Petition for *Inter Partes* Review of USPN 8,618,135

Filed on behalf of Coalition for Affordable Drugs VIII, LLC
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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.

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner, based on Electronic Records of PTO
U.S. Patent 8,618,135 to Rader
Filing Date: March 11, 2011
Issue Date: December 31, 2013
TITLE: METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS

IPR Trial No. TBD

Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135

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EXHIBIT LIST PURSUANT TO 37 C.F.R. § 42.63(e) AND TABLE OF ABBREVIATIONS

Ex. No.	Description
1001	Certified U.S. Patent No. 8,618,135 to Rader.
1002	Declaration of Randall M. Zusman, M.D.
1003	Declaration of Michael Mayersohn, Ph.D.
1004	Affidavit of Christopher Butler, Office Manager, Internet Archive, authenticating Internet Archive URLs (June 16, 2015) (attaching as Ex. A: *PPD News & IR Presentations (2004/04/15)* (available at https://web.archive.org/web/20040415065142/http://ppdi.com/PPD_6_12.htm)).
1005	Affidavit of Christopher Butler, Office Manager, Internet Archive, authenticating Internet Archive URLs (June 12, 2015) (attaching as Ex. A: *PPD News Releases(2004/02/13)* (available at https://web.archive.org/web/20040213233245/http://www.ppdi.com/PPD_U6.htm?ID=126662); *PPD News & IR Presentations(2003/12/12)* (available at https://web.archive.org/web/20031212193444/http://ppdi.com/PPD_6_12.htm); *PPD News & IR Presentations (2004/06/04)* (available at https://web.archive.org/web/20040604203252/http://www.ppdi.com/PPD_6_12.htm)).
1006	Certified U.S. Provisional Patent Application No. 60/550,915.
1007	U.S. Patent No. 8,618,135 (highlighting dosing information not present in U.S. Provisional Patent Application No. 60/550,915).
1008	U.S. Patent Application No. 13/046,118.
1009	*In re Application of: Rader*, U.S. Patent Application No. 13/046,118, Amendment and Response to Oct. 2, 2012 Office Action (Mar. 4, 2013).

1010	*In re Application of: Rader*, U.S. Patent Application No. 13/046,118, Declaration of William Sasiela, Ph.D. (Apr. 8, 2010).
1011	*In re Application of: Rader*, U.S. Patent Application No. 13/046,118, Notice of Allowance (May 10, 2013).
1012	*In re Application of: Rader*, U.S. Patent Application No13/046,118, Notice of Allowance (Sept. 3, 2013).
1013	*Bayer/PPD Implitapide Development Follows Zetia Model As Statin Add-On*, 66 THE PINK SHEET 17 (Feb. 16, 2004).
1014	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).
1015	George Chang et al., *Microsomal triglyceride transfer protein (MTP) inhibitors: Discovery of clinically active inhibitors using high-throughput screening and parallel synthesis paradigms*, 5 CURRENT OPINION IN DRUG DISCOVERY & DEV. 562 (2002).
1016	Charles E. Chandler et al., *CP-346086: an MTP inhibitor that lowers plasma cholesterol and triglycerides in experimental animals and in humans*, 44 J. OF LIPID RES. 1887 (2003).
1017	*FDA approves Zetia -- first new class to treat cholesterol since statins introduced*, DRUGS.COM (Oct. 28, 2002), http://www.drugs.com/news/fda-approves-zetia-first-new-class-cholesterol-since-statins-introduced-3164.html (last visited July 22, 2015).
1018	John R. Wetterau et al., *An MTP Inhibitor That Normalizes Atherogenic Lipoprotein Levels in WHHL Rabbits*, 282 SCI. 751 (1998).
1019	U.S. Patent No. 5,712,279 to Biller et al.
1020	Evan Stein, OPPOSITION AGAINST EUROPEAN PATENT NO. 1 725 234 B9 (filed Aug. 21, 2013).

1021	THOMPSON PDR, PHYSICIANS' DESK REFERENCE 506-09, 1101-06, 1813-21, 2036-41, 2126-31, 2547-51, 2729-31, 2865-68 (57th ed. 2003) (excerpting product information for Tricor®, Pravachol®, Advicor®, Niaspan®, Mevacor®, Zocor®, Lipitor®, Colestid®, and Lescol®).
1022	THOMPSON PDR, PHYSICIANS' DESK REFERENCE 2118-23, 3085-89 (58th ed. 2004) (excerpting product information for Zetia®).
1023	U.S. FOOD & DRUG ASS'N, ESTIMATING THE MAXIMUM SAFE STARTING DOSE IN INITIAL CLINICAL TRIALS FOR THERAPEUTICS IN ADULT HEALTHY VOLUNTEERS: GUIDANCE FOR INDUSTRY (2005).
1024	*Prices and coupons for 30 capsules of Juxtapid 5mg, 10mg, 20mg, 30mg, 40mg and 60mg (brand)*, GOODRX.COM, http://www.goodrx.com/juxtapid (last visited July 16, 2015).
1025	Dan Mangan, *'Fast Money' faux pas: Firm draws FDA warning, DOJ subpoena*, CNBC.COM (Jan. 13, 2014), http://www.cnbc.com/id/101327742 (last visited July 22, 2015).
1026	Malcolm Rowland & Thomas N. Tozer, CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS 57 (3d ed. 1995).
1027	Curriculum Vitae of Randall M. Zusman, M.D.
1028	Documents considered by Randall M. Zusman, M.D.
1029	Curriculum Vitae of Michael Mayersohn, Ph.D.
1030	Documents considered by Michael Mayersohn, Ph.D.
1031	*Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report*, 106 CIRCULATION 3143 (2002).
1032	Michael Mayersohn, *Principles and Applications of Pharmacokinetics*, *in* MEDICAL TOXICOLOGY 282 (Richard C. Dart ed., 3d ed. 2004).

1033	Masashi Shiomi & Takashi Ito, *MTP inhibitor decreases plasma cholesterol levels in LDL receptor-deficient WHHL rabbits by lowering the VLDL secretion*, 431 EUR. J. OF PHARMACOLOGY 127 (2001).
1034	Declaration of Jeffery A. Marx.
1035	Press Release, Cigna Corp., *Cigna Announces Appearance at CIBC Healthcare Conference* (Nov. 7, 2003), http://newsroom.cigna.com/article_display.cfm?article_id=236.
1036	Press Release, Gilead Scis., *Gilead Sciences to Present at the 7th Annual Lehman Brothers Global Healthcare Conference on Friday, March 5th; Webcast Available Through Gilead Corporate Website* (Mar. 4, 2004), http://gilead.com/news/press-releases/2004/3/gilead-sciences-to-present-at-the-7th-annual-lehman-brothers-global-healthcare-conference-on-friday-march-5th-webcast-available-through-gilead-corporate-website?mode=print.
1037	Press Release, PR Newswire, *Dot Hill to Present at Robert W. Baird 2004 Growth Stock Conference* (May 4, 2004), http://www.prnewswire.com/news-releases/dot-hill-to-present-at-robert-w-baird-2004-growth-stock-conference-73777807.html.
1038	Margaret A. McDowell et al., *Anthropometric Reference Data for Children and Adults: U.S. Population, 1999-2002*, CDC ADVANCE DATA FROM VITAL & HEALTH STATS. NO. 361 (2005).
1039	*In re Application of: Rader*, U.S. Patent Application No. 13/046,118, Amendment (Sept. 25, 2013).
1040	*In re Application of: Rader*, U.S. Patent Application No. 13/046,118, Supplemental Information Disclosure Statement (Sept. 25, 2013).
1041	*In re Application of: Rader*, U.S. Patent Application No. 13/046,118, Notice of Allowance (Oct. 29, 2013).

TABLE OF ABBREVIATIONS

Abbreviation	Definition
‘915 Provisional	U.S. Provisional Patent Application No. 60/550,915
‘268 patent	U.S. Patent No. 7,932,268
‘923 application	U.S. Patent Application No. 10/591,923 (issued as ‘268 patent)
‘135 patent	U.S. Patent No. 8,618,135
‘118 application	U.S. Patent Application No. 13/046,118 (issued as ‘135 patent)
ApoB	Apolipoprotein B
CFAD	Coalition For Affordable Drugs VIII, LLC
Credes	Hayman Credes Master Fund, L.P.
HCM	Hayman Capital Management, L.P.
HCMF	Hayman Capital Master Fund, L.P.
HDL	High density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HI	Hayman Investments, L.L.C.
HOF	Hayman Orange Fund SPC – Portfolio A
HoFH	Homozygous familial hypercholesterolemia
HOM	Hayman Offshore Management, Inc.
IDL	Intermediate-density lipoprotein
LDL	Low density lipoprotein

Abbreviation	Definition
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
Mayersohn	Declaration of Michael Mayersohn, Ph.D. in Support of Coalition for Affordable Drug's Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135
MTP	Microsomal triglyceride transfer proteins
TG	Triglycerides
Total-C	Total cholesterol
VLDL	Very low density lipoprotein
WHHL	**W**atanabe-**h**eritable **h**yper**l**ipidemic
Zusman	Declaration of Randall M. Zusman, M.D. in Support of Coalition for Affordable Drug's Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135

TABLE OF AUTHORITIES

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Federal Cases

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Federal Regulations

Coalition For Affordable Drugs VIII LLC ("CFAD" or "Petitioner") requests *inter partes* review (35 U.S.C. § 312 and 37 C.F.R. § 42.108) seeking cancellation of Claims 1-10 of U.S. Patent No. 8,618,135 ("the '135 patent") (Exhibit ("CFAD Ex.") 1001) issued December 31, 2013 to Daniel J. Rader. A Power of Attorney (37 C.F.R. § 42.10(b)) and an Exhibit List (37 C.F.R. § 42.63(e)), are concurrently-filed. Please charge the required $23,000 fee (37 C.F.R. § 42.15(a)) to Deposit Acct. No. 50-3626 (Customer ID No. 60024). The Office is authorized to charge any fee deficiencies and credit any overpayments to Deposit Acct. No. 50-3626 (Customer ID No. 60024).

