether Chang was comparing lomitapide to implitapide (BAY-13-9952) or to CP-346086, which is also discussed in Chang." *Id*. at 46.

Patent Owner contends further that Chang does not present any clinical trial data, but references a Pink Sheet article from 2000, which reports the discontinuation of trial by Bristol-Meyers Squib. *Id.* at 46–47 (citing Ex. 1015, 5 n. 43).

Patent Owner concludes that Petitioner

> has not established that a person of ordinary skill in the art would have understood Chang's statement regarding "similar efficacy" to mean that similar dosages of implitapide and lomitapide in

> humans could be expected to have the same or similar efficacy and toxicity. [Petitioner] has failed to carry its burden of showing that a person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed method.

Id. at 47.

We determine that Petitioner has set forth a sufficient reasonable expectation of success of combining Pink Sheet with Chang to arrive at the method of challenged claim 1. Initially, we note that all that is required is a reasonable expectation of success, not absolute predictability of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). While Pink Sheet does not report the results of its study with implitapide, that is not fatal to the challenge. Pink Sheet specifically acknowledges the toxicity seen in other studies, noting that was most likely due to high doses used, and thus an escalating dose would be used to determine a safe and tolerable dose. Ex. 1013. Chang notes that both implitapide and lomitapide have been the subject of clinical studies. Ex. 1015, 566. Chang also reports the results of a study performed in WHHL rabbits, an animal model for homozygous familial hypercholesterolemia, in which administration of with lomitapide (BMS-201038) and implitapide (BAY-13-9952) showed a reduction in total plasma cholesterol and triglycerides. *Id.* at 565.

Moreover, as to Chang's discussion of the clinical studies, Chang initially discusses CP-346086. *Id.* at 566. In the following paragraph, it discusses implitapide (BAY-13-9952) and BMS-201038 (lomitapide). *Id.* In context, therefore, the inference is that the similar efficacy of both implitapide and lomitapide is to CP-346086. That inference does not detract from Petitioner's contention that Chang provides a reasonable expectation of success, as both implitapide (BAY-13-9952) and lomitapide (BMS-201038)

had similar efficacies to CP-346086 in clinical studies. We note further that claim 1 recites first, second, and third dosage levels of about 2 to about 13 mg/day, about 5 to about 30 mg/day, and about 10 to about 50 mg/day, respectively. 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. Finally, we note that we have addressed Patent Owner's argument that Bristol-Meyers Squib discontinued its clinical trials of lomitapide above.

Therefore, for the reasons discussed above, we conclude Petitioner has shown a reasonable likelihood that it would prevail in showing that independent claim 1 is unpatentable as being rendered obvious by the combination of Pink Sheet and Chang.

Petitioner presents a claim chart demonstrating where each limitation of the dependent claims 2 and 5–8 may be found in Pink Sheet and Chang (Pet. 33–37), and also discusses each of those claims (*id.* at 45). Patent Owner does not specifically address the patentability of dependent claims 2 and 5–8 over the combination of Pink Sheet and Chang. We have reviewed the claim chart, the Pink Sheet and Chang references, as well as the supporting Declarations, and based on the record currently before us, we conclude also that Petitioner has shown a reasonable likelihood that dependent claims 2 and 5–8 are unpatentable as being rendered obvious by the combination of Pink Sheet and Chang.

b. Claims 3 and 4

As to dependent claims 3 and 4, Petitioner contends that claims 3 and 4 are inherent results of the method of claim 1. Pet. 45.

Patent Owner responds that Pink Sheet "does not suggest that the protocol would actually result in LDL reduction in the 18–24% range." Prelim Resp. 40. In particular, Patent Owner argues that Pink Sheet appears to be disclosing a "proof-of-concept" study, which had not yet started. *Id*. Thus, Patent Owner asserts, nothing in Pink Sheet

> allows a person of skill in the art to conclude what dosage (if any) of implitapide was safe and effective to achieve the 18-24% reduction of LDL that Dr. Stein sought, and thus would not have led a person of ordinary skill in the art to choosing the dosage ranges and step-wise dosing of lomitapide recited in the '135 Patent claims.

Id. at 41.

Dependent claim 3 recites the "method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-1, A-11, B, and E are reduced by at least 15%, compared to control levels." Dependent claim 4 recites the "method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-1, A-11, B, and E are reduced by at least 25%, compared to control levels." We agree with Petitioner that claims 3 and 4 are drawn to the inherent result of the method of claim 1. Moreover, Patent Owner has not demonstrated on this record that those limitations are anything more than the inherent result of the method of claim 1. Therefore, at this stage of the proceeding, we construe those limitations to be the inherent result of the method of claim 1.

