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 No. 8,618,135

PATENT OWNER PRELIMINARY RESPONSE

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I. INTRODUCTION

Petitioner Coalition for Affordable Drugs VIII, LLC ("CFAD") has not shown a reasonable likelihood of demonstrating that at least one claim of U.S. Patent 8,618,135 ("the '135 Patent") is unpatentable, and its petition should therefore be denied.

The '135 Patent claims a method of treating high levels of fats (hyperlipidemia) and cholesterol (hypercholesterolemia) in the blood through the step-wise administration of increasing doses of lomitapide, an inhibitor of "microsomal triglyceride transfer protein" ("MTP"). This invention helped to solve a problem regarding the safety and tolerability of lomitapide that had stymied others in the pharmaceutical industry.

Starting in the late 1990's, Bristol-Myers Squibb ("BMS") was developing compounds in the MTP inhibitor class, including BMS-201038 (lomitapide), for treating hyperlipidemia and hypercholesterolemia. Ex. 1001 at 5:47-49. BMS discontinued development of lomitapide when clinical trials with fixed doses of the drug revealed liver and gastrointestinal adverse effects that limited the drug's usefulness for treating patients with hyperlipidemia. Ex. 1001 at 6:20-25; Ex. 2002 at 34. It subsequently donated rights to the drug to the University of Pennsylvania. Ex. 2001 at 1.

Dr. Daniel Rader, a professor at the Perelman School of Medicine at the University of Pennsylvania, and the inventor of the '135 Patent, began pursuing clinical development of lomitapide using a different approach. Whereas BMS had attempted to develop a fixed dose of the drug, Dr. Rader sought to reduce the side effects that had led to BMS discontinuing development of lomitapide by starting with a low dose of the drug and using a step-wise administration of increasing doses. Dr. Rader discovered that in many patients this administration regimen surprisingly reduced the incidence and intensity of side effects that had impacted the tolerability of the drug, while still allowing effective treatment of patients' hyperlipidemia. Ex. 1010 at 2-3, ¶¶ 9-14; Ex. 1001 at 13:30-62.

The '135 Patent claims embody Dr. Rader's discovery that hyperlipidemia and hypercholesterolemia can be treated through administration of lomitapide in increasing step-wise dosages, wherein each dose level is administered for a number of weeks. *See e.g.*, Ex. 1001, claim 1. Dr. Rader's discovery is particularly significant to patients who suffer from homozygous familial hypercholesterolemia ("HoFH"), a condition characterized by extremely high cholesterol levels, which was generally not effectively treated with the therapeutic agents that were known in the art.

CFAD's Petition, which attempts to undermine Dr. Rader's invention, is deficient in a number of different ways. First, CFAD has failed to identify all of the real parties in interest to this proceeding, as required by 35 U.S.C. § 312. 35 U.S.C. § 312(a)(2). CFAD's other IPR petitions identify real parties in interest that have not been identified here.

Second, CFAD relies on three purported prior art references (all of which were considered by the Examiner during prosecution), but fails to meet its burden to prove that two of them—Stein 2004 and the Pink Sheet 2004—are prior art under 35 U.S.C. §§ 102(a) or 102(b). CFAD does not present proof that these references were publicly available prior to the priority date.

Third, CFAD's references relate to a different drug, implitapide, and to a study which sought to establish a fixed dose of that drug. None of the prior art relied on by CFAD teaches or suggests a step-wise escalating dose treatment regimen with lomitapide.

Because CFAD has failed to meet its burden of proving that a person of skill would have been motivated by the prior art to develop the step-wise, escalating dose regimen claimed in the '135 Patent, and that they would have had a reasonable expectation of success in doing so, the Board should deny CFAD's petition.

II. BACKGROUND FACTS

A. Hypercholesterolemia and Hyperlipidemia

Hypercholesterolemia, a condition characterized by very high levels of cholesterol in the blood, is a well-known risk factor for atherosclerotic cardiovascular disease ("ASCVD"), the major cause of mortality in the Western world. Ex. 1001 at 1:24-25. Patients with ASCVD experience a build-up of plaque inside their arteries, making it difficult for the arteries to carry oxygen-rich blood to the heart, brain, and other parts of the body. It is well understood that lowering total cholesterol ("TC") and low-density lipoprotein ("LDL") cholesterol ("LDL-C") is associated with a significant reduction in clinical cardiovascular events. Ex. 1001 at 1:26-30.

Hypercholesterolemia is a form of hyperlipidemia, a condition in which elevated levels of lipids are detected in blood. Triglycerides are one type of fat (lipid) found in the blood. Although triglycerides store unused calories and provide the body with energy, higher-than-normal triglyceride levels are often associated with known risk factors for heart disease. Ex. 1001 at 1:49-52. Elevated triglyceride levels may also contribute to thickening of artery walls, a physical change that is believed to be a predictor of atherosclerosis. *Id.* at 1:52-54.

B. Treatment of Hypercholesterolemia and Hyperlipidemia

At the time of the invention, a number of drug treatments were available for lowering serum cholesterol and triglycerides. The most well-known class of agents was (and perhaps still is) statins. Ex. 1001 at 2:23-25; 31-32. Other well-known treatments included niacin and fibric acid derivatives ("fibrates"). *Id.* at 2:50-52; 59-63.

However, prior to the invention of the '135 Patent, treatment in patients with a severe form of familial hypercholesterolemia known as homozygous familial hypercholesterolemia ("HoFH") was challenging because LDL levels remained extremely elevated despite aggressive use of known combination therapy. Ex. 1001 at 1:33-38; 4:24-29. HoFH is a rare genetic condition in which the LDL receptors are minimally (if at all) functional. Ex. 2002 at 11-12. Conventional lipid-lowering therapies such as statins were generally not effective in HoFH patients, because statins require a functioning LDL receptor to work. *Id.* at NDA at 13, 29. Patients with HoFH develop early and severe ASCVD due to elevated LDL-C levels, which may lead to early cardiac-related death. *Id.* at 12. Effective medical therapy was therefore urgently needed for this group of high-risk patients.

Accordingly, although a number of treatments were available to the general population for lowering serum cholesterol and triglycerides, "each [had] its own

drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population." Ex. 1001 at 2:4-7. And in terms of the high-risk HoFH patients, there was an extremely limited range of treatment options that were considered both safe and efficacious. *Id.* at 3:56-58. Accordingly, there was a need in this field for therapeutics which did not suffer from the limitations of the then-existing drug treatments for hypercholesterolemia and hyperlipidemia.

C. The Development of Lomitapide

In June 1996, BMS submitted an Investigational New Drug Application ("IND") for BMS-201038 (lomitapide), which is an MTP inhibitor. Ex. 2002 at 34. MTP is a protein responsible for shuttling lipid molecules between membranes, as well as assembling lipoproteins that contain apolipoprotein B ("apo-B"). It is thought that MTP mediates triglyceride absorption from the intestine and lipoprotein secretions from the liver by linking lipids to apo-B. Accordingly, inhibition of MTP typically leads to decreases in circulating levels of apo-B-containing lipoproteins, including LDL-C. Ex. 2002 at 14.

1. BMS Abandons Lomitapide

The BMS development program included clinical studies designed to assess the safety, pharmacokinetics, and pharmacodynamics of lomitapide as a monotherapy at fixed doses in subjects with hypercholesterolemia. Ex. 2002 at

34. Although substantial dose-related decreases in serum lipid parameters were observed, the clinical trials revealed severe, dose-limiting adverse events. These adverse events, occurring at fixed doses ranging from 25 mg/day to 100 mg/day, included gastrointestinal events (*e.g.*, diarrhea) and aminotransferase elevations (an indicator of liver damage, most likely related to the known MTP side effect of increased hepatic fat) that led to a high rate of treatment discontinuations. Ex. 1001 at 6:20-25; Ex. 2001 at 30, ¶ B; Ex. 2002 at 34. Ultimately, BMS abandoned the development of lomitapide in 2000 due to the drug's side effects. Ex. 2002 at 34.

2. The Rader Study

Specifically citing the "significant and serious hepatotoxicities in the dosages used" in the BMS development program, and noting that lomitapide "could not be developed as a pharmaceutical product of general or wide utility[,]" in 2003 BMS transferred the IND for BMS-201038 to the University of Pennsylvania. Exhibit 2001 at 30, ¶ B. Prior to this time, Dr. Daniel Rader, a professor at the Perelman School of Medicine at the University of Pennsylvania, began advancing the idea of the clinical development of lomitapide as a treatment for HoFH, and requested the transfer of the IND from BMS.