I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8.

Petitioner provides the following mandatory notices under 37 C.F.R. §§ 42.8(a)(1) and 42.8(b).

A. Real Party-in-Interest (37 C.F.R. § 42.8(B)(1)).

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Coalition For Affordable Drugs VIII LLC, Hayman Credes Master Fund, L.P. ("Credes"), Hayman Orange Fund SPC – Portfolio A ("HOF"), Hayman Capital Master Fund, L.P. ("HCMF"), Hayman Capital Management, L.P. ("HCM"), Hayman Offshore Management, Inc. ("HOM"), Hayman Investments, L.L.C. ("HI"), J. Kyle Bass, and Erich Spangenberg are the real parties in interest (collectively "RPI"). The RPI hereby certify the following information: CFAD VIII is a wholly owned subsidiary

of Credes. Credes is a limited partnership. HOF is a segregated portfolio company. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative general partner of Credes and HCMF. HI is the general partner of HCM. J. Kyle Bass is the sole member of HI and the sole shareholder of HOM. CFAD VIII, Credes, HOF and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is the Manager and majority member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the Manager and majority member of IPNav. Other than J. Kyle Bass in his capacity of the Chief Investment Officer of HCM, and nXnP and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD VIII, Credes, HOF, HCMF, HCM, HOM, HI, nXnP or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this petition will be borne by HCM, CFAD VIII, Credes, HOF and/or HCM.

B. Related Matters (37 C.F.R. § 42.8(b)(2)).

Petitioner is concurrently filing a Petition for *Inter Partes* Review of U.S. Patent No. 7,932,268, which is a member of the same family as the '135 patent.

C. Notice of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)).

Lead Counsel	Back-Up Counsel
Dr. Gregory Gonsalves Reg. No. 43,639 2216 Beacon Lane Falls Church, Virginia 22043 (571) 419-7252 gonsalves@gonsalveslawfirm.com	Christopher Casieri Reg. No. 50,919 MCNEELY, HARE & WAR, LLP 12 Roszel Road, Suite C104 Princeton, NJ 08540 Phone: (609) 731-3668 Fax: (202) 478-1813 chris@miplaw.com

D. Service Information under 37 C.F.R. § 42.8(b)(4).

Please address all correspondence to the Lead Counsel at the above address. Petitioner consents to electronic service by email to: gonsalves@gonsalveslawfirm.com and chris@miplaw.com.

E. Service on Patent Owner Under 37 C.F.R. §§ 42.106(a) and 42.105(a).

This petition is being served by Express Mail on The Trustees of the University of Pennsylvania, owners of the '135 patent, at their address of record according to the USPTO PAIR database: The Trustees of the University of Pennsylvania, 3160 Chestnut Street Suite 200, Center for Technology Transfer, Philadelphia, PA 19104-6283.

II. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(A).

Petitioner certifies that the '135 patent is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition. No RPI has filed a civil action challenging the validity of the '135 patent, nor has any RPI been served with a complaint alleging infringement of the '135 patent more than one year prior to the filing of this Petition.

The public interest requires ensuring monopoly privileges are not granted by an invalid patent, particularly because Juxtapid® sells for more than $900.00 per pill, and costs nearly $330,000 per patient per year. (*See* CFAD Ex. 1024; CFAD Ex. 1025). Patentee and its licensee, Aegerion Pharmaceuticals, Inc., have secured such pricing through FDA regulatory exclusivity and BMS's lomitapide molecule patents, but cannot extend it with the obvious '135 patent.

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

Petitioner respectfully requests *inter partes* review and cancellation of claims 1-10 of the '135 patent based on the grounds set forth in the table below:

Ground	Challenged Claims	Statutory Basis	References
1	1-10	§ 103	Pink Sheet 2004 in view of Chang
2	1-10	§ 103	Stein 2004 in view of Chang

Sections IV-X below explain how the '135 patent claims—properly construed—are unpatentable on the grounds listed above. *See Graham v. John*

Deere Co., 383 U.S. 1, 17-18 (1966) (reciting four-factor obviousness test).

In support of these grounds for unpatentability, Petitioner submits the expert declaration of Randall M. Zusman, M.D. to discuss the relevant field and art in general, and the factual and opinion bases for each of the *Graham* factors underlying Petitioner's Grounds 1 and 2. (CFAD Ex. 1002). Petitioner also submits the declaration of pharmacokinetics expert Michael Mayersohn, Ph.D., on the specific dosing-related teachings. (CFAD Ex. 1003). Petitioner further relies on the Exhibits set forth on the concurrently filed Exhibit List, including the Pink Sheet 2004 (CFAD Ex. 1013), Stein 2004 (CFAD Ex. 1014), and Chang (CFAD Ex. 1015) references. Pink Sheet 2004 and Stein 2004 publications were not before the examiner during the substantive prosecution of the application leading to the '135 patent; patentee submitted those references in September 2013 *only* after receiving a second Notice of Allowance. Chang was cited but never substantively discussed.

IV. INTRODUCTION AND SUMMARY OF ARGUMENT.

The '135 patent claims are invalid. They merely claim methods of using a known drug, to treat known medical conditions, for which the drug was known to be effective, with known dose-titration methods disclosed in the prior art.

The '135 patent issued on December 31, 2013 from Application No. 13/046,118 (the '118 Application) filed March 11, 2011, itself a continuation of

Application No. 10/591,923 (the '923 Application) filed March 7, 2005.[1] The patent recognizes hyperlipidemia and hypercholesterolemia are characterized by elevated serum levels of cholesterol (total and LDL-C) and lipids (*e.g.*, triglycerides (TG)), which increase the risk of cardiovascular disease. (CFAD Ex. 1001, col. 1:24 – col. 2:3). The '135 patent characterizes as inventive treating hyperlipidemia or hypercholesterolemia with drugs that inhibit microsomal triglyceride transfer proteins ("MTP"), *i.e.*, MTP inhibitors, by applying step-wise escalating dosing regimens. (*See id.* at col. 7:11-24; col. 11:60 – col. 13:23).

Administering anti-cholesterol drugs in step-wise escalating doses was standard practice with, *e.g.*, statins, fibrates, and niacin. (CFAD Ex. 1002 ("Zusman") ¶¶ 37-38, 40, 43-47). Dr. Evan Stein specifically taught applying step-wise escalating dosing to the MTP inhibitor implitapide to treat hyperlipidemia and hypercholesterolemia—facts published before the relevant filing date. (*See* CFAD Ex. 1013; CFAD Ex. 1014). Dr. Stein also disclosed the rationales for this dosing approach: minimizing side effects, rendering MTP inhibitors marketable as adjunct therapy to statins; and treating patients not effectively treated by statins. (Zusman, ¶¶ 69-70, 103-04; CFAD Ex. 1003 ("Mayersohn") ¶¶ 57, 59-60).

[1] Patentee cannot claim priority to its March 5, 2004 provisional application given the elements of the issued claims of the '135 patent. (*See* Section V, below).

The '135 patent's named inventor, Dr. Rader, was a clinical investigator on the September 2003 implitapide studies Dr. Stein designed and led. (CFAD Ex. 1020:8). Dr. Rader filed his provisional application in March 2004. But before then, two February 2004 publications (one by Dr. Stein and another by The Pink Sheet) had already disclosed Dr. Stein's implitapide step-wise escalating dosing. (*See* Section IX, below). Yet Dr. Rader initially claimed he invented step-wise dosing for *all* MTP inhibitors. (*See* CFAD Ex. 1008:28-31). As issued, the '135 patent claims merely apply Dr. Stein's step-wise escalating dosing approach to the MTP inhibitor lomitapide. (*See* CFAD Ex. 1001, col. 19:42-67 (claim 1)).

The ordinarily-skilled artisan required no great leap to apply Dr. Stein's implitapide dosing regimen to other MTP inhibitors such as lomitapide. (Zusman, ¶ 33; Mayersohn, ¶ 27). Lomitapide was a known, potent MTP inhibitor. (*See* CFAD Ex. 1001, col. 5:47–col. 6:19; Zusman, ¶ 24). The prior art taught lomitapide's efficacy *in vitro*, in animal models, and in humans, and also taught lomitapide had clinical effects similar to implitapide. (Zusman, ¶¶ 62-63, 96-99; Mayersohn, ¶¶ 18-19; *see also* CFAD Ex. 1015:563-66).