In addition, even if the added recitations of claims 3 and 4 were to be considered as adding a limitation to the method of claim 1, as noted by Petitioner, Pink Sheet teaches that the planned dose range of implitapide will lower LDL-C by 18-24 %. Pet. 34. Chang teaches that in clinical trials of implitapide, a reduction of 45% in total cholesterol, 55% in LDL cholesterol, and 29% in triglycerides were seen in clinical trials, with similar results being shown for lomitapide. *Id.* (citing Ex. 1015, 566). Thus, we conclude that Petitioner has demonstrated a reasonable likelihood that the combination of Pink Sheet and Chang suggests lowering one or more of total cholesterol, LDL, fasting triglycerides, VLDL, lipoprotein (a), and apolipoproteins A-1, A-11, B, and E by 15 to 25%.

Therefore, for the reasons discussed above, we conclude Petitioner has shown a reasonable likelihood that it would prevail in showing that claims 3 and 4 are unpatentable as being rendered obvious by the combination of Pink Sheet and Chang.

c. Claims 9 and 10

Independent 9 requires that the first dosage level is administered for about two weeks, and the second and third dosage levels are administered for about two to about four weeks. Independent claim 10 requires that the first dosage level is administered for about one to about twelve weeks, and the second and third dosage levels are administered for about four weeks.

Patent Owner contends that, even if Pink Sheet could be read as teaching an escalating dose, it only discloses adjusting the amounts after five weeks, and does not disclose the intervals required by independent claims 9 and 10. Prelim. Resp. 57. Patent Owner notes that Petitioner appears to argue that varying the intervals of each dosage level would be routine

optimization, but asserts that it does not associate that contention with any particular claim or time period. *Id.* at 58.

Petitioner in its discussion of the combination of Pink Sheet and Chang, notes:

> A skilled artisan considering the teachings of Pink Sheet 2004 would also understand that the disclosed dosing schedule (5-week steps) is a conservative approach in a clinical trial designed to evaluate safety and tolerability. (*See* Zusman, ¶¶ 135, 180; Mayersohn, ¶¶ 66, 71). They would also understand that acceptable results at the 4-week mark indicate that intervals shorter than 5 weeks (*i.e.* 4 weeks or less) would be acceptable. (*See* Zusman, ¶¶ 135, 180; Mayersohn, ¶¶ 66, 71). Indeed, dose-titration at 2-4 week intervals was established clinical practice for many cholesterol-lowering medications (*see* Section VI). Finally, varying the timing of the dose escalation according to the patient's clinical response represents obvious, routine optimization for persons of ordinary skill in the art; it has been practiced for many years with lipid-lowering medications. (*See* Zusman, ¶¶ 168, 175, 180, 185; Mayersohn, ¶¶ 20, 66, 71, 74).

Pet. 39.

Thus, Petitioner asserts, the "claimed dosing intervals . . . reflect routine variation when applying the combined teachings of Pink Sheet [ ]and Chang," and the claimed dosing intervals would have been obvious to the ordinary artisan at the time of invention. *Id*. at 42 (citing Ex. 1002 ¶¶ 168, 175, 180, 185; Ex. 1003 ¶¶ 20, 66, 71, 74).

We determine that Petitioner has reasonably demonstrated that the dosing schedules required by independent claims 9 and 10 would have been obvious to the ordinary artisan at the time of invention. In particular, at this stage of the proceeding, we credit Dr. Zusman's testimony that

> it would have been obvious to a person of ordinary skill in the art to modify the escalating dose titration regimen taught by the Pink Sheet to administer each dose level based on the

> subject's clinical response, which would include appropriate adjustments within, *e.g.*, the 4 week time interval taught by the Pink Sheet as well as within the claimed first dose interval of "about 2 weeks". . . . [O]rdinarily skilled artisans would have been familiar with side effects of lipid-lowering drugs and experienced with how to minimize them. This knowledge is reflected in the PDR teaching escalating dose titration regimens for common cholesterol-lowering drugs such as statins, fibrates and niacin, ***each and every one of which includes a 4 week period between adjusting dose levels, and many of which also include a 2 week period.*** The dosing instructions for NIASPAN include administration for 1-4 weeks between escalating doses. LIPITOR should be analyzed within 2-4 weeks and adjusted accordingly. ADVICOR "must be titrated" and "[d]ose adjustments should be made at intervals of 4 weeks or more." PRAVACHOL dosing should be analyzed "within 4 weeks" and dosage adjusted based on the patient's response. LESCOL dosing should likewise be analyzed "within 4 weeks" and dosage adjusted based on the patient's response. ZOCOR dosage adjustments "should be made at intervals of 4 weeks or more." MEVACOR also teaches that dosing adjustments "should be made at intervals of 4 weeks or more." TRICOR dosing "should be adjusted if necessary . . . at 4 to 8 week intervals." COLESTID dosage increases "should occur at 1- or 2- month intervals." Thus, the timing of the dosage adjustment in claim 9 represents nothing more than what skilled artisans already knew how to do, and did as a matter of routine with drugs and dose titration in this field.