At least as early as June 2003, Dr. Rader and his colleague, Dr. Marina Cuchel, initiated a Phase II study designed to evaluate the efficacy and safety of lomitapide in the treatment of subjects with HoFH (Clinical Trial Identifier NCT01556906 ("the Rader Study")). *See* Ex. 2002 at 34-35; Ex. 2003 at 2-3. This was the first study to evaluate the administration of an MTP inhibitor using a dose-titration strategy of step-wise, increasing dose levels in an attempt to improve tolerability and render the drug useful for treating patients. Dr. Rader and his team employed a dosing regimen of administering lomitapide at a low dose (0.03 mg/kg) and progressively escalating to higher doses every 4 weeks (0.1 mg/kg, 0.3 mg/kg, and 1.0 mg/kg, respectively). Ex. 2002 at 35; see also Ex. 2004 at 3-4.

The Rader Study showed a substantially improved tolerability profile and significant lipid-lowering effects when lomitapide was administered using this dose-titration strategy. Ex. 2004 at 8 (". . . [W]e devised a dose-titration strategy that might allow the intestine to accommodate the increasing inhibition of [MTP]. Under these conditions, all six patients tolerated the drug up to the highest dose . . . with relatively minor gastrointestinal side effects."); *id.* at 7-8 ("Plasma levels of all other apolipoprotein B-containing lipoproteins were similarly reduced by inhibition of the microsomal triglyceride transfer protein"). The study concluded prior to February 4, 2004. Ex. 2005 at 8.

3. U.S. Provisional Application No. 60/550,915

On March 5, 2004, after the Rader Study was completed, Dr. Rader filed U.S. Provisional Patent Appl. No. 60/550,915 with the United States Patent and Trademark Office. This application, entitled "Methods For Treating Hyperlipidemia And Hypercholesterolemia While Minimizing Side-Effects," disclosed and claimed a method of treating hyperlipidemia and hypercholesterolemia by administering an effective amount of an MTP inhibitor such as lomitapide in a series of escalating doses. *See*, *e.g.*, Ex. 1006 at 31.

Subsequently, on March 7, 2005, Dr. Rader filed PCT/US2005/007435. A national stage entry application, U.S. Appl. No. 10/591,923 ("the '923 Application"), was filed on September 5, 2006. The '923 Application issued as U.S. Pat. No. 7,932,268 on April 26, 2011. On March 11, 2011, while the '923 Application was pending, Dr. Rader filed U.S. Pat. Appl. No. 13/046,118 ("the '118 Application") as a continuation application. The '118 Application eventually issued as the '135 Patent.

4. Prosecution of U.S. Appl. No. 13/046,118 and Issuance of the '135 Patent

The arguments advanced during prosecution of the '118 Application overcame rejections by Examiner under 35 U.S.C. §§ 102(b) and 103(a) based on references that did not suggest how to overcome the difficulty inherent in

effectively dosing MTP inhibitors while minimizing side effects. Ex. 1009 at 7 (noting that the cited prior art failed to recognize that constant, high doses of MTP inhibitor would cause GI-related disorders and increase hepatic fat). The Applicant established that the cited prior art did not teach either a specific dosing regimen with a step-wise increase in doses as set forth in the claims, or that a step-wise dosing of an MTP inhibitor such as lomitapide would reduce adverse effects while maintaining efficacy compared to a corresponding constant dosing level. *Id.* at 7-8.

During prosecution the Applicant submitted the declaration of Dr. William Sasiela, Ph.D. ("the Sasiela Declaration"), who was then Executive Vice President and Chief Medical Officer of licensee Aegerion Pharmaceuticals, Inc. ("Aegerion"). Dr. Sasiela explained the severity of side effects associated with lomitapide and the fact that BMS had discontinued its study of the compound. Ex. 1010 at 1, ¶¶ 5, 7. The Sasiela Declaration reviewed data from the lomitapide clinical trials, and described the dramatic decrease in adverse effects in patients who received a treatment regimen of step-wise, increasing dose levels versus patients who received a fixed dose of lomitapide. Ex. 1010 at 3, ¶ 14.

After a rigorous substantive examination, and removal from allowance by the Applicant on two occasions for consideration of previously unexamined art, including the art cited by CFAD, the '135 Patent issued on December 31, 2013.

5. Juxtapid®

In 2006, Aegerion and the Trustees of the University of Pennsylvania entered into a license agreement for lomitapide under which Aegerion obtained exclusive worldwide rights to lomitapide for the treatment of HoFH and certain other therapeutic areas. Based on the favorable results of the Rader Study, additional clinical studies were carried out,[1] culminating in Aegerion's submission of a New Drug Application for Juxtapid® (lomitapide) to the FDA. The FDA approved Juxtapid® in December 2012, as an adjunct to a low-fat diet and other lipid-lowering therapies for the treatment of adult patients with HoFH. Ex. 2006.

III. THE BOARD SHOULD DENY CFAD'S PETITION AS STATUTORILY DEFICIENT FOR FAILURE TO IDENTIFY ALL REAL PARTIES IN INTEREST

An IPR petition "may be considered only if . . . the petition identifies all real parties in interest." 35 U.S.C. § 312(a)(2). This statutory requirement is a "threshold issue." *ZOLL Lifecor Corp. v. Philips Elec. N. Am. Corp.*, Case IPR2013-00606, Paper 13 at 8 (P.T.A.B. Mar. 20, 2014). A real party in interest is

[1] *See, e.g.*, Ex. 2002 at 35-36; Ex. 2007.

a party that "desires review" of the patent, and "may be the petitioner itself, and/or it may be the party or parties at whose behest the petition has been filed." *Id.* at 9. CFAD's petition here fails to meet this basic, threshold requirement.

The Board is very familiar with the petitioner here. CFAD has filed numerous petitions requesting *inter partes* review of pharmaceutical patents. *See, e.g.*, IPR2015-00720 (*Coalition for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutics, Inc.*); IPR2015-01018 (*Coalition for Affordable Drugs III LLC v. Jazz Pharmaceuticals, Inc.*); IPR2015-01076 (*Coalition for Affordable Drugs IV LLC et al. v. Pharmacyclics, Inc.*); IPR2015-01169 (*Coalition for Affordable Drugs VI LLC et al. v. Celgene Corp.*). As has been widely reported, CFAD is a petitioner for high net worth investors who profit by bringing IPRs. Ex. 2008.

In its Petition, CFAD lists nine real parties in interest. CFAD, however, has not named IP Navigation Group, LLC ("IP Nav") and nXn Partners, LLC ("nXnP") as real parties in interest. Pet. at 1-2. These two firms are listed as real parties in interest in a number of other CFAD petitions. *See, e.g.*, *Coalition for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutics, Inc.*, IPR2015-00720, Paper 1 at 1-2 (naming IP Nav and nXnP as real parties in interest); *Coalition for Affordable Drugs III LLC v. Jazz Pharmaceuticals, Inc.*, IPR2015-01018, Paper 1

at 2-3 (same); *Coalition for Affordable Drugs V LLC et al. v. Biogen MA Inc.*, IPR2015-01993, Paper 1 at 1-2 (same).

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. *Atlanta Gas Light Co. v. Bennett Regulator Guards, Inc.*, IPR2013-00453, Paper 91 at 7 (P.T.A.B. Feb. 23, 2015) (". . . [A]s evidenced by the statutory requirement, the burden of persuasion or proof that the petitioner has named *all* real parties-in-interest remains with the petitioner.") (emphasis in original). If the Board finds that CFAD has indeed failed to name all real parties in interest, Patent Owner requests that the Board dismiss the petition as "incomplete." 37 C.F.R. 42.106(b); *ZOLL Lifecor Corp.*, Case IPR2013-00606, Paper 13 at 16.

IV. THE BOARD SHOULD NOT INSTITUTE IPR BECAUSE CFAD HAS NOT CARRIED ITS BURDEN OF DEMONSTRATING A LIKELIHOOD THAT THE '135 PATENT CLAIMS ARE UNPATENTABLE

CFAD advances two obviousness grounds. In Ground 1, CFAD argues that claims 1-10 are obvious over the Pink Sheet 2004 in view of Chang. In Ground 2,

CFAD argues that claims 1-10 are obvious over the Stein Presentation or the Stein Slides (which CFAD collectively calls "Stein 2004") in view of Chang.

Throughout an *inter partes* review, "the burden of persuasion to prove unpatentability of the challenged claims remains with the petitioner." *Corning Inc. v. DSM IP Assets B.V.*, IPR2013-00053, Paper 66 at 6-7 (P.T.A.B. May 1, 2014). CFAD has failed to carry its burden of demonstrating that the alleged prior art renders the claims of the '135 Patent obvious. Patent Owner therefore respectfully requests that the Board deny CFAD's Petition for failing to show a reasonable likelihood of success in proving that the claims of the '135 Patent are unpatentable.

A. All of the Asserted Prior Art Was Before the Patent Office During Prosecution

Each of the references CFAD relies on—Chang, Pink Sheet, and Stein 2004—was before the Examiner during prosecution. After receiving a Notice of Allowance (*see* Ex. 1012), the Applicant properly filed a Supplemental Information Disclosure Statement ("Supplemental IDS") disclosing Stein 2004 and Pink Sheet 2004 along with an Amendment and Request for Continued Examination. Ex. 2009 at 16 (identifying C10 (Chang)); Ex. 1040 at 4 (identifying C59 (Stein 2004), C60 (Pink Sheet)).