As detailed below, the published prior art disclosures and the skilled artisan's motivation to apply step-wise escalating dosing regimens to MTP inhibitors (including lomitapide) with a reasonable expectation of success render independent claims 1, 9, and 10, and dependent claims 6-8 of the '135 patent obvious at the time

of filing. The additional elements found in dependent claims 2-5 merely reflect uses, targets, and results already known or inherent in the dosing method itself. (Zusman, ¶¶ 150-165; CFAD Ex. 1015:562, 565-66).

For the reasons set forth herein, under 37 C.F.R. § 42.22(A), Petitioner requests *Inter Partes* Review and cancellation of claims 1-10. Petitioner's detailed statement of the reasons for the relief requested appears in Sections V-X below.

V. THE '135 PATENT PRIORITY DATE IS MARCH 7, 2005; THE '915 PROVISIONAL DOES NOT SUPPORT THE ISSUED CLAIMS.

The '135 patent claims receive the benefit of U.S. Provisional Patent Application 60/550,915 ("the '915 Provisional") **only** if that application "describe[s] an invention, and . . . in sufficient detail that one skilled in the art can clearly conclude that [Dr. Rader] invented the claimed invention as of the filing date sought," such that he was "in possession of" the invention. *See Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997); *Trading Techs. Int'l Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1359 (Fed. Cir. 2010). The '915 Provisional does not support the claimed dose ranges ***or*** the piperidine N-oxide derivatives.

A. No Support for the Full Scope of the Claimed Dose Ranges.

Independent claim 1 recites a step-wise escalating dose method where the first dose ranges from "about 2 to about 13 mg/day"; the second "from about 5 to about 30 mg/day" and the third "from about 10 to about 50 mg/day," with dose escalation at "about 1 to about 5 weeks." (CFAD Ex. 1001, col. 19:40–67). Independent claims

9 and 10 recite similar dosing steps, but change the timing of the dose escalation. (*See id.*, col. 20:23 – col. 21:18). The '135 patent's specification lists various dose ranges and numbers of dosing steps for MTP inhibitors. (*See id.* at col. 11:60 – 13:29). That section includes the particular dose ranges claimed (*id.* at col. 12:45-51), but this language was conspicuously *absent* from the '915 Provisional, which focused on different dose-range combinations. (*Compare* CFAD Ex. 1006:14-15). The claimed dose ranges are new matter. (Zusman, ¶ 82; *see* CFAD Ex. 1007 ("Demonstrative")).

While the claim terms need not appear *in haec verba*, the provisional lacks any equivalent description of the claimed subject matter. 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. (Zusman, ¶¶ 83-90; Mayersohn, ¶¶ 76-103). Nor can Patentee support the full scope of the claimed ranges merely by pointing to a species within, or a genus beyond, the '915 Provisional. *See Trading Techs.*, 595 F.3d at 1359 (skilled artisan must understand from the application "the genus that is being claimed has been invented, not just the species of a genus") (citations omitted); *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008) (skilled artisan must visualize or recognize from the specification all members of the claimed genus). Nor may Patentee support the claimed mg/day doses from the other dose

amounts, sometimes expressed as mg/day, other times as mg/kg, found in the '915 Provisional. *See Ex parte Zeying Ma & Yubai Bi*, Appeal 2013-001589, 2014 WL 1005343, at *3-*4 (P.T.A.B. January 27, 2014) (specification's thirty-five embodiments across six tables omitted specifically-claimed ranges).

Patentee's specification deliberately *added* new matter reciting the claimed dose/range combinations to the '923 Application filed in March 2005, confirming the '915 Provisional lacked the "illustrative examples or terminology" or "blaze marks" skilled artisans require to identify and determine the particular genus ultimately claimed. *See In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991); *Purdue Pharma, L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000). Without the '915 Provisional date, the '135 patent's priority date is March 7, 2005.

B. In Addition, No Support for "the Piperidine N-oxide Thereof".

The '135 patent claims require using an MTP inhibitor that is either the illustrated compound (lomitapide), salts thereof, or "the piperidine N-oxide thereof." (CFAD Ex. 1001, col. 19:40 – col. 21:18). The specification lacks any example by structure, chemical language, synthetic process or clinical test showing a lomitapide "piperidine N-oxide" derivative. The '915 Provisional nowhere uses the term, or presents by structure, a "piperidine N-oxide." 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." (CFAD Ex. 1006:11). The '915 Provisional thus fails to adequately describe or support the claimed "piperidine N-oxide" lomitapide derivative or its therapeutic use.

Patentee cannot rely on the many patents incorporated by reference in the '915 Provisional's specification, which encompass a massive genus of structures, to support a purported lomitapide piperidine N-oxide derivative. *See Novozymes A/S v. Dupont Nutrition Biosciences APS*, 723 F.3d 1336, 1343, 1346 (Fed. Cir. 2013). In *Novozymes*, the patentee's provisional disclosed "a potentially enormous number" of structural variants with myriad combination possibilities at multiple structural locations. *Id.* at 1343. Like the '915 Provisional, *Novozymes*' "did not point out the specific [structural] variants later claimed in the [issued] patent," but gave "only generalized guidance." *Id.* at 1343, 1346. The '915 Provisional's generalized piperidine discussion never identifies an N-oxide "variant that actually satisfies the claims, nor is there anything to suggest that [patentee] actually possessed such a variant at the time of filing." *Id.* at 1348. The '915 Provisional fails to adequately describe or support the "piperidine N-oxide thereof" limitation.

Because the ordinarily-skilled artisan would not accept that Dr. Rader "possessed" treatment methods using piperidine N-oxide compounds of lomitapide at the time of filing, the '135 patent claims do not receive the benefit of the '915 Provisional filing date. The references presented below are therefore prior art under

pre-AIA 35 U.S.C. § 102(a) whatever the priority date, and also under pre-AIA 35 U.S.C. § 102(b) because, as shown below, they were published more than a year before the filing of the '923 Application.

VI. SCOPE AND CONTENT OF THE PRIOR ART.

Subsections A and B below discuss the state of the art before March 5, 2003, while subsection C covers up to March 5, 2004.

A. Elevated Serum Cholesterol and Lipid Levels Were Recognized Risk Factors For Cardiovascular Disease.

Decades ago, doctors and scientists recognized hypercholesterolemia (high serum cholesterol levels) and hyperlipidaemia (high serum lipid levels) as key atherosclerotic cardiovascular disease ("ASCVD") risk factors. ASCVD was and remains a major cause of premature mortality in the Western world. (*See* Zusman, ¶¶ 35-42; CFAD Ex. 1001, col. 1:24-25). The field has been actively researched for decades; cholesterol- and lipid-lowering drugs are commonplace in the physician's armamentarium and patients' medicine cabinets. (Zusman, ¶¶ 43-49).

B. Known Drug Classes and Dosing Regimens Pre-March 2003.

Fibrates, statins and niacin were known drug classes used with hypercholesterolemic patients to reduce lipid levels before March 2003. (*Id.*) Due to their side effect profiles, such drugs were frequently administered using step-wise dose escalation. (*See id.* at ¶¶ 43-47, 65; *see also* CFAD Ex. 1021 (fibrate doses "individualized according to patient response" and "adjusted if necessary" at "4 to 8

week intervals."); CFAD Ex. 1021, (LIPITOR®, ZOCOR®, MEVACOR®) (recommending starting patients on the drug at low doses and titrating upward according to "patient response" at intervals of "4 weeks or more."); CFAD Ex. 1021, (NIASPAN®) (drug dosed beginning "at 500 mgs qhs in order to reduce the incidence and severity of side effects;" after four weeks, the dose doubles; and after the eighth week the physician is to "titrate to patient response and tolerance" up to a maximum recommended dose of 2000 mg daily with the daily dose not "increased more than 500 mg in a 4-week period.")).

MTP inhibitors. Microsomal triglyceride transfer proteins (MTP) play a central role in lipoprotein assembly. They mediate triglyceride absorption from the intestine and lipoprotein secretions from the liver by linking lipids to apolipoprotein B (apoB). MTP inhibitors reduce plasma levels of LDL-C, VLDL lipoproteins and chylomicrons. (*See* Zusman, ¶¶ 55-58; CFAD Ex. 1015:562-63). By 2003, some MTP inhibitors had shown significant animal and human efficacy, including with subjects with familial hypercholesterolemia ("FH"). (*See* Zusman, ¶¶ 59-61; CFAD Ex. 1015:564-67). But, administering MTP inhibitors as a monotherapy at higher doses—needed to achieve lipid-lowering effects comparable to statins—unsurprisingly produced comparatively higher side effects, including liver-fat accumulation. (*See* Zusman, ¶¶ 64, 69; CFAD Ex. 1015:567).