Ex. 1002 ¶ 180; *see also* ¶ 185 (referencing ¶ 180 as to claim 10).

Therefore, for the reasons discussed above, we conclude Petitioner has shown a reasonable likelihood that it would prevail in showing that independent claims 9 and 10 are unpatentable as being rendered obvious by the combination of Pink Sheet and Chang.

iy. Conclusion

For the reasons set forth above, we conclude that Petitioner has established a reasonable likelihood that claims 1–10 are rendered obvious by the combination of Pink Sheet and Stein,

F. Obviousness over Stein (Ex. 1014) and Chang (Ex. 1015)

Petitioner contends that claims 1–10 are rendered obvious by the combination of Stein and Chang. Pet. 46–56. Patent Owner disagrees. Prelim. Resp. 48–52, 56–58.

i. Availability of Stein (Ex. 1014) as Prior Art

"The determination of whether a reference is a 'printed publication' under 35 U.S.C. § 102(b) 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). "The 'printed publication' bar is grounded on the principle that once an invention is in the public domain, it is no longer patentable by anyone." *Id.* at 1349 (quoting *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986)) (internal brackets removed).

Thus, "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d at 899. "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)).

As to disclosures at communal events, in *In re Klopfenstein* the Federal Circuit set out a list of "factors [to] aid in resolving whether or not a

temporarily displayed reference that was neither distributed nor indexed was nonetheless made sufficiently publicly accessible to count as a 'printed publication' under § 102(b)." *Klopfenstein*, 380 F.3d at 1350. The court listed those factors as follows: "[1] the length of time the display was exhibited, [2] the expertise of the target audience, [3] the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and [4] the simplicity or ease with which the material displayed could have been copied." *Id.*

According to Petitioner, 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.* Moreover, it was reported in The Pink Sheet. *Id.* at 16–17 (citing Ex. 1002 ¶¶ 106–110; Ex. 1003 ¶¶ 23–25).

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.

Patent Owner responds that the presentation of Stein is not a printed publication, as Petitioner "has provided no corroboration that the presentation took place as scheduled, or that the slides of interest were actually displayed." Prelim. Resp. 24. Patent Owner argues further that consideration *Klopfenstein* factors do not help Petitioner. *Id.* at 25–30.

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. Citing *In re Hall*, 781 F.2d 897, 899

(Fed. Cir. 1986), 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." *Id.* at 20. Petitioner contends that press release issued by PPD, Inc., 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, Inc. "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).

Patent Owner responds that Petitioner has not demonstrated that the slides were publicly accessible, as the Wayback Machine screen relied upon by Petitioner does not display the slides themselves, but only a hyperlink. Prelim. Resp. 32 (citing Ex. 1004, 4–5). Patent Owner contends further that Petitioner "has also failed to offer credible evidence of the alleged publication date." *Id*. According to Petitioner, the "Wayback Machine 'evidence' in this case only shows at most that the slides were available on April 15, 2004, and none of CFAD's other proofs bridge the gap to demonstrate that the slides were available to skilled persons prior to March 5, 2004." *Id.* at 35.

As discussed above, for purposes of this decision, Petitioner has reasonably shown that the '135 patent is not entitled to the filing date of the '915 provisional, and thus has an effective filing date of March 7, 2005.

Moreover, we conclude for purposes of this decision that Petitioner has 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). Although Patent Owner contends that it will demonstrate that Dr. Rader conceived the dose escalation protocol prior to February 4, 2004, that evidence is not currently of record. Thus, as Stein qualifies as prior art at least under § 102(a), we need not determine at this preliminary stage of the proceeding whether it qualifies as prior art as well under § 102(b).

ii. Overview of Stein (Ex. 1014)

Stein is a slide set prepared by Evan Stein, M.D., Ph.D., for PPD, Inc. Ex. 1014, 4. According to Stein, the lipid lowering market is one of the largest therapeutic segments, of which statins are the largest component. *Id.* at 7. Thus, "[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, have developed MTP inhibitors, noting further that some of the companies 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 a low doses of 10 mg, and then titrated by 5 mg "based on 'safety' every 5 weeks." *Id.* at 37.

iii. Analysis

Petitioner relies on Stein for essentially the same teachings as Pink Sheet, as discussed above. Pet. 46; *see also id.* at 52 (discussing the specific teachings of Stein). Petitioner notes, however, that Stein provides additional, non-cumulative information, such as providing clinical data from previous implitapide trials in humans and animals, as well as the challenges presented by the use of MTP inhibitors. *Id.* at 46.