CFAD inexplicably makes much of the fact that the Supplemental IDS was filed after Allowance. Pet. at 27. However, there is no question that the Supplemental IDS was timely filed and, in view of the RCE, properly considered by the Examiner. *See* 37 C.F.R. § 1.97 (b)(4) ("An information disclosure statement shall be considered by the Office if filed by the applicant . . . [b]efore the mailing of a first Office action after the filing of a request for continued examination under § 1.114."); Manual of Patent Examining Procedure § 609.05(b) (2015) ("The information contained in information disclosure statements which comply with both the content requirements of 37 CFR 1.98 and the requirements, based on the time of filing the statement, of 37 CFR 1.97 will be considered by the examiner. Consideration by the examiner of the information submitted in an IDS means that the examiner will consider the documents in the same manner as other documents in Office search files are considered by the examiner while conducting a search of the prior art in a proper field of search.").

CFAD's obviousness arguments, therefore, raise issues that were already considered and ultimately rejected by the Examiner during prosecution. This is an independent basis on which the Board should exercise its discretion to deny CFAD's petition. 35 U.S.C. § 325(d) ("In determining whether to institute or order a proceeding . . . 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.").

B. The Provisional Application Fully Supports the '135 Patent Claims, and Thus CFAD's Stein 2004 and Pink Sheet 2004 References Qualify as Prior Art (if At All) Under Only 35 U.S.C. § 102(a)

CFAD argues (by way of attorney argument only) that the claims of the '135 Patent are entitled only to the March 7, 2005 priority date of the '923 Application, and are not entitled to the filing date of the March 5, 2004 provisional application. Pet. at 8-12. Under this faulty argument, CFAD argues that the Pink Sheet 2004 and Stein 2004 are prior art under 35 U.S.C. § 102(b). Pet. at 16; 22. CFAD, however, is wrong. The provisional application supports the '135 Patent claims, and accordingly the Pink Sheet 2004 and Stein 2004 could only qualify as prior art, if at all, under 35 U.S.C. § 102(a).

CFAD argues that the claimed numerical ranges "cannot be teased out of the multiplicity of dose ranges" described in the provisional application. Pet. at 9. It is well understood that "claims deserve the provisional application's earlier filing date so long as that application contains adequate written description under 35 U.S.C. § 112" and enables one of ordinary skill in the art to practice the invention claimed in the non-provisional application. *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1371 (Fed. Cir. 2011). As CFAD concedes, the

support for the non-provisional application "need not appear *in haec verba*" in the provisional application. Pet. at 9 (emphasis in original).

The claimed dosage ranges are supported in the provisional application. 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,[2] 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.

[2] The provisional application also discloses that patient weights may vary around the 70 kg mark, and that dosing may be adjusted accordingly. Ex. 1006 at 22 (Example 5) ("BMS-201038-treated subjects whose weight is between 62.5 and 74.9 kg, will titrate up to 62.5 mg/day for an additional 4 weeks. BMS-201038-treated subjects whose weight is ≥ 75 kg, will titrate up from 50 mg to 75 mg/day for an additional 4 weeks. Subjects who[se] weight is < 62.5 kg will remain at 50 mg/d (or the maximum tolerated dose) for the remaining 28 weeks.").

Likewise, for the second claimed dose level of "from about 5 to about 30 mg/day," Paragraph 0047 also recites that "[i]n some embodiments, the second dose level is from about 0.06 to about 0.19 mg/kg/day. In some embodiments, third dose level is from about 0.2 to about 0.59 mg/kg/day." *Id.* at 14. In light of the exemplary embodiments which use a 70 kg person, a person of ordinary skill in the art would calculate a range between 4.2 mg/day to 41.3 mg/day, which supports "about 5 to about 30 mg/day." *Id.* at 23.

Finally, the third dose level "from about 10 to about 50 mg/day," is also disclosed in Paragraph 0047, which discloses that "[i]n some embodiments, the third dose level is from about 0.2 to about 0.59 mg/kg/day." *Id.* at 14. Once again, based on a 70 kg person, a person of ordinary skill in the art could calculate the range to be 14 mg/day to 41.3 mg/day, which is "about 10 to about 50 mg/day." *Id.* at 23.

These calculations are depicted in the graphics below:

CLAIM LANGUAGE	PROVISIONAL SUPPORT
WHEREIN A FIRST DOSE LEVEL IS FROM ABOUT 2 TO ABOUT 13 MG/DAY →	[0047] In some embodiments, the first dose level is from about 0.02 to about 0.059 mg/kg/day. In some embodiments, second dose level is from about 0.06 to about 0.19 mg/kg/day… Ex. 1006 at 14. [0097]… 70 kg man… Ex. 1006 at 23. Where: $\frac{0.02mg/kg}{1day} \times 70kg = 1.4\frac{mg}{day}$ $\frac{0.19mg/kg}{1day} \times 70kg = 13.3\frac{mg}{day}$
A SECOND DOSE LEVEL IS FROM ABOUT 5 TO ABOUT 30 MG/DAY →	[0047] In some embodiments, second dose level is from about 0.06 to about 0.19 mg/kg/day. In some embodiments, the third dose level is from about 0.2 to about 0.59 mg/kg/day. Ex. 1006 at 14. [0097]… 70 kg man… Ex. 1006 at 23. Where: $\frac{0.06mg/kg}{1day} \times 70kg = 4.2\frac{mg}{day}$ $\frac{0.59mg/kg}{1day} \times 70kg = 41.3\frac{mg}{day}$
AND A THIRD DOSE LEVEL IS FROM ABOUT 10 TO ABOUT 50 MG/DAY →	[0047] In some embodiments, the third dose level is from about 0.2 to about 0.59 mg/kg/day. Ex. 1006 at 14. [0097]… 70 kg man… Ex. 1006 at 23. Where: $\frac{0.2mg/kg}{1day} \times 70kg = 14\frac{mg}{day}$ $\frac{0.59mg/kg}{1day} \times 70kg = 41.3\frac{mg}{day}$

CFAD relies on the declaration of Dr. Mayersohn, who attempts to make the provisional application look confounding by listing out the various doses specified in the provisional application and then reverse-calculating the weight of the patient. Ex. 1003 at 34-48. Dr. Mayersohn, noting that another paragraph in the provisional application discussed a starting dose of 6.25 mg/day, concludes that in order to take 6.25 mg at 0.03mg/kg/day, the patient would have to weigh 208 kg (458 lb). Ex. 1003 at 45, ¶ 91.

Dr. Mayersohn's logic, however, ignores the wording of the provisional application itself. Rather than being linked, the disclosures of 0.03 mg/kg/day and 6.25 mg/day are separate embodiments of the claimed invention:

> [0049] ***In some embodiments*** the inhibitor is administered at:
>
> (a) 0.03mg/kg/day for a first interval;
>
> (b) 0.1 mg/kg/day for a second interval;
>
> (c) 0.3 mg/kg/day for a third interval; and
>
> (d) 1.0 mg/kg/day for a fourth interval . . .
>
> [0050] ***In some embodiments*** the first dose level is 6.25 mg/day, the second dose level is 12.5mg/day, and the third dose level is 50mg/day . . .

Ex. 1006 at 14-15 (emphasis added).

Still further, to perform this calculation and reach the 208 kg weight, Dr. Mayersohn appears to have used the following calculation: 1 ÷ (0.03 mg/kg ÷ 6.25 kg) = 208 kg.[3] Mayersohn Decl. at ¶ 91. However, without any explanation as to how or why the skilled artisan would have used this particular calculation, Dr. Mayersohn's analysis amounts to nothing more than cherry picking numbers from unrelated paragraphs of the provisional application. In fact, 0.03 mg/kg/day, when administered to a 70 kg person, would result in administration of 2.1 mg per day (0.03 mg/kg x 70 kg = 2.1 mg). And of course, both 2.1 mg and 6.25 mg fall within the first claimed dosing range of the '135 Patent ("from about 2 to about 13 mg/day"). Ex. 1001, claim 1.

Accordingly, the claims of the '135 Patent are supported by the provisional application, and Dr. Mayersohn's reverse calculations do not alter this conclusion. *See e.g.*, *Star Sci.,* 655 F.3d at 1371 ("Claims deserve the provisional application's earlier filing date so long as that application contains adequate written description under 35 U.S.C. § 112.").

CFAD's additional argument that the claimed "piperidine N-oxide" of lomitapide lacks support in the provisional application also fails. The provisional application discloses a piperidine. Ex. 1006 at 11 ("In some embodiments the

[3] Dr. Mayersohn did not disclose his calculation in his declaration.

MTP inhibitors are piperidine, pyrrolidine or azetidine compounds."). 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.