Chang highlighted three MTP inhibitors as having progressed to human

clinical trials by 2003: Pfizer's CP-346086; Bayer's 13-9952 (implitapide); and BMS's 201038 (lomitapide). Chang reported the three drugs had "similar efficacy" in clinical studies. (CFAD Ex. 1015:566). Chang also recognized that "MTP inhibitors have demonstrated impressive lipid lowering efficacy in clinical studies," but also that "potentially significant adverse effects surround this mechanism." (*See id*. at 567). Several drug companies looking at MTP inhibitors as *monotherapy* alternatives to statins had dropped their MTP inhibitor programs—including BMS with lomitapide. (*See id.*; CFAD Ex. 1001, col. 8:27-30). As Chang explained, those decisions were not because the drugs didn't work; rather, "statins have raised the hurdles for successfully *marketing* MTP inhibitors, or any other future lipid lowering approach." (CFAD Ex. 1015:567) (emphasis added). Chang concluded that "a readily managed therapeutic index will be critical for the progression of inhibiting MTP as a viable chronic lipid lowering therapy." (*Id.*)

Combination therapy. In November 2002 FDA granted Merck approval to market ezetimibe (ZETIA®), alone or combined with a statin, to reduce elevated total-C, LDL-C, and Apo B in primary hyperlipidemia patients, and in combination to reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH). (Zusman, ¶¶ 70-71; CFAD Ex. 1017:2; CFAD Ex. 1022, (ZETIA®)). Merck's ZETIA® success renewed interest in MTP inhibitors. Shortly after ZETIA®'s approval, and at least by September 2003, Dr. Stein was

pursuing clinical trials of implitapide for adjunctive therapy, combination use, and use in HoFH patients. (*See* CFAD Ex. 1020:2-3, 8-9 (citing ref. D8)).

C. The Content of the MTP Inhibitor Art Pre-March 2004.

The literature resolved Chang's concerns about managing MTP inhibitors' therapeutic index for commercial marketing purposes, in: (1) a February 5, 2004 presentation by Dr. Evan Stein discussing PPD, Inc.'s plans for the MTP inhibitor implitapide (Stein 2004); and (2) a February 16, 2004 Pink Sheet article—"Bayer/PPD Implitapide Development Follows Zetia Model As Statin Add-On"—reporting on Dr. Stein's presentation and publishing his dosing strategy for MTP inhibitors (Pink Sheet 2004). (*See* Zusman, ¶¶ 137-40, 142-43, 206, 208-11, 213-15). Dr. Stein acknowledged the marketing hurdles Chang noted, but taught ZETIA®'s success created an opportunity and model for MTP inhibitors. (*See* CFAD Ex. 1013:1). Dr. Stein's publications also disclosed step-wise dosing of MTP inhibitors addressing Chang's therapeutic index concerns. (*See* CFAD Ex. 1014:37-38; *see also* CFAD Ex. 1015:567; Zusman, ¶¶ 103-05, 110).

In Section X below, Petitioner relies on Pink Sheet 2004 in view of Chang (Ground I), or Stein 2004 in view of Chang (Ground II) to demonstrate that claims 1-10 of the '135 patent are invalid for obviousness.

1. Pink Sheet 2004 is Prior Art.

"The Pink Sheet" is a printed publication directed to the pharmaceutical and

biopharmaceutical industries which provides "[u]p-to-date pharma/biotech news—at your desk—from your trusted source for over 65 years." (*See* CFAD Ex. 1013:1). In addition to print and mail circulation, the Pink Sheet is available online and circulated in electronic format to subscribers, providing headlines and breaking news alerts with links to stories analyzing notable events, industry news, and trends. (*See* http://www.pharmamedtechbi.com/publications/the-pink-sheet-daily; Zusman, ¶¶ 106-07; Mayersohn, ¶¶ 23-24). The Pink Sheet was and would have been reviewed and considered by persons of ordinary skill in the art. (Zusman, ¶¶ 106-07; Mayersohn, ¶¶ 23-24). The Pink Sheet 2004 reference was published and dated February 16, 2004. (*See* CFAD Ex. 1013; Mayersohn, ¶ 23). There is thus no reasonable dispute that Pink Sheet 2004 is within the scope and content of the prior art under pre-AIA Section 102(a) irrespective of priority date. It is also prior art under pre-AIA Section 102(b) since Patentee cannot claim priority to the '915 Provisional. (*See* Section V above).

2. Stein's 2004 Presentation – Published Before March 5, 2004 and Again by At Least April 15, 2004 – is Prior Art.

The February 5, 2004 Stein presentation was given (and webcast) at PPD, Inc.'s Analyst Day and publicized weeks beforehand. PPD distributed a hyperlink for "all interested parties" to register for the event or the webcast. (*See* CFAD Ex. 1005:4). Stein 2004 was targeted to financial analysts, investors, and skilled artisans interested in drug discovery and development; it was reported in The Pink Sheet, a

publication targeting the pharmaceutical industry. (Zusman, ¶¶ 106-10; Mayersohn, ¶¶ 23-25). The presentation itself and the underlying slide set are each "printed publication" prior art under pre-AIA 35 U.S.C. §§ 102(a) and (b).

To be a prior art "printed publication" under 35 U.S.C. § 102, "the reference [must be] made sufficiently accessible to the public interested in the art before the critical date." *See, e.g., Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2012) (internal quotations and citations omitted). Stein's presentation and his underlying slides (later posted online) were two separate publications of Stein 2004 under the four-factor test used to determine whether "ephemeral" or transient presentations qualify as "printed publications" under 35 U.S.C. § 102. *See In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004) ("[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.").

The Stein Presentation itself qualifies under *Klopfenstein* as Section 102 prior art when presented. *Klopfenstein*'s first factor (time displayed) focuses on "the opportunity of the public in capturing, processing and retaining the information conveyed by the reference." 380 F.3d at 1350. This factor confirms Stein 2004 was published, since a skilled artisan could have captured (or recorded), processed and

retained the relevant material—including the material arguably of most interest to an ordinarily-skilled artisan: the "Proposed MTP Development Plan" describing the implitapide trials and dosing regimen. (*See* CFAD Ex. 1014:36-38). The Pink Sheet 2004 captured and published the salient concepts—including the increased step-wise dosing regimen. (*See* CFAD Ex. 1013).

The second factor (expertise of the target audience) also confirms Stein 2004 as a Section 102 publication. "A reference, 'however ephemeral its existence,' may be a 'printed publication' if it 'goes direct to those whose interests make them likely to observe and remember whatever it may contain that is new and useful.'" *Klopfenstein*, 380 F.3d at 1351 (citations omitted). PPD, Inc., through the Stein 2004 presentation, reported its plans to develop the MTP inhibitor implitapide (licensed from Bayer), which was a member of a promising new class of lipid-lowering drugs with a new mechanism of action. (*See* Zusman, ¶ 20 (skilled artisans were "particularly interested in drugs under development from a different drug class with a different mechanism of action"). Implitapide was known in the art to have shown success in early clinical studies. (*See* CFAD Ex. 1015:566). PPD had publicized its Investor Day presentation for weeks, and provided a hyperlink for "all interested parties" to register for the event or the webcast. (CFAD Ex. 1005:4). The skilled artisan would have taken great interest in this presentation. (*See* Zusman, ¶¶ 20-22). Stein 2004 was targeted directly to skilled artisans and others interested in

drug discovery and development, and was reported in The Pink Sheet, a publication targeting the pharmaceutical industry. (*See* Zusman, ¶¶ 106-10; Mayersohn, ¶¶ 23-25). The information was available "direct[ly] to those whose interests make them likely to observe and remember" what Stein offered that was "new and useful." *See Klopfenstein*, 380 F.3d at 1351.

The third factor (expectation of copying) again favors finding Stein 2004 was a publication. There is no evidence Stein or PPD intended to keep Stein's presentation private; no expectation of privacy in a webcast presentation exists absent attempts to keep it private. *See Klopfenstein*, 380 F.3d at 1351. Finally, the fourth factor (ease of copying) favors Stein 2004's publication. It would have been simple for the skilled artisan to copy the relevant information from the Stein presentation. The Pink Sheet *did* copy and distribute the step-wise escalating dosing regimen. (*See* CFAD Ex. 1013). Under *Klopfenstein*, Stein 2004 became a "printed publication" when delivered; it is Section 102 prior art to the '135 patent.

The Stein Presentation Slides, once posted online for viewing/download, were a second, re-publication of Stein 2004. Stein 2004's slides meet *Klopfenstein* for all of the reasons discussed above for the Stein 2004 presentation. And, PPD posted the Stein 2004 slides on a clearly marked, tabbed and indexed page ("PPD News and IR Presentations") (*see* CFAD Ex. 1004:4-5) on a public website (www.ppdi.com) (*see id.*), making the presentation available for review or download

before the critical date by anyone with a browser and Internet connection. Such an online document/recording is a Section 102 printed publication. *See Suffolk Techs., LLC v. AOL Inc.*, 752 F.3d 1358, 1364-65 (Fed. Cir. 2014); *Voter Verified*, 698 F.3d at 1380-81.

Stein was available for download before March 5, 2004: Petitioner 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. *See, e.g.*, *In re Hall*, 781 F.2d 897 (Fed. Cir. 1986). Evidence of routine business practices may establish the performance of a specific act. *Id.* at 899 (doctoral thesis was "most probably" publicly available before the critical date based on the "library's general practice" and "estimating the time it would have taken to make the [thesis] available."). Here, PPD, Inc.'s January 2004 press release for the February 5, 2004 Analyst Day stated that it would make Stein 2004 available online "shortly after the call for on-demand replay." (CFAD Ex. 1005:4). This statement suggests that Stein 2004 was posted online for download within days of the February 5, 2004 presentation, and thus well before March 5, 2004.