Petitioner relies on Chang as discussed above, and presents similar arguments for why the ordinary artisan would have combined Stein with Chang, as well as had a reasonable expectation of success of arriving at the claimed invention. *Id.* at 52–56. Petitioner notes that Stein further "clarified the nature of the market opportunity for MTP inhibitors as adjunctive therapy." *Id.* at 54.

Patent Owner incorporates the arguments it made with respect to the challenge over Pink Sheet and Chang (Prelim. Resp. 48–52, 56–58). Those arguments are not convincing for the reasons set forth in the analysis of that challenge.

iv. Conclusion

Upon review of the Petition and Preliminary Response, and for reasons already discussed as to the challenge over the combination of Pink Sheet and Stein, we determine that Petitioner has shown a reasonable likelihood that claims 1–10 are rendered obvious by Stein and Chang.

G. Secondary Considerations

Patent Owner contends that secondary considerations, such as unexpected results, commercial success, and long-felt need, support the patentability of the challenged claims. Prelim. Resp. 52–56.

As to unexpected results, Patent Owner contends that "the escalating dosing regimen claimed in the '135 Patent showed a decrease in side effects at higher doses as compared to patients who were administered the higher dose without the prior step-wise dosing." *Id.* at 52. Patent Owner notes that Bristol-Meyers Squib had abandoned lomitapide, asserting that "Dr. Rader was the first to evaluate the efficacy and safety of lomitapide using a dose-titration strategy of step-wise, increasing dose levels, and surprisingly found a substantially improved tolerability profile and significant lipid-lowering effects using this strategy." *Id.* at 52–53.

At this early stage of the proceeding, however, Patent Owner presents little evidence demonstrating unexpected results. Moreover, as discussed above, both Pink Sheet and Stein, which were published around the time of invention of the challenged claims, acknowledge that companies had abandoned MTP inhibitors. Both references, however, disclose that MTP inhibitors may have efficacy in combination therapy at reduced doses, and both disclose using an escalating dosing regimen to determine an efficacious safe dose.

As to commercial success, Patent Owner argues that commercial success of Juxtapid® supports the patentability of the claims, because "in its first year on the market it generated approximately $48.5 million in revenue from net product sales." Prelim. Resp. 53. According to Patent Owner, the 2015 sales are expected to be between $205 and $215 million. *Id.* at 54.

Patent Owner duplicates also the label of Juxtapid® which discloses the recommended dosing, arguing that the "dosing scheme falls squarely within the ranges claimed in the '135 patent." *Id.* at 54.

At this early stage, Patent Owner's evidence, however, is insufficient to establish commercial success. For example, the statements are general claims of net sales, without any market share data.

As to long-felt need, Patent Owner contends that the invention met a long-felt need in the treatment of homozygous familial hypocholesteremia, which is minimally responsive to other, conventional, lipid-lowering therapies. Prelim. Resp. 55–56.

At this stage of the proceeding, Patent Owner presents little evidence, however, showing specifically how long this need existed, and, therefore, falls short of demonstrating that an art-recognized problem existed for a long period of time without solution. *See, e.g. Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) ("long-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem"). Moreover, where Pink Sheet and Stein suggest the claimed method of treatment, the record at this stage indicates that a prior art solution to the alleged problem was available at the time of the invention.

Based on the information presented at this stage of the proceeding, we are not persuaded that Patent Owner has shown sufficiently that the claimed invention resulted in unexpected results, commercial success, or that the claimed invention satisfied a long-felt need. Our factual findings and conclusions at this stage of the proceeding are based on the evidentiary

record developed thus far, that is, prior to Patent Owner's Response. Our final decision will be based on the record as fully developed during trial.

III. CONCLUSION

For the foregoing reasons, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–10 of the '135 patent are unpatentable under 35 U.S.C. §103(a).

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or any underlying factual and legal issues.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. §314(a), an *inter partes* review is hereby instituted on the following grounds:

Claims 1–10 as obvious over Pink Sheet and Chang; and

Claims 1–10 as obvious over Stein and Chang.

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized; and

FURTHER ORDERED that 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 commencing on the entry date of this decision.

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