There is no requirement, as CFAD has conceded, that the support for the non-provisional application appear "*in haec verba*" in the provisional application. Pet. at 9. Accordingly, for the reasons set forth above, the '135 Patent is entitled to the March 5, 2004 priority date of the provisional application.

C. Neither the Stein Presentation Nor the Stein Slides Qualify As Prior Art Under Either 35 U.S.C. §§ 102(a) or 102(b)

CFAD has the burden of establishing the prior art status of its purported prior art references. *Coalition for Affordable Drugs III LLC v. Jazz Pharmaceuticals, Inc.*, IPR2015-01018, Paper 17 at 13 (P.T.A.B. Oct. 15, 2015). To satisfy this burden, the Board has "often . . . required Petitioner to come forward with sufficient evidence to make a threshold showing, at the institution stage, that the reference relied upon is available prior art." *Id.* Thus, for references like the Stein Presentation or Stein Slides, CFAD bears "the burden of proving . . . that the [claimed invention] was described in a printed publication before the critical date[.]" *Mass. Inst. of Tech. v. Harman Int'l Indus.*, 584 F. Supp. 2d 297,

315 (D. Mass. 2008) (granting summary judgment of validity where accused infringer failed to prove that the asserted "printed publication" had been "freely disseminated or otherwise kept nonconfidential").[4]

CFAD argues that both "Stein's presentation and his underlying slides (later posted online) were two separate publications of Stein 2004[.]" Pet. at 17 (emphasis omitted). CFAD, however, has failed to carry its burden of showing that either is a "printed publication" within the meaning of 35 U.S.C. §§ 102(a) or 102(b).

1. The Stein Presentation Is Not a "Printed Publication" and is Thus Not Prior Art

CFAD asserts that the Stein Presentation took place on February 5, 2004, and qualifies as a "printed publication" under 35 U.S.C. § 102 as of this date.[5]

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[4] As used herein, "Stein Presentation" refers to the oral presentation allegedly given by Dr. Stein on February 5, 2004, which allegedly includes the transient presentation of the Stein Slides. "Stein Slides" refers to the document referred to in CFAD's Ex. 1014. CFAD uses "Stein 2004" to reference both the Stein Presentation and Stein Slides, and Patent Owner does the same here.

[5] The Stein Presentation purportedly took place on February 5, 2004. If it qualifies as a "printed publication"—an assertion that remains unproven—it would qualify

This argument is untenable. CFAD has provided no corroboration that the presentation actually took place as scheduled, or that the slides of interest were actually displayed.

"Whether a reference qualifies as a printed publication involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *Coalition for Affordable Drugs IV LLC v. Pharmacyclics, Inc.*, IPR2015-01076, Paper 33 at 6 (P.T.A.B. Oct. 19, 2015) (quoting *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) (internal quotations omitted). To qualify as a printed publication within the meaning of §§ 102(a) or 102(b), a reference must have been sufficiently accessible to the public interested in the art before the critical date. Public accessibility has been called the "touchstone" in determining whether a reference constitutes a "printed publication." *SRI Int'l Inc. v. Internet Sec. Sys., Inc. et al.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008).

CFAD appears to be arguing that a transient presentation of slides during the Stein Presentation is sufficient to render the slides a printed publication. Pet. at 17-

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as prior art under § 102(a) using the March 5, 2004 filing date of the provisional patent application, and under § 102(b) using the March 7, 2005 filing date of the non-provisional application.

20. In such a situation, evaluation of the *Klopfenstein* factors is appropriate to resolve "whether or not a temporarily displayed reference that was neither distributed nor indexed was nonetheless made sufficiently publicly accessible[.]" *In re Klopfenstein*, 380 F.3d at 1350; *Coalition for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutics, Inc.*, IPR2015-00817, Paper 12 at 4 (P.T.A.B. August 24, 2015). The four *Klopfenstein* factors are: "[a] the length of time the display was exhibited, [b] the expertise of the target audience, [c] the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and [d] the simplicity or ease with which the material displayed could have been copied." *Klopfenstein*, 380 F.3d at 1350. None of these factors support a finding that the Stein Presentation is a printed publication within the meaning of §§ 102(a) or 102(b).

The first *Klopfenstein* factor, the length of time the reference was displayed, "is important in determining the opportunity of the public in capturing, processing and retaining the information conveyed by the reference." *Klopfenstein*, 380 F.3d at 1350. CFAD, however, has not proffered any evidence on the duration of the Stein Presentation. In fact, it has not proffered any corroboration that the Stein Presentation actually took place as scheduled, or that Dr. Stein actually displayed the slides on which CFAD relies. For example, it is conceivable that Dr. Stein

skipped over the slides of interest to CFAD. *See, e.g.*, *Air Liquide Large Indus. U.S. LP v. Praxair Tech., Inc.*, IPR2015-01074, Paper 11 at 6 (P.T.A.B. Oct. 26, 2015) (finding that petitioner did not carry burden of proving prior art status where it offered no corroborating evidence that the slides relied upon were ever presented at a particular conference). CFAD has offered nothing to carry its burden on this point.

Further, taking CFAD's documents at face value, it appears that the Stein Presentation—which consists of over forty slides—was scheduled to last a mere twenty minutes. Ex. 1014 at 1 (showing "Implitapide" presentation scheduled from 8:50-9:10); *Id.* at 4-45. Assuming then that each slide was shown, and that the speaker started through the slides without any introductory remarks, each slide would have been displayed for a maximum of thirty seconds. The scientific poster at issue in *Klopfenstein*, by contrast, was displayed continuously for a cumulative three days at two separate industry association meetings. *Klopfenstein*, 380 F.3d at 1351; *see also id.* at 1350 ("The more transient the display, the less likely it is to be considered a 'printed publication.'") (internal quotations omitted).

CFAD asserts that the Pink Sheet 2004 purportedly reported on the Stein Presentation, and argues that the time of display (whatever it may have been) was sufficient to allow the public to capture the information. Pet. at 17-18. But the

one-page Pink Sheet 2004 article can hardly be said to have "captured" the complicated data in the forty-plus slide Stein Presentation. In fact, it is clear from the brevity and high level nature of the reporting in the Pink Sheet 2004 that the transience of the Stein Presentation made any data reported in the Stein Presentation difficult to capture and process. Ultimately, CFAD has failed to proffer any corroboration that the Stein Presentation took place, that the slides of interest were actually displayed, or any evidence of the duration of the presentation. The inferences that can be made from the evidence of record show that to the extent it took place, the Stein Presentation was a short, condensed presentation of complicated and dense data. The Board should find that the first *Klopfenstein* factor favors Patent Owner.

CFAD has also failed to produce any evidence on the second *Klopfenstein* factor, expertise of the target audience. While the Stein Presentation may or may not have been of "great interest" to the skilled artisan as CFAD urges (Pet. at 18), CFAD has proffered no evidence to establish who, if anyone, attended PPD's February 5, 2004 "Investor Day" presentations, who the target audience would have been, and whether the attendees "possessed ordinary skill in the art" of the '135 Patent. *Klopfenstein*, 380 F.3d at 1351. Further, CFAD offers no evidence as to how each of PPD's "Investor Day" presentations were marketed, or whether Dr.

Stein's presentation on implitapide was specifically promoted to persons of skill in the art (and if so, to whom).

CFAD attempts to proffer some "evidence" on the second *Klopfenstein* factor in the form of expert testimony regarding why skilled artisans might have been interested in the development of MTP inhibitors. Pet. at 18 (*citing* Ex. 1002 (Zusman) at ¶¶ 20-22). Even accepting the testimony wholesale, it does not speak to the question of why a skilled artisan would have been aware of and attended PPD's "Investor Day" conference. CFAD also presents testimony that the Pink Sheet 2004 was targeted to those in the pharmaceutical industry. Pet. at 19 (*citing* Ex. 1002 (Zusman) at ¶¶ 106-10; Ex. 1003 (Mayersohn) at ¶¶ 23-25 (where Pink Sheet 2004 "reported" on content of Stein Presentation)). This testimony is not relevant to the query at hand, which is the "intended target audience" of the Stein Presentation, not the Pink Sheet. *Klopfenstein* at 1351.

In addition, taking CFAD's evidence at face value, the documents demonstrate that only about half of the Agenda for PPD's Investor Day related to drug development, and the remaining portions had more to do with business-side initiatives and planning. Ex. 1014 at 1 (listing "Business Units/initiatives," "Business Development," "Wrap-up and Q&A"); *see also* Ex. 1005 at 4 ("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"). The poster board displayed at the meeting of the American Association of Cereal Chemists in *Klopfenstein* clearly went "direct to those whose interests make them likely to observe and remember whatever it may contain that is new and useful." *Klopfenstein* at 1346, 1351. By contrast, it is unclear why a person of skill in the chemical arts would have attended PPD's business-heavy "Investor Day" conference in the first place. The agenda for the event would not necessarily have attracted persons of skill in the chemical arts in the same way that an industry conference would. Accordingly, CFAD has failed to meet its burden of proof on this factor. The small amount of evidence on record shows that the PPD "Investor Day" was not geared directly to those of skill in the chemical arts, but rather primarily to business people. The Board should find that the second *Klopfenstein* factor favors Patent Owner.