Furthermore, the Internet Archives' recorded images of the same "PPD News and IR Presentations" webpage on which Stein 2004 was posted show that PPD, Inc. had an established pattern and practice in 2003-2004, *i.e.*, an ordinary course of business, of uploading presentations to its website for review and download within

a few days of their delivery. (*See id.* at 5-6 (11/11/03 presentation at CIBC Healthcare Conference posted within 6 days); CFAD Ex. 1004:4-5 (3/5/04 presentation at Lehman Brothers 7Th Annual Global Healthcare Conference posted within 21 days); and CFAD Ex. 1005:7-8 (5/6/04 presentation at Robert W. Baird 2004 Growth Stock Conference posted within 1 day)).[2]

The Table below reports the Wayback Machine's archived versions of the "PPD News and IR Presentations", and illustrates this practice:

Archive Date[3]	**Date Webpage "Last Modified"[4]**	**Most Recent Presentation[5]**	**Presentation Posted Within:**
Dec. 12, 2003	Nov. 17, 2003	Nov. 11, 2003	6 days
April 15, 2004	March 26, 2004	March 5, 2004	21 days
June 4, 2004	May 7, 2004	May 6, 2004	1 day

Even assuming the longest delay noted above (21 days), the Stein 2004 presentation was "most probably" posted no later than February 26, 2004—thus before March 5,

[2] The Marx Declaration and exhibits establish the conference dates for these PPD presentations. (*See* CFAD Ex. 1034; CFAD Ex. 1035 (Cigna Press Release); CFAD Ex. 1036 (Gilead Press Release); CFAD Ex. 1037 (PR Newswire)).

[3] The date the Internet Archive captured the image of the webpage.

[4] The date the imaged PPD webpage was last modified, as stated on that page.

[5] The conference dates. (*See* CFAD Ex. 1035; CFAD Ex. 1036; CFAD Ex. 1037).

2004. *See Hall*, 781 F.2d at 899.

Thus, Stein 2004 became a printed publication on the day it was presented, but at least by the time it was posted to the PPD website "shortly after"—which per PPD's own statement, custom and practice was "most probably" before the March 5, 2004 filing date of the '915 Provisional. *See Hall*, 781 F.2d at 899.

Finally, 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. (*See* CFAD Ex. 1004:4-5). This information, coupled with the affidavit provided by the Internet Archive (CFAD Ex. 1004), also establishes Stein 2004 as a prior art printed publication. Stein 2004 is prior art under at least 35 U.S.C. §§ 102(a) and (b). (*See* Section V, above).

3. The Prior Art Taught Step-Wise MTP Inhibitor Dosing Over Seven Levels; the Rationale; and Expected Efficacy.

As noted above, Chang seemingly left open the question of how to position MTP inhibitors to make them commercially attractive given the success of statins. Pink Sheet 2004 and Stein 2004 each answered this question by publishing PPD's planned approach with the MTP inhibitor implitapide. (Zusman, ¶¶ 69, 100-10; CFAD Ex. 1013, *passim*; CFAD Ex. 1014:19-45).

Pink Sheet 2004 recognized Dr. Stein had identified a different way to view MTP inhibitors. Rather than *replacing* statin therapy, artisans could follow the pathway established with ZETIA®: use them as add-on therapy in combination with

statins. (Zusman, ¶¶ 69, 77-78, 108; CFAD Ex. 1013:2). This option was attractive, because ZETIA® had "come onto the market and obtain[ed] a significant market share." (CFAD Ex. 1013:2 (quoting Stein)). As Stein 2004 noted, "Even 3% of [the lipid-reducing] Market is "Block Buster". (CFAD Ex. 1014:45).

The Pink Sheet 2004 and Stein 2004 provide another reason to pursue MTP inhibitors: "even high-dose statins are ineffective or inadequate" for patients with homozygous and severe heterozygous familial hypercholesterolemia ("HoFH" and "HeFH"). (Zusman, ¶¶ 50-54, 69, 102-04, 110; CFAD Ex. 1013:2 (quoting Stein); CFAD Ex. 1014:40-42). Stein 2004 taught for HeFH patients (~500,000 in the U.S.), "current drug therapies lower LDLC about 50-60%, but about 50% of subjects still have LDLC higher than current treatment goals." (CFAD Ex. 1014:40). For HoFH patients (hundreds in the U.S.) "current drug therapies lower LDLC about 30-40%, but seldom below 300-400 mg/dl," with "'heroic' treatments such as LDL apheresis every 1-2 weeks, or liver transplantation." (*Id.* at 42).

Both the Pink Sheet 2004 and Stein 2004 also taught an efficacy range MTP inhibitors could *safely* target, and market as adjunct therapy based on ZETIA®'s success producing about 18% to 24% LDL-C reduction over statin therapy alone. (Zusman, ¶¶ 69, 103, 108; CFAD Ex. 1014:33-34; CFAD Ex. 1013:2). The Pink Sheet also published Stein's guidance that the toxicity seen in previous MTP inhibitor clinical trials resulted from the high doses used to seek LDL-C reduction

comparable to statins. Those trials did not seek reductions in the ~20% range, which could be accomplished using lower doses. (Zusman, ¶ 69, 108; CFAD Ex. 1013:2). Pink Sheet 2004 and Stein 2004 both identified the proposed implitapide dosing regimen designed to produce an expected additional ~18% to 24% LDL-C reduction: a starting dose of 10 mg daily; escalating by 5 mg/day every five weeks (*e.g.*, 15, 20, 25, 30, 35 mg) to a maximum dose of 40 mg/day. (Zusman, ¶¶ 105, 110; Mayersohn, ¶¶ 58, 61; CFAD Ex. 1013:2; CFAD Ex. 1014:37-38). The ordinarily-skilled artisan would have reasonably expected this proposed dosing regimen to resolve Chang's expressed concerns about managing an appropriate "therapeutic index" for MTP inhibitors. (*See* CFAD Ex. 1015:567; *see also* Zusman ¶¶ 137-40, 142-43, 206, 208-11, 213-15).

As described below, the Examiner had neither Pink Sheet 2004 nor Stein 2004 during the substantive prosecution of the '118 Application; patentee submitted those only after the second Notice of Allowance. Chang was before the Examiner, but never substantively relied on. Thus, the PTO was unable to fully evaluate the scope and teachings of the prior art on step-wise escalating dosing.

VII. U.S. PATENT NO. 8,618,135 AND ITS FILE HISTORY.

A. The '135 Patent Repeats Information Already Known to Ordinarily-Skilled Artisans.

The '135 patent suggests it was surprising and inventive to discover "methods of treating a subject suffering from a disorder associated with hyperlipidemia while

reducing side-effects" by administering "at least three step-wise, increasing doses of the MTP inhibitor." (CFAD Ex. 1001, col. 7:11-24; col. 6:65-7:3). As noted above, this was Stein's published approach for implitapide.

The '135 patent concedes "MTP inhibitors, methods of use and preparation thereof are known to the art skilled," including BMS-201038 (lomitapide). (*Id.* at col. 8:5-6; 8:20-24). It states a study in "the best accepted" HoFH animal model showed BMS-201038 "effectively reduced plasma cholesterol levels in a dose dependent manner" (*id.* at col. 6:9-10), with an ED_{50} value of 1.9 mg/kg, and a dose of 10 mg/kg "essentially normaliz[ing] cholesterol levels with no alteration in plasma AST or ALT." (*Id.* at col. 6:8-15). This in turn indicated "MTP inhibition by BMS-201038 might be effective in substantially reducing cholesterol levels in patients with hoFH." (*Id*. at col. 6:16-19). Chang reported this information. (Zusman, ¶¶ 96-99; *see* CFAD Ex. 1015:565 ("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")).

The '135 patent recognized that HoFH patients were treated with statins plus ezetimibe (ZETIA®) as combination therapy, as Dr. Stein taught in the Pink Sheet and Stein 2004. The patent characterizes the resulting total reduction of LDL-C by 27% as "far from optimal." (CFAD Ex. 1001, col. 3:56-64). The '135 patent asserts

there was a "tremendous unmet medical need for new medical therapies for hoFH." (*Id.* at col. 4:20-21). Yet the '135 patent nowhere shows that its purportedly inventive lomitapide dosing regimen could or would reduce LDL-C levels by more than 27% in HoFH patients. Indeed, patentee originally sought claims to at least 30 or 50% reductions (CFAD Ex. 1006:25-28); issued dependent claims 3 and 4 only claim 15% and 25% comparative reductions—aligned with Dr. Stein's implitapide targets and ZETIA®'s performance. (*See* CFAD Ex. 1001, col. 20:3-11; Zusman, ¶¶ 69, 103, 108. *Cf.* CFAD Ex. 1014:33-34; CFAD Ex. 1013:2).