The third (expectation of copying) and fourth (ease of copying) *Klopfenstein* factors also favor Patent Owner. Given the brevity of the alleged 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. CFAD does not advance any argument as

to how the skilled artisan might have copied the information from the presentation. For example, CFAD does not allege that viewers had the ability to download the presentation in real time. CFAD essentially argues that because the presentation was a webcast, it would have been expected and simple for a skilled artisan to copy it. Pet. at 19. Again, however, this is belied by CFAD's own documents, which showed that the Stein presentation included "relatively dense material in a small space." *Coalition for Affordable Drugs (ADROCA) LLC v. Acorda Therapeutics, Inc.*, IPR2015-00817, Paper 12 at 5 (P.T.A.B. August 24, 2015) (internal citation omitted); *see also id.* (the "'more complex a display, the more difficult it will be for members of the public to effectively capture its information.'") (*citing Klopfenstein*, 380 F.3d at 1351).

Accordingly, in view of the four *Klopfenstein* factors, CFAD has failed to make a threshold showing that the Stein Presentation—to the extent it took place at all—was sufficiently publicly accessible to qualify as a "printed publication" under §§ 102(a) or 102(b).

2. The Stein Slides Are Not a "Printed Publication"

CFAD separately asserts 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, and thus are also a "printed publication" within the meaning of 35

U.S.C. §§ 102(a) and 102(b).[6] Pet. at 17, 22. Accordingly, CFAD bears the burden to show that the Stein Slides were publicly accessible as of the priority date. *See In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989) (". . . dissemination and public accessibility are the keys to the legal determination whether a prior art

[6] As discussed in Section IV.B. above, the provisional application fully supports the '135 claims, and thus the claims are entitled to claim priority to the March 5, 2004 filing date of the provisional application. Using this priority date, if the slides qualify as a printed publication published "well before March 5, 2004" (Pet. at 20)—an assertion Patent Owner disputes—they would qualify as prior art under § 102(a). If the slides qualify as a printed publication "no later than April 15, 2004" (Pet. at 22)—an assertion that Patent Owner also disputes—they would not be prior art to the '135 Patent claims.

In the event the claims are accorded the March 7, 2005 filing date of the non-provisional application, the slides would qualify as prior art under § 102(b) using the alleged "well before March 5, 2004" publication date, and under § 102(a) using the alleged publication date of "no later than April 15, 2004." Pet. at 22.

To the extent the slides are deemed to qualify as prior art under § 102(a), Patent Owner would antedate the reference because Dr. Rader made his invention prior to the alleged publication date. *See* Section IV.D below.

reference was 'published.'"). CFAD has failed to offer credible evidence in support of its theories.

Again, "public accessibility" is the touchstone in determining whether a reference constitutes a "printed publication." *SRI Int'l, Inc.*, 511 F.3d at 1194. CFAD relies on print-outs from the "Internet Archive: Wayback Machine" ("Wayback Machine") to assert that the Stein Slides were available on PPD's website prior to the critical date.[7] Pet. at 19-21. The Wayback Machine screen that purports to show the Stein Slides on the PPD website does not display the slides themselves, but rather shows only a hyperlink. Ex. 1004 at 4-5. CFAD presents no evidence that the hyperlink to the Stein Slides was functional—or that the slides labeled as Exhibit 1014 were found at that link—prior to the priority date. Ex. 1004 at 4. The Butler Declaration makes no representations regarding the functionality of the web links found on the Wayback Machine pages. *Id.* at 1. Accordingly, CFAD has failed to prove that the Stein Slides were publicly accessible.

CFAD has also failed to offer credible evidence of the alleged publication date. Using the Wayback Machine, the accessibility of a particular web page

[7] The Wayback Machine purports to collect archived versions of web pages in existence as of their date of capture by web crawlers. *See, e.g.*, Ex. 1005 at 1.

cannot be established before its earliest archive date. The Wayback Machine shows, at most, that the Stein Slides were posted on PPD's website on April 15, 2004—***more than a month after the filing date of the provisional application***. *Id.* at 5.

Acknowledging this limitation, CFAD attempts to show that the Stein Slides were posted before April 15, 2004 (actually, before March 5, 2004) by constructing a table illustrating PPD's purported "routine business practice" regarding how long after a given conference it posted presentations on its website. Pet. at 20-22. In the table, CFAD purports to compare the date PPD webpages were "last modified" with the dates of the other conferences to arrive at a number of dates after the conference that the slides were purportedly posted. *Id.* at 21. CFAD's approach places great weight on the "last modified" date seen on the Wayback Machine documents, but the meaning and accuracy of this date is unclear. The Butler Declaration (Ex. 1005) is silent on this question, and CFAD offers no evidence as to why the date should be understood to be accurate.

Further, the table shows a variety of time periods—ranging from 1 to 6 to 21 days—which hardly amounts to evidence of a routine business practice. It is also abundantly clear that CFAD has 'cherry-picked' three presentations in hopes of proving that PPD had a routine business practice within the meaning of *In re Hall*,

781 F.2d 897 (Fed. Cir. 1986). *In re Hall* involved a dispute over whether a single thesis catalogued and shelved in Germany qualified as a printed publication under § 102(b). *Id.*, 781 F.2d at 897-98. In *In re Hall*, the Federal Circuit relied on "competent evidence," in particular a declaration from the director and manager at the library regarding the "indexing, cataloging, and shelving of theses," to establish routine library practice. *Id.* at 899. CFAD's evidence, which relies on cobbled-together dates and confusing time stamps, can hardly be said to rise to the level of "competent evidence" set forth in *In re Hall*.

In re Hall is inapplicable to the facts here for another important reason. In that case, the evidence showed that the reference in question was made available to the public "toward the beginning of the month of December, 1997." *Id.* at 898. The Federal Circuit was not troubled by the fact that the date was somewhat imprecise, noting that such an approximation "works no injustice here because the critical date . . . is some two and one half months later." *Id.* at 899. Such is not the case here, where the critical date, March 5, 2004, falls between February 5, 2004 (the date of the purported Stein Presentation) and April 15, 2004 (the latest date the Stein Slides were purportedly publicly posted, according to CFAD). In other words, there is no room here for the type of approximation that "work[ed] no injustice" in *In re Hall*. *Id.* at 899.

CFAD has previously—and unsuccessfully—relied on the Wayback Machine to prove a publication date. In *Coalition for Affordable Drugs III LLC v. Jazz Pharmaceuticals, Inc.*, IPR2015-01018, Paper 17 at 14 (P.T.A.B. Oct. 15, 2015), the Board rejected a similar attempt by CFAD to rely on a transcript and slides from an FDA Advisory Committee Meeting. When the Wayback Machine failed to demonstrate that the transcript had been made publicly available as of the critical date, CFAD presented a Federal Register Notice from 2001 which stated that these meeting materials were "generally posted about 3 weeks after the meeting." Paper 17 at 15. The Board concluded that

> This statement, by itself, however, is not sufficient under the circumstances to show that the [reference] *actually* was made available to the extent that interested, ordinarily skilled persons, exercising reasonable diligence, could have located it . . . three weeks after the date of the Advisory Committee meeting.

Id. (emphasis in original). CFAD's evidence here that the Stein Slides were published prior to the '135 priority date is similarly lacking. 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.

Accordingly, CFAD has not established that the Stein Slides are prior art, much less that they were available "well before March 5, 2004." Pet. at 20.

D. To the Extent Stein 2004 and Pink Sheet 2004 Qualify As Prior Art Under Only 35 U.S.C. § 102(a), They Are Not Prior Art Because They Published After Dr. Rader's Invention

As detailed above, Dr. Rader began the Rader Study in June 2003. Accordingly, he conceived of the dose escalation protocol used in this study well before the filing of the provisional application on March 5, 2004. In the case of the currently pending U.S. Appl. No. 14/075,483, which is a continuation of the '135 Patent, Dr. Rader has filed a declaration under 37 C.F.R. § 1.131 showing that he conceived of and reduced to practice the escalating lomitapide dosing regimen claimed in the '135 Patent prior to February 4, 2004.[8] Ex. 2005 at 7.

The earliest possible date for either the Stein Presentation or the Stein Slides is February 4, 2004 (the date of the Stein Presentation), and the Pink Sheet 2004 is dated February 16, 2004. Accordingly, Dr. Rader invented the subject matter prior to the dates of the references relied on by CFAD. The Board should find that the claims of the '135 Patent are entitled to the March 5, 2004 date of the provisional application, and that none of the Stein Presentation, the Stein Slides, or the Pink

[8] In the event that the Board institutes trial, Dr. Rader will be submitting a similar declaration here.

Sheet 2004 are prior art due to Dr. Rader's earlier invention. In the event the Board finds that the claims should be accorded only the March 7, 2005 filing date of the non-provisional application, and to the extent the Board finds that CFAD has proven a publication date of the Stein Slides of no earlier than April 15, 2004, the Stein Slides are not prior art due to Dr. Rader's earlier invention.

E. Ground 1 is Deficient Because the Combination of Pink Sheet 2004 and Chang is Redundant of the Art Relied on in Ground 2, and Nevertheless Fails to Render the Claims Obvious

1. Ground 1 (Pink Sheet 2004 plus Chang) Should be Rejected Because it Adds Nothing Over Ground 2 (Stein plus Chang)

Grounds 1 and 2 both rely on Chang plus an additional reference (Pink Sheet 2004 in Ground 1; Stein 2004 in Ground 2). CFAD, however, asserts that the Pink Sheet 2004 merely reports on the Stein Presentation. Pet. at 15. This renders Ground 1 redundant of Ground 2, because the combination of the Pink Sheet 2004 and Chang in Ground 1 does not present anything additional beyond the combination of Stein 2004 and Chang in Ground 2.

To avoid dismissal of a redundant ground of unpatentability, a petitioner must "provide a meaningful distinction between the different, redundant rejections." *Illumina, Inc. v. Trustees of Columbia Univ.*, IPR2012-00006, Paper 43 at 12 (P.T.A.B. May 10, 2013) (*citing* 37 C.F.R § 42.1(b)); *Liberty Mut. Ins.*

Co. v. Progressive Casualty Ins. Co., CBM-2012-00003, Paper 7 at 2 (P.T.A.B. October 25, 2012). This means that where a petitioner cites more than one reference for the same purported facts, the petitioner must explain the differences between the references and "how this difference would impact the unpatentability challenge." *Id*. It is not enough for a petitioner to "speculate[] that in certain publications an element may be more clearly set forth in one publication rather than another." *Id*. (confirming denial of ground as redundant where petitioner cited multiple references for same facts and did not provide a meaningful distinction between the redundant grounds).

Here, CFAD acknowledges that the Pink Sheet merely reports on the content of the Stein Presentation. Pet. at 15. While CFAD purports to identify additional "non-cumulative" information found in Stein 2004 over the Pink Sheet (Pet. at 46-47), it fails to articulate how or why the Pink Sheet 2004 meaningfully differs from Stein 2004. Accordingly, the Board should reject Ground 1 as redundant of Ground 2.

2. Pink Sheet 2004 and Chang Do Not Render the Claims Unpatentable

The combination of the Pink Sheet 2004 and Chang fails to teach or suggest the subject matter claimed in the '135 Patent.[9] The Pink Sheet 2004 does not disclose a step-wise dosing treatment regimen for implitapide, and it certainly does not disclose such a regimen for lomitapide. The addition of Chang does not remedy this failing, as it provides no motivation to select lomitapide from among the other MTP inhibitors discussed therein, and says nothing about step-wise dosing of lomitapide. Moreover, nothing in CFAD's references suggests a reasonable expectation of success in using a method of step-wise administration of increasing doses of lomitapide.

a. The References Fail to Teach or Suggest Both the Claimed Method of Step-Wise Administration of Increasing Doses of Lomitapide and the Specific Claimed Dosage Ranges

The Pink Sheet 2004 is a single-page article relating to PPD's attempt to develop implitapide as an add-on to statin therapy. *See generally* Ex. 1013. It does not disclose a method of step-wise administration of increasing doses of

[9] Patent Owner reserves the right to address CFAD's claim construction proposals and definition of one of ordinary skill in the art in its Patent Owner's Response, should trial be instituted.

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. Instead, the Pink Sheet 2004 makes clear that Dr. Stein's clinical trial was designed to establish a ***single, low dose*** of implitapide that would be effective to reduce LDL by about 20%. Ex. 1013 at 2 ("While 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***.") (emphasis added). The Pink Sheet 2004 mentions that Dr. Stein's protocol for the Phase II study included increasing doses every five weeks based on safety and tolerability (Ex. 1013 at 2), but CFAD fails to explain why a person of skill in the art would have interpreted this as a step-wise, increasing dose treatment regimen, instead of taking this disclosure for what it is: mention of a Phase II dose-finding study.

Even assuming that the Pink Sheet 2004 teaches a dosing treatment regimen, it does not suggest that the protocol would actually result in LDL reduction in the 18-24% range, as CFAD contends. Pet. at 40. In fact, that the Pink Sheet 2004 refers to the study as a "proof-of-concept" study, appears to indicate that the study had not yet started (the studies "***will enroll*** approximately 200 patients;" "starting

dose ***will be*** 10 mg daily"), and does not report any study results. Ex. 2013 at 2 (emphasis added). Accordingly, nothing in this reference 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.

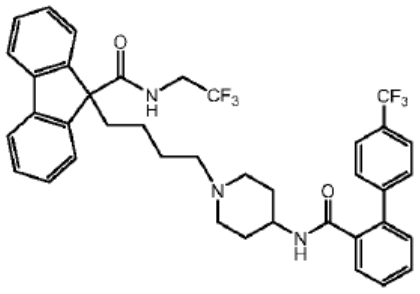
With respect to dependent claims 3 and 4, which CFAD treats in two sentences of a single paragraph that addresses all of the dependent claims in cursory fashion, the prior art similarly fails to teach or suggest the claimed parameters. Pet. at 45. Claims 3 and 4 recite that the levels of one or more of total cholesterol, LDL, or lipoproteins are reduced by at least 15% or 25%, respectively. Ex. 1001 at 20:3-11. Nothing in the Pink Sheet 2004 or Chang explains what dose or dosing regimen of implitapide would lower total cholesterol, LDL, or lipoproteins by the claimed amounts, and thus nothing indicates the dose or dosing regimen of lomitapide that would achieve these reductions.

b. CFAD Fails to Articulate a Motivation to Substitute Lomitapide for Implitapide in Dr. Stein's Protocol

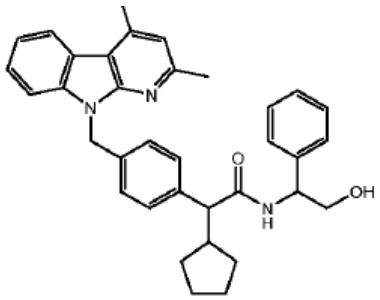
Although both implitapide and lomitapide are MTP inhibitors, CFAD has failed to explain why a person of skill in the art would have been motivated to substitute lomitapide, a compound that BMS abandoned due to the adverse effects

associated with the drug, into the protocol of a trial that was not specifically designed to ameliorate MTP-inhibitor associated side effects. CFAD's arguments are based solely on the fact that both compounds are MTP inhibitors. *See, e.g.*, Pet. at 41. Its experts, however, offer 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.

It is well-established that "[t]he mere structural similarity of . . . chemical compounds is insufficient for a prima facie showing of obviousness because chemicals must be assessed with their respective properties." *Bayer AG v. Carlsbad Tech., Inc.*, 2001 WL 34125673, *5 (S.D. Cal. Oct. 24, 2001) (*citing In re Papesch*, 315 F.2d 381, 391 (C.C.P.A.1962)). Here, although both lomitapide and implitapide are MTP inhibitors, it cannot be said that they are structurally similar. In fact, they have different, chemically distinct structures:



Lomitapide



Implitapide

Ex. 2010 at 5.

CFAD relies on Chang for a purported motivation to apply Dr. Stein's protocol to lomitapide. Pet. at 41-42. According to CFAD, Chang identified three MTP inhibitors that "had advanced to human clinical trials, and of the two performing at least comparably to implitapide, one was lomitapide." Pet. at 41. But CFAD fails to adequately explain why a person of ordinary skill in the art would have chosen lomitapide among the other disclosed MTP inhibitors. CFAD merely states that lomitapide had been tested in a type of rabbit that is an animal model for human HoFH (Pet. at 44), but does not elaborate on why a person of ordinary skill in the art would have focused on this one test in the context of all other pre-clinical and clinical data discussed in Chang.

Chang actually teaches away from the use of MTP inhibitors generally, concluding in its "Future directions" section that "[a]lthough MTP inhibitors have demonstrated impressive lipid lowering efficacy in clinical studies, potentially significant adverse effects surround this mechanism." Ex. 1015 at 6. A skilled artisan, therefore, would not have read Chang to endorse the use of lomitapide and would not have been motivated to modify the Pink Sheet 2004 by substituting implitapide with lomitapide.