B. The '135 Patent File History.

Patentee filed the '118 Application (CFAD Ex. 1008) leading to the '135 patent on March 11, 2011 as a continuation of the '923 Application which led to the '268 patent (filed March 7, 2005). The '118 application's original claims encompassed using **any** MTP inhibitor to treat "a disorder associated with hyperlipidemia or hypercholesterolemia" with at least three step-wise increasing dose levels. (CFAD Ex. 1008:28). On March 4, 2013, in response to various rejections, the patentee limited independent claim 1 to treating hyperlipidemia or hypercholesterolemia, using "[lomitapide] . . . or the piperidine N-oxide thereof," added certain dosing ranges formerly found in dependent claims, and specified "wherein each dose level is administered . . . for about 1 to 5 weeks." The patentee also added application claim 26 (now issued claim 9). (*See* CFAD Ex. 1009:2, 4).

To overcome the § 103 rejection, patentee relied in part upon a declaration from Dr. William Sasiela, who noted that dosing patients with MTP inhibitors at a constant level creates significant adverse effects, and previous developers of MTP inhibitors had discontinued development. (*See id.* at 7; CFAD Ex. 1010). Sasiela also opined on alleged unexpected results produced by the claimed method. (CFAD Ex. 1010:3). ***At that time, no one disclosed that Dr. Stein had already done step-wise dose escalation with implitapide, or that Dr. Rader had served as a clinical researcher for Dr. Stein during the implitapide trials.*** On May 10, 2013, the PTO issued the first Notice of Allowance. (CFAD Ex. 1011).

After patentee submitted a Request for Continuing Examination (RCE) and another Initial Disclosure Statement (IDS), the PTO issued a second Notice of Allowance on September 3, 2013. (CFAD Ex. 1012). But three weeks later, patentee filed another RCE along with amendments and another IDS. The amendments added what is now issued claim 10 (CFAD Ex. 1039:4-5), while the IDS enclosed prior art including Pink Sheet 2004 and Stein 2004, and the European Opposition briefs. (CFAD Ex. 1040:3-5).

So, Pink Sheet 2004 and Stein 2004 took their places among the five columns of prior art listed on the face of the '135 patent. Neither these references nor Chang 2002 were substantively discussed during prosecution; the Examiner issued a third Notice of Allowance without comment. (*See* CFAD Ex. 1041).

C. The European Opposition Proceedings.

On August 21, 2013, Dr. Evan Stein—the author of Stein 2004 and subject of Pink Sheet 2004—opposed a foreign counterpart to the '268 patent, European Patent 1 725 234 B9 ("the '234 patent"). (*See* CFAD Ex. 1020). The Opposition asserted the '234 patent claims are unpatentable for various reasons, including obviousness over prior art including Stein 2004. (*See id.*, *passim*). In the opposition Dr. Stein stated that the patentee, Dr. Rader, had been "a consultant and clinical investigator in clinical research projects with implitapide." (*Id.* at 2).

In addition to Stein 2004, the Opposition cites excerpts from the implitapide clinical trial reports posted on www.ClinicalTrials.gov [reference D8]. (*Id.* at 2-3). It notes that the trials began in September 2003 and assessed implitapide as a treatment for "homozygous as well as heterozygous familial hyperlipidemia and hypercholesterolemia." (*Id.* at 8). The Opposition states that the implitapide studies "***were designed, conducted and guided by Dr. Stein***, who included Dr. Rader, inventor of the opposed patent, as a consultant and one of the clinical investigators for these studies." (*Id.* (emphasis added)). The parties settled.

VIII. THE LEVEL OF ORDINARY SKILL IN THE ART.

A person of ordinary skill in the art as relevant to this proceeding would have had a high level of education (graduate and/or post-graduate degrees) in a pertinent discipline such as medicine, medicinal chemistry, pharmacology, pharmacokinetics,

or drug development and delivery. Such a person with a medical degree (M.D.) would also have 3-5 years of experience treating patients in the cardiovascular/cardiac field, which would itself provide knowledge of dose-titration; dose-selection as balanced against side effects in individual patients; and developments in the clinical field. (Zusman, ¶¶ 28-29, 32; Mayersohn, ¶ 26). A non-M.D. would have a similarly advanced education, and the experiences and skill sets appropriate to their specialty. (*See* Zusman, ¶¶ 30-32; Mayersohn, ¶ 26).

IX. CLAIM CONSTRUCTION STATEMENT (37 C.F.R. § 42.104(B)(3)).

Under 37 C.F.R. § 42.100(b), the claim terms of the '135 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation ("BRI") of the claim language in light of the specification. Petitioner proposes the following as at least included in the BRI:

- "A subject suffering hyperlipidemia or hypercholesterolemia" includes humans and non-human mammals, *e.g.* rabbits. (CFAD Ex. 1001, col. 11:31-32; Zusman, ¶¶ 91-92).
- "effective amount" includes drug amounts improving any hyperlipidemia or hypercholesterolemia disease marker, or inhibiting MTP activity (including by as little as 10%). (*See, e.g.*, CFAD Ex. 1001, col. 8:66-col.9:2; Zusman, ¶¶ 91-92).
- "about" means approximately. (Zusman, ¶¶ 91-92).
- "piperidine N-oxide thereof" is undefined by structure or chemical name within

the '135 patent's specification. A general chemistry understanding of "N-oxide" upon a piperidine ring found in lomitapide requires adding an oxygen atom (O) to the nitrogen atom (N):  . (*See* CFAD Ex. 1019, col. 11:26-35, col. 124:20-56). The claims encompass this and other devisable piperidine N-oxides.

- "Severe" hypercholesterolemia means a subject's cholesterol values cause increased cardiovascular disease risks, and did not satisfactorily respond to initial lipid-lowering treatment. (*See* CFAD Ex. 1001, col. 4:63-67; Zusman, ¶¶ 91-92).
- "control levels" must at least include, when applied to a particular blood component, "a level of a particular blood component" obtained from the subject either: (a) "in the absence of treatment" or (b) "receiving a placebo"; or (c) "receiving a different treatment," including a subject receiving treatment "not including at least three step-wise, increasing dosages of an MTP inhibitor." (*See* CFAD Ex. 1001, col. 10:55-65; Zusman, ¶¶ 91-92).

X. EXPLANATION OF GROUNDS FOR UNPATENTABILITY.

To support institution, this petition for *inter partes* review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. § 314(a). Petitioner should prevail here because each element of '135 patent claims 1-10 are taught by, or would have been obvious over, the Pink Sheet 2004 in view of Chang; and Stein 2004 in view of Chang. *See* 35 U.S.C. § 103(a).

Petitioner has analyzed the proper priority date (Section V), and the claims are obvious under any possible date. The level of ordinary skill in the art was high (*see* Section VIII). Petitioner's cited references are prior art. (*See* Sections V-VI). The ordinarily-skilled artisan had motivation to combine teachings from Pink Sheet 2004 with Chang (Ground I); and Stein 2004 with Chang (Ground II) and reasonably expect success. No non-obvious differences exist between either combination and the claimed subject matter; the claims are invalid.

A. Ground I: Obviousness Over Pink Sheet 2004 in View of Chang.

To issue the claims, the Examiner accepted representations in the Sasiela Declaration that MTP inhibitor development was discontinued due to side effects, so it was unexpected that MTP inhibitors could work as claimed. (*See* Section VII, above). Patentee's representations were inaccurate, as shown by the cited prior art.

The core issue is whether it would have been obvious for one of ordinary skill to administer MTP inhibitors via an escalating dosing regimen falling anywhere within the claimed ranges to treat hyperlipidemia and/or hypercholesterolemia. *See Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370 (Fed. Cir. 2011) (claims to dosing "6 to 8 milligrams" and "7.5 milligrams" of temazepam obvious given prior art teaching doses of "5 to 15 mg"). "Yes."

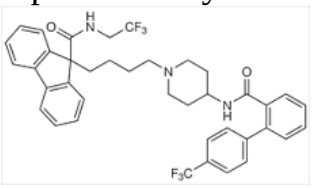
As discussed above, the person of ordinary skill in the art had advanced degrees and experience with medical research. (*See* Section VIII, above). Chang is

prior art under pre-AIA 35 U.S.C. § 102(b). (*See* Section VI, above). Pink Sheet 2004 is prior art under pre-AIA 35 U.S.C. § 102(a) no matter which priority date applies; and prior art under pre-AIA 35 U.S.C. § 102(b) because the '135 patent cannot benefit from the '915 Provisional. (*See* Sections V & VI, above).