Ultimately, nothing in Chang resolves the failure of the Pink Sheet 2004 to provide any explanation or rationale as to why a person of ordinary skill in the art

in March 2004, aware that a Phase II study of implitapide was beginning and knowing that the clinical development of lomitapide had been previously halted due to safety concerns, would have chosen to devise a treatment regimen with step-wise dosing involving lomitapide. Indeed, BMS, which had every incentive to develop the product, had abandoned the compound and donated its rights to the drug. Ex. 2001 at 30.

c. CFAD Fails to Articulate a Reasonable Expectation of Success of Arriving at the Claimed Subject Matter

CFAD fails to prove that a person of ordinary skill in the art would have had a reasonable expectation that substituting lomitapide into Dr. Stein's implitapide protocol would have resulted in a safe and effective dosing regimen for lomitapide. CFAD argues a reasonable expectation of success based on the purported "similar mechanism and degree of action" of lomitapide and implitapide, and a purported suggestion in the prior art that the two drugs should be "dosed similarly." Pet. at 44-45. CFAD's generic argument is faulty for several reasons.

As a threshold issue, the prior art had not reported any results from Dr. Stein's implitapide study, and thus CFAD has not even shown that the alleged protocol worked for implitapide. Because the prior art did not show success with implitapide, this work could not have contributed to a reasonable expectation of success for lomitapide.

Further, as noted above, CFAD's experts offer nothing to suggest that MTP inhibitors are interchangeable with one another with respect to the anticipated benefit of a dose escalation regime. It bears mentioning that in the European Opposition proceedings that CFAD referenced in its Petition (Pet. at 28), Dr. Stein (the Opponent) actually took the opposite position from the one now espoused by CFAD. European Patent 1 725 234 B9 ("the '234 Patent"), the subject of the Opposition proceedings, originally claimed three step-wise dosages of an MTP inhibitor (*i.e.*, not specifically lomitapide). In an attempt to limit the claims of the '234 Patent, Dr. Stein argued that

> 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***.

Ex. 1020 at 6 (emphasis added). In other words, even Dr. Stein—the author of CFAD's Stein 2004 reference—concedes that one MTP inhibitor may not be simply substituted for another.

CFAD's expert Dr. Zusman suggests that a person of ordinary skill would have recognized that implitapide and lomitapide "showed similar effects at similar doses when tested in the same animal model," and thus CFAD appears to be arguing that a person of ordinary skill would have expected lomitapide and implitapide to show similar effects at similar doses when administered in humans. Pet. at 45; Ex. 1002 at ¶ 62. But this conclusory argument fails to explain why purportedly similar results in rabbits would be expected to translate to similar results in the more complex environment of the human body.

CFAD's reasonable expectation of success argument also places far too much reliance on a brief statement in Chang, which says lomitapide "also showed similar efficacy in phase I and phase II clinical trials." Ex. 1015 at 5. Read 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*. It is also unclear what efficacy parameters Chang is referencing. With regard to lomitapide, Chang presents no clinical trial data. Instead, for the proposition that "BMS-201038 also showed similar efficacy in phase I and phase II clinical trials," Chang

cites a Pink Sheet article from 2000 ***reporting on the discontinuation of the BMS trials***. *Id. at* 5, n.43. The cited article reads, in its entirety:

> 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 at 1. CFAD 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. CFAD 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.

In view of the above arguments as a whole, CFAD has failed to carry its burden of showing the likelihood of unpatentability of any of the '135 claims based on the combination of the Pink Sheet 2004 and Chang, and the Board should thus decline to institute IPR with respect to Ground 1.

F. Ground 2 is Deficient Because the Combination of Stein 2004 and Chang Fails to Render the Claims Obvious

Assuming that the Stein Presentation and/or the Stein Slides are prior art, which they are not (*see supra* at Section IV.C), they do not teach the step-wise dose escalation method of the '135 Patent claims. Neither reference discloses a step-wise dosing treatment regimen for implitapide. Stein 2004 simply notes a dose-finding study intended to establish a *single* effective dose of implitapide that would work in combination with a statin. For example, slide 31 lists several effects of high doses of implitapide, and concludes that there is a "[p]otential to control both fat malabsorption and GI side effects with ***lower doses***." Ex. 1014 at 31 (emphasis added). Slides 36-37 outline a plan to "Establish ***a*** safe and effective ***dose*** (probably ***between*** 15 and 40 mg/day)" of implitapide. *Id.* at 36 (emphasis added). Dr. Stein's studies would start with the most severe and resistant forms of hypercholesterolemia and hyperlipidemia, and would start at low doses and increase the dose every five weeks to identify a safe and effective dose. *Id.* at 36-37.

It is clear that Stein 2004 refers not to a method of treatment as CFAD contends, but to a dose-finding study designed to find a single effective dose. This reading is supported by the slides, which conclude that "Once long term 'safety' assessed (at least 6 months) ***at effective dose*** move to lower risk groups." *Id.* at 37

(emphasis added). Thus, Stein 2004 merely describes work directed towards finding an effective dose of implitapide. It does not teach a method of using implitapide in an escalating dose regimen to treat patients in an attempt to maximize efficacy while minimizing side effects.

Further, Stein 2004 does not mention lomitapide or suggest that the side-effects of lomitapide (or implitapide) could be reduced by administering it in at least three step-wise, increasing doses. Indeed, CFAD concedes that Stein 2004 relates solely to implitapide and does not mention lomitapide. Pet. at 52 ("Stein 2004 does not specifically disclose the MTP inhibitor represented by [lomitapide], or a pharmaceutically acceptable salt or piperidine N-oxide thereof.").

CFAD fails to argue the unpatentability of any specific claim in Ground 2 in the text of the petition, choosing instead to rely on a cursory claim chart. To the extent its claim chart is credited, a word is needed regarding CFAD's citations to Stein slides 27-29 and 32 for claims 3 and 4, and regarding the table CFAD included in the claim chart for claim 4. Pet. at 49. Claims 3 and 4 recite that the levels of one or more of total cholesterol, LDL, or lipoproteins are reduced by at least 15% or 25%, respectively. Ex. 1001, claims 3-4. Slides 27-29 and 32 appear to relate to prior clinical studies performed by Bayer, who was apparently developing implitapide before transferring rights in the drug to PPD and Dr. Stein.

See, e.g., CFAD Ex. 1013 at 2. It appears that CFAD extracted data from these slides to create the table depicted in its claim chart for claim 4. Pet. at 49. CFAD cites no expert testimony in Ground 2 to explain what this data is, how it was generated, or how it shows unpatentability of the claims. No information is provided about the tolerability of the doses included in the table. CFAD appears to suggest that a 40 mg dosage of lomitapide reduced LDL-C by 31%, but if true, and assuming *arguendo* that a person of skill in the art would have been motivated to substitute lomitapide for implitapide (which is not the case for the reasons discussed above), this would at best have motivated a person of skill in the art to experiment with a fixed dose of lomitapide, not an escalating dose regimen as claimed.

Motivation to Combine. Even assuming that Stein 2004 does teach a step-wise dose escalation of implitapide, CFAD fails to explain why a person of skill in the art would have substituted lomitapide for implitapide in Stein 2004's protocol. Because CFAD incorporates by reference its arguments from Ground 1 (Pet. at 53), the Patent Owner does the same with regard to the arguments in Section IV.E.2 above. CFAD argues that additional content in Stein 2004, namely information on the size of the "lipid lowering market" and the suggestion of an unmet need for moderately-effective LDL-C lowering agents, would have further

motivated the skilled artisan to combine Stein 2004 and Chang. Pet. at 53-54. CFAD is wrong. The market size and unmet need CFAD cites do not address the deficiencies discussed above that detract from CFAD's argument about motivation to combine. Nor does the quote from the Stein Slides regarding modest results (Pet. at 54-55) address the deficiencies discussed above that detract from CFAD's argument about a purported reasonable expectation of success.

Reasonable Expectation of Success. Assuming a person of ordinary skill in the art would have been motivated to substitute lomitapide for implitapide, CFAD fails to explain why he or she would have had a reasonable expectation of success in doing so. Because CFAD incorporates by reference its arguments from Ground 1 (Pet. at 55), the Patent Owner does the same with regard to the arguments in Section IV.E.2 above. CFAD argues that additional content in Stein 2004, namely implitapide trial data and "Dr. Stein's teachings that the success required need only be modest to justify pursuing MTP inhibitors," further "confirm" a reasonable expectation of success. Pet. at 55. As an initial matter, CFAD merely mentions these additional factors; its petition lacks the required analysis as to how these factors support a reasonable expectation of success. *See id.* at 55-56; 37 C.F.R. § 42.22(a)(2). Further, the existing implitapide trial data would not have provided either a motivation to try an escalating dose regimen (*see, e.g.*, discussion of claims

3 and 4 above), or a reasonable expectation of success, at least because there is nothing to suggest that MTP inhibitors are interchangeable with one another with respect to dosages or minimization of side effects.

For at least the above reasons, the combination of Stein 2004 (the Stein Presentation or the Stein Slides) and Chang fails to render the claims of the '135 Patent obvious under 35 U.S.C. § 103, and institution on Ground 2 should be denied.

G. Secondary Considerations Support the Patentability of the '135 Patent Claims

1. Unexpected Results Support the Patentability of the '135 Patent's Claims

Previously unknown and unexpected properties of a new and nonobvious invention constitute additional, objective evidence of nonobviousness. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015). Such is the case here, where 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.

Well before Dr. Rader began his clinical trial investigation in June 2003, BMS had abandoned lomitapide and donated it to the University of Pennsylvania because of the compound's "significant and serious hepatotoxicity at the dosages

used." Ex. 2001 at 30. BMS had concluded that while lomitapide was "apparently efficacious . . . [it] could not be developed as a pharmaceutical product of general or wide utility." *Id.*

As discussed above, there was no suggestion in the prior art that an escalating dosing regimen would ameliorate the side effects that deterred BMS, and which possibly derailed Stein's 2004 study. 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. *See, e.g.*, Ex. 1010 at 3, ¶ 14. Particularly in view of the lack of understanding in the prior art regarding the mechanism by which tolerability was improved, this result was unexpected.

2. Commercial Success Supports the Patentability of the '135 Patent

The commercial success of Juxtapid® also supports the patentability of the '135 Patent's claims. HoFH is a rare disorder, estimated to affect approximately 3-6.25 per million people in the U.S. *See*, Ex. 2012 at 12. In December 2012, Juxtapid® was approved for the treatment of HoFH, and in its first year on the market it generated approximately $48.5 million in revenue from net product sales. Ex. 2012 at 95; Ex. 2013; *In re McLaughlin*, 443 F.2d 1392, 1396 (C.C.P.A. 1971)

(commercial success shown by high volume of first-year sales). Currently, Aegerion expects "full-year 2015 global net product sales of [Juxtapid®] to be between $205 million and $215 million." Ex. 2014 at 8.

Without Dr. Rader's invention, lomitapide would never have been brought to market. BMS shelved its development of the drug due to tolerability and safety issues that arose in early clinical studies, and it was not until Dr. Rader discovered his inventive step-wise, increasing dose-titration strategy that a pathway was found to bring the drug to market in a safe and effective manner. There is no question that the use of Juxtapid® falls within the scope of the '135 Patent claims. For example, the label depicts the recommended dosing as follows:

Table 1: Recommended Regimen for Titrating Dosage

DOSAGE	DURATION OF ADMINISTRATION BEFORE CONSIDERING INCREASE TO NEXT DOSAGE
5 mg daily	At least 2 weeks
10 mg daily	At least 4 weeks
20 mg daily	At least 4 weeks
40 mg daily	At least 4 weeks
60 mg daily	Maximum recommended dosage

Ex. 2015 at 5. This dosing scheme falls squarely within the ranges claimed in the '135 patent. *See, e.g.*, Ex. 1001 at 19:46-49 ("wherein a first dose level is from about 5 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"). Thus, the

commercial success of Juxtapid® has a nexus with the claimed invention, which supports a finding that the claims of the '135 patent are not obvious. *See Syntex (U.S.A.) LLC v. Apotex Inc.*, No. C 01-02214 MJJ, 2006 WL 1530101, at *26 (N.D. Cal. June 2, 2006) (finding that "commercial success derives from its embodiment of the entire combination taught by the '493 patent . . . "); *Phigenix, Inc. v. Immunogen, Inc.*, IPR2014-00676, Paper 39 at 22-26 (P.T.A.B. Oct. 27, 2015).

3. The Claimed Invention Met a Long-Felt, Unmet Need

As discussed above, HoFH is a rare genetic disorder that can lead to early and severe ASCVD due to elevated LDL-C levels, which may lead to early cardiac-related death. *Supra* at II.B. Because statins primarily work via upregulation of the LDL receptor in the liver, "patients with HoFH who lack functional LDL receptor activity generally respond very poorly" to statins (Ex. 2002 at 13; *see also id.* at 26) and are "minimally responsive" to other conventional lipid-lowering therapies. *Id.* at 26.

Thus, prior to the claimed invention, treatment options were inadequate, and HoFH patients suffered from the resulting consequences of their "marked elevation in plasma LDL-C levels," including ASCVD and possible early death. *Id.* at 11; Ex. 2016 at 3-4. Accordingly, because existing treatments were not adequately

efficacious, the '135 Patent's development of an effective treatment for adult HoFH patients met a long-felt, but unmet need. Indeed, CFAD has also acknowledged this unmet need. *See* Pet. at 54. This supports a finding that the claims of the '135 patent are not obvious. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009).

V. IF IPR IS INSTITUTED, IT SHOULD NOT BE INSTITUTED FOR ALL CLAIMS

Many of the claims recite limitations that are not taught or suggested in the prior art. The law requires that a petition for *inter partes* review "identif[y], in writing ***and with particularity, each claim challenged, the grounds*** on which the challenge to each claim is based, ***and the evidence*** that supports the grounds for the challenge to each claim." 35 U.S.C. § 312(a)(3) (emphasis added). CFAD does not set forth a detailed analysis of how the dependent claims are rendered obvious over the prior art. Instead, CFAD gives the claims cursory treatment in its claim charts. Pet. at 32-37; 47-52. (In fact, in Ground 2, CFAD does not separately argue the alleged unpatentability of any specific claim.) Accordingly, if the Board is inclined to institute review, it should not do so with respect to every claim.

As discussed above, CFAD has not adequately argued the alleged unpatentability of claims 3 and 4 under either proposed ground. *Supra* at IV.E.2.a. and IV.F.

In addition, independent claim 9 recites that the first dosage level be administered for 2 weeks, and the second and third dosage levels be administered for 2-4 weeks. Ex. 1001 at 20:23-54. Independent claim 10 recites that the second and third dosage levels be administered for about 4 weeks each. *Id.* at col. 20:55-21:17.

For the sake of argument, assuming the Pink Sheet 2004 and Stein 2004 disclose an escalating dosing regimen (which they do not), these references disclose, at most, adjusting dosage amounts after 5 weeks. Ex. 1014 at 38 ("Starting dose is 10 mg daily with escalation by 5 mg ***every 5 weeks*** to maximum of 40 mg.") (emphasis added); Ex. 1013 at 2 ("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.") (emphasis added). Neither reference discloses the time periods set forth in claims 9 and 10. The asserted prior art references also do not suggest varying the amount of time the patients stays at each dosing level (compare Stein 2004 and Pink Sheet 2004's "every 5 weeks" to the

different periods specified in the claims). Accordingly, the prior art cited by CFAD does not disclose each limitation of claims 9 and 10.

CFAD appears to suggest that varying the period of time a patient remains at each dosage level would be merely routine optimization (*see, e.g.*, Pet. at 39), but it does not tie these arguments to any particular claim or describe with particularity how this relates to any particular claimed time period. Accordingly CFAD has not carried its burden of proof on at least claims 9 and 10 under either Grounds 1 or 2.

Under Board precedent, CFAD has failed to meet its statutory burden, and the Board should not institute review on at least claims 3, 4, 9, and 10, and any other claims which do not meet the standard for petition for *inter partes* review.

VI. CONCLUSION

For all of the foregoing reasons, the Board should decline to institute *inter partes* review on either of the grounds identified in the Petition.

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Respectfully Submitted,
GOODWIN PROCTER LLP

/William G. James/
William G. James
(Reg. No. 55,931)
GOODWIN PROCTER LLP
901 New York Avenue NW
Washington, DC 20001
Tel: 202-346-4046
Fax: 2022-346-4444

wjames@goodwinprocter.com

Nicholas K. Mitrokostas
(to seek *pro hac vice* admission)
GOODWIN PROCTER LLP
Exchange Place
53 State Street
Boston, MA 02109-2881
Tel: 617-570-1913
Fax: 617-523-1231
nmitrokostas@goodwinprocter.com

Cynthia Lambert Hardman
(Reg. No. 53,179)
GOODWIN PROCTER LLP
The New York Times Building
620 Eighth Avenue
New York, NY 10018-1405
Tel: 212-459-7295
Fax: 212-355-3333
chardman@goodwinprocter.com

Attorneys for Patent Owner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing document captioned "PATENT OWNER'S PRELIMINARY RESPONSE" was served electronically via e-mail on this 8th day of December, 2015, as follows:

Dr. Gregory Gonsalves
2216 Beacon Lane
Falls Church, Virginia 22043
(571) 419-7252
gonsalves@gonsalveslawfirm.com

Christopher Casieri
McNeely, Hare & War LLP
12 Roszel Road, Suite C104
Princeton, NJ 08540
(609) 731-3668
chris@miplaw.com

Counsel for Petitioner Coalition for Affordable Drugs VIII, LLC

Respectfully submitted,

Dated: December 8, 2015

/William G. James/
William G. James
GOODWIN PROCTER LLP