1. The Claimed Lomitapide Escalating-Dosing Approach was Already Taught for Implitapide.

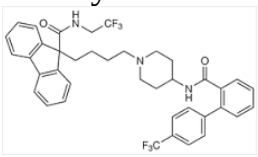
The following claim chart (bold emphasis added) compares the '135 patent claims to the combination of the Pink Sheet 2004 and Chang. There are no non-obvious differences from the skilled artisan's perspective:

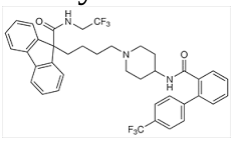
U.S. 8,618,135	Pink Sheet 2004 in view of Chang
Claim 1. A method of treating a subject suffering hyperlipidemia or hypercholesterolemia,	Pink Sheet 2004 discloses PPD sought to demonstrate "implitapide's safety and efficacy in homozygous and severe heterozygous familial hypercholesterolemia" in humans and that implitapide "is also being studied for hypertriglyceridemia." CFAD Ex. 1013:2. Patients "targeted for implitapide therapy will likely be the 5%-7% of high cholesterol patients that are statin intolerant, and the 10%-15% who are at high risk for cardiovascular disease and have not reached their LDL goals, Stein indicated." *Id*. at 2. "The lipid lowering and anti-atherosclerosis effects of MTP inhibitors have been consistently observed and broadly demonstrated across all series evaluated using a wide variety of representative animal models." CFAD Ex. 1015:564.
the method comprising	

U.S. 8,618,135	Pink Sheet 2004 in view of Chang
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	"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." CFAD Ex. 1013:2. Pink Sheet 2004 discloses that the planned dosage ranges of **implitapide** – used as adjunct therapy - **will lower LDL-C by "another 18-24%**." *See id*.
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	"The starting dose will be 10 mg daily, escalating by 5 mg/day every five weeks to a maximum 40 mg/day." *Id*. [*i.e.* 10 mg/day for 5 weeks; 15 mg/day for 5 weeks; 20 mg/day for 5 weeks; 25 mg/day for 5 weeks; 30 mg/day for 5 weeks; 35 mg/day for 5 weeks; and 40 mg/day for 5 weeks]
wherein the MTP inhibitor is represented by:  [lomitapide], or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof, and	Chang reports the MTP inhibitor CP-346086 lowers plasma cholesterol and triglycerides in humans and animals dependent on the dosage and incubation time. CFAD Ex. 1015:564-66. "Similar efficacy was reported for BAY-13-9952 [implitapide], 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 [lomitapide] also showed similar efficacy in phase I and phase II clinical trials.**" *Id.* at 566; *see also id.* at Fig. 2.
wherein each dose level is administered to the subject for about 1 to about 5 weeks.	"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." CFAD Ex. 1013:2.
Claim 2. The method of claim 1 wherein the	PPD hopes to "demonstrate implitapide's safety and efficacy in . . . **severe** heterozygous familial

U.S. 8,618,135	Pink Sheet 2004 in view of Chang
disorder is severe hypercholesterolemia.	**hypercholesterolemia** 'where even high-dose statins are ineffective or inadequate,' Stein said." *Id*. To "treat[] patients with dyslipidemias that extends **beyond primary hypercholesterolemia,** the pharmaceutical industry has targeted inhibition of microsomal triglyceride transfer protein (MTP)" CFAD Ex. 1015:562.
Claim 3. The method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-I, A-II, B, and E are reduced by at least 15%, compared to control levels.	Pink Sheet 2004 states planned implitapide dose ranges (used as adjunct therapy) will lower LDL-C by "another **18-24%**." *See* CFAD Ex. 1013:2. "While Stein acknowledged that MTP inhibitor projects have been pursued by a number of companies, . . . he argued that the toxicity seen with some of those projects was related to the high doses used during trials. 'None of them were looking at LDL reductions or cholesterol reductions' **as low as the 20% range**, he said." *Id*. "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 [lomitapide] also showed similar efficacy** in phase I and phase II clinical trials." CFAD Ex. 1015:566.
Claim 4. The method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-I, A-II, B, and E are reduced by at least 25%, compared to control levels.	*See* Claim 3, *supra*.

U.S. 8,618,135	Pink Sheet 2004 in view of Chang
Claim 5. The method of claim 1 wherein the MTP inhibitor is administered orally.	"Similar efficacy was reported for BAY-13-9952 … 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 [lomitapide] also showed similar efficacy in phase I and phase II clinical trials." CFAD Ex. 1015:566.
Claim 6. The method of claim 1 wherein said increasing dose levels further comprise a fourth dose level.	"The starting dose will be 10 mg daily, escalating by 5 mg/day every five weeks to a maximum 40 mg/day." CFAD Ex. 1013:2. [*i.e.* 10 mg/day for 5 weeks; 15 mg/day for 5 weeks; 20 mg/day for 5 weeks; 25 mg/day for 5 weeks; 30 mg/day for 5 weeks; 35 mg/day for 5 weeks; and 40 mg/day for 5 weeks]
Claim 7.The method of claim 1 wherein said increasing dose levels further comprise a fourth and a fifth dose level.	*See* Claim 6, *supra*.
Claim 8. The method of claim 1, wherein said fourth dose level is from about 20 to about 60 mg/day, and said fifth dose level is from about 30 to about 75 mg/day.	*See* Claim 6, *supra*.
Claim 9. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising	*See* Claim 1, *supra*.
administering to the subject an effective amount of an MTP inhibitor,	*See* Claim 1, *supra*.
wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor	*See* Claim 1, *supra*.

U.S. 8,618,135	Pink Sheet 2004 in view of Chang
wherein a first dose level is from about 2 to about 13 mg/day, administered to the subject for about 2 weeks; a second dose level is from about 5 to about 30 mg/day, administered to the subject for about 2 weeks to about 4 weeks; and a third dose level is from about 10 to about 50 mg/day, administered to the subject for about 2 weeks to about 4 weeks; and	*See* Claim 1, *supra*. "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." CFAD Ex. 1013:2.
wherein the MTP inhibitor is represented by:  [lomitapide], or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof.	*See* Claim 1, *supra*.
Claim 10. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising	*See* Claim 1, *supra*.
administering to the subject an effective amount of an MTP inhibitor,	*See* Claim 1, *supra*.
wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor	*See* Claim 1, *supra*.

U.S. 8,618,135	Pink Sheet 2004 in view of Chang
wherein a first dose level is from about 2 to about 13 mg/day, administered to the subject for about 1 to about 12 weeks; a second dose level is from about 5 to about 30 mg/day, administered to the subject for about 4 weeks; and a third dose level is from about 10 to about 50 mg/day, administered to the subject for about 4 weeks; and	*See* Claim 1, *supra*. "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." CFAD Ex. 1013:2.
wherein the MTP inhibitor is represented by:  [lomitapide], or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof.	*See* Claim 1, *supra*.

(*See* Zusman, ¶¶ 116-86, 261 (confirming each element and that the skilled artisan's general knowledge renders dose escalation timing obvious)).

As described in the chart above, the Pink Sheet 2004 teaches a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor (implitapide), wherein said administration comprises at least three (actually up to seven) step-wise increasing dose levels of the MTP inhibitors. (*See* CFAD Ex. 1013:2; Zusman, ¶¶ 110, 123, 126-27, 129-30). The first dose level taught therein is between about 2 to about 13 mg/day, a second dose level is between about 5 to

about 30 mg/day, and a third dose level is between about 10 to about 50 mg/day (*see id.*), and each dose level is administered to the subject for about 1 to about 5 weeks (CFAD Ex. 1013:2; Zusman, ¶¶ 110, 131-32, 135). Lipid-lowering drugs generally were titrated upwards at intervals that ranging from 2 to 4 weeks or more. (Zusman, ¶ 47). Thus, the claimed intervals fall within the known dose titration ranges already known for evaluating safety/tolerability. *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2013) (obviousness of prior art range).

The Pink Sheet 2004 does not specifically disclose the MTP inhibitor represented by: [lomitapide], or a pharmaceutically acceptable salt or piperidine N-oxide thereof. Chang teaches a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia using MTP inhibitors specifically including lomitapide (CFAD Ex. 1015:564-66, Zusman, ¶¶ 124-25, 133-34).

The sole difference between Chang and subject matter encompassed by the claims is that while Chang disclosed lomitapide and its clinical activity as an MTP inhibitor, Chang did not expressly teach using lomitapide in an escalated-dose regimen. (*See* Zusman, ¶¶ 123-28, 133-34). But Pink Sheet 2004 teaches the escalating-dose regimen not found in Chang. (*Id.* at ¶¶ 129-32, 135). The Pink Sheet 2004 dosing regimen escalates the dose by the 5 week mark, which meets the "about 1 to about 5 weeks", "about four weeks", and "about 1 to about 12 weeks" limitations in claims 1, 9 and 10. (Zusman, ¶¶ 178-79, 184-85).

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).

"With every limitation of the asserted claims thus disclosed in the cited references, the question . . . becomes whether a person of ordinary skill in the art would have been motivated to combine those teachings to derive the claimed subject matter with a reasonable expectation of success." *Bayer Healthcare Pharms. Inc. v. Watson Pharms. Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013).

2. Motivation to Combine Pink Sheet 2004 with Chang.

"[A]ny need or problem known in the field of endeavor at the time of invention . . . can provide a reason for combining the elements in the manner

claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). The ordinarily-skilled artisan was motivated to combine the Pink Sheet 2004 with Chang, and *vice versa*. (Zusman, ¶¶ 136-44; Mayersohn, ¶¶ 19, 46-48, 63-65).

Chang identified three MTP inhibitors furthest along in clinical evaluation—CP-346086, implitapide, and lomitapide— and taught each worked in humans and were similarly effective. (Zusman, ¶¶ 96-99, 136-68; CFAD Ex. 1015:566-67). Chang recognized the problem with MTP inhibitors' side-effect profiles: they could not compete commercially with statins as *monotherapy*. (*See* CFAD Ex. 1015:566-67; CFAD Ex. 1001, col. 8:27-30). Chang's statement of the problem was motivation to look to other references for solutions. *See Bayer*, 713 F.3d at 1375-76. As in *Bayer*, "the references in this case go beyond illuminating a known problem, they also expressly propose the claimed solution." *Id.*

Pink Sheet 2004 reports Dr. Stein's solution to the problem Chang articulated: 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. (Zusman, ¶¶ 108-10, 139-43; Mayersohn, ¶¶ 45-46). As in *Bayer*, "the prior art's direct recommendations to use [escalated step-wise] dosing regimens . . . would have motivated one of ordinary skill in the art

to implement" the dosing regimen "for use with known" MTP inhibitors, including lomitapide, "as recited in the asserted claims." *Bayer*, 713 F.3d at 1376; *see also id.* at 1371 (a known "strategy to reduce side effects has been to reduce the . . . dose provided in each pill").

Likewise, the person of ordinary skill in the art reading Pink Sheet 2004 would have been motivated to identify other MTP inhibitors that would work for the same purposes and patients. (Zusman, ¶¶ 93-95, 144; Mayersohn, ¶¶ 45-48). A review of the literature—or any one of a number of basic electronic searches—would have readily led that person to Chang. (Zusman, ¶¶ 93-95, 144). Chang confirmed three MTP inhibitors had advanced to human clinical trials, and of the two performing at least comparably to implitapide, one was lomitapide. (*Id.* at ¶¶ 97-98; Mayersohn, ¶¶ 49-56; CFAD Ex. 1015:566-67). Thus, the skilled artisan would have been motivated to combine the Pink Sheet 2004 and Chang teachings, and to apply the implitapide dosing strategy to lomitapide.

At the very least, given these facts, lomitapide would have been obvious to try in place of implitapide. *See* KSR, 550 U.S. at 402-03 (when "there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp", and resulting success "is likely the product not of innovation but of ordinary skill and common sense."); *Merck & Co., Inc. v. Teva Pharms., USA, Inc.*, 395 F.3d 1364,

1375 (Fed. Cir. 2005) (to find patentee's "weekly-dosing idea non-obvious because it went against prevailing wisdom, the court must still explain why [patentee] and not [the prior art] should get credit for the idea" when patentee's "idea added nothing to what came before").

Ordinarily-skilled artisans are also motivated to engage in routine experimentation to optimize the subject matter they study. *See Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1353 (Fed. Cir. 2015) (choosing 0.01% w/v EDTA for ophthalmic formulation was "not unexpected or surprising," but obvious "product of routine optimization"). This principle applies to any minor modification to Stein's dosing regimen, *e.g.*, increasing the dose "about" every two weeks, or "about" every four weeks, or "about" every two to four weeks, or "about" one to 12 weeks as claimed rather than *evaluating* at 4 weeks and increasing the dose by the 5-week mark. To a skilled artisan, increasing the dose at five week intervals **is** increasing the dose at "about four weeks" (Zusman, ¶¶ 135, 178-79, 184-85), and dose-titration of cholesterol-lowering drugs at two to four week intervals was and remains routine clinical practice. (*Id.* at ¶¶ 43-47, 64-67).

The claimed dosing intervals also reflect routine variation when applying the combined teachings of Pink Sheet 2004 and Chang (*Id.* at ¶¶ 168, 175, 180, 185; Mayersohn, ¶ 20, 66, 71, 74), and were thus obvious to the ordinarily-skilled artisan by March 2004. (Zusman, ¶¶ 168, 175, 180, 185). The other limitations of the

dependent claims are also obvious for all the reasons set forth above (*see* pp. 32-39), and in the case of claims 3-4 are inherent results of the method of claim 1. (Zusman, ¶¶ 150-86).

Having established the motivation to combine Pink Sheet 2004 and Chang, we next ask whether the skilled artisan would reasonably expect to succeed using lomitapide rather than implitapide in the Stein dosing regimen. "Yes."

3. Reasonable Expectation of Success With Lomitapide.

Reasonable expectation of success "does not require a *certainty* of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (emphasis original). To create a reasonable expectation, the prior art must provide enough guidance, parameters or direction to the skilled artisan (in light of their background and knowledge), versus merely general ideas or vague suggestions. *See id.* Here, the detailed teachings of Pink Sheet 2004 and Chang provide the ordinarily-skilled artisan a reasonable expectation of success that applying the Pink Sheet 2004's dosing regimen to lomitapide would help patients in the manner claimed.

For a skilled artisan reading Pink Sheet 2004, it would have been obvious to: identify other MTP inhibitors that performed at least comparably to implitapide in the clinic; use them in the escalating dosing regimen; and reasonably expect them to again work comparably to implitapide. (Zusman, ¶¶ 145-48, Mayersohn, ¶¶ 18-19, 48). Chang identifies two other MTP inhibitors that had progressed into human

clinical trials: the Pfizer compound CP-346086 and lomitapide [BMS 201038]. (Zusman, ¶¶ 96-99; CFAD Ex. 1015:566-67). Even if the skilled artisan had to choose between those two, lomitapide would have been preferred because it had been successfully tested in WHHL rabbits, the animal model for human HoFH. (*See* Zusman, ¶¶ 97, 146; Mayersohn, ¶¶ 18, 51-53; CFAD Ex. 1015:565). One of ordinary skill would expect—based on the public data on implitapide in animals and humans, and lomitapide in animals—to be able to substitute lomitapide into the implitapide escalating dose regimen and achieve a working treatment method with no more than routine adjustments. (Zusman, ¶¶ 145-48; Mayersohn, ¶¶ 18, 54, 65). *See Bayer*, 713 F.3d at 1376; *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1295 (Fed. Cir. 2006) (prior art creating expectation of "a general, albeit imperfect, correlation between a drug's lipophilicity and its colonic absorptivity" supported motivation and reasonable expectation of success); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1369-70 (Fed. Cir. 2003) (combination obvious where "several other well-known antidiarrheals with simethicone had been described in the prior art").

The ordinarily-skilled artisan also would have a reasonable expectation of success with lomitapide at least because, as described above: (a) Stein pursued the identical approach with implitapide; (b) as MTP inhibitors, implitapide and lomitapide possessed a similar mechanism and degree of action (*see, e.g.*, CFAD Ex.

1015:562-64); (c) the existing lomitapide data suggested that it should be dosed similarly to implitapide; and (d) escalating step-wise dosing, adjusted to account for side effects at the claimed intervals, was routine clinical practice. (Zusman, ¶¶ 43-47, 59-67, 97-98, 103-05; Mayersohn, ¶¶ 18-19, 47-54).

As for the dependent claims, both the Pink Sheet 2004 and Chang taught using MTP inhibitors for severe hypercholesterolemia (claim 2). (Zusman, ¶¶ 152-54). Claims 3 and 4 recite reductions of 15% and 25% in known markers for MTP inhibition activity, which fall within the ranges the prior art taught to target. (*Id.* at ¶¶ 155-62; Section VI, above). The claimed reductions also result inherently from the treatment. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (limitation was "an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations"). Claim 5's oral dosing was known and expected to work; Chang teaches lomitapide and implitapide were designed as oral drugs. (Zusman, ¶¶ 163-65). The Pink Sheet 2004 teaches the fourth and fifth dose steps and amounts recited in claims 6-8. (*Id.* at ¶¶ 166-76). Finally, the degree of efficacy and severity of side-effects of MTP inhibitors are dose-dependent. (*See* CFAD Ex. 1015:564-567; Zusman, ¶¶ 64-67; Mayersohn, ¶¶ 17-18, 51, 53-56). So, starting with a lower dose was expected to reduce side effects. This was the general practice and result with many lipid-lowering drugs, *e.g.* fibrates, statins and niacin.

(Zusman, ¶¶ 64-67, 174; *see* Section IX, above).

Given the above, there are no non-obvious differences between the claims and the prior art. Further, as discussed below, the alleged secondary considerations of nonobviousness are weak at best, and cannot undermine or refute this strong showing of obviousness. Subject matter encompassed by claims 1-10 would have been obvious when filed, so those claims are invalid.

B. Ground II: Obviousness Over Stein 2004 in View of Chang.

The central issue for Ground II is similar to that stated above for Ground I. The level of ordinary skill in the art (Section VIII) and the scope and content of the prior art (Section VI) are identical, so there is no need to repeat them here. The February 5, 2004 Stein presentation (Stein 2004) is "printed publication" prior art under pre-AIA 35 U.S.C. §§ 102(a) and (b) as set forth above in Sections V-VI.

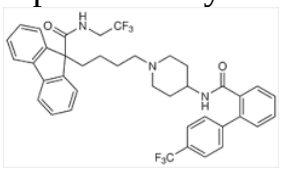
1. There Are No Non-Obvious Differences.

The critical teachings of Stein 2004 are similar to the critical teachings of Pink Sheet 2004. Yet Stein 2004 provides additional *non-cumulative* information. For example, Stein 2004 goes into detail about the background of the art; the challenges faced by MTP inhibitors; Stein's proposed solutions; the proven efficacy of implitapide; the role for MTP inhibitors as useful therapies; and an even more detailed marketing strategy and rationale. (CFAD Ex. 1014:7-45). Stein 2004 also provides clinical data from previous implitapide trials in animals and humans. (*Id.*

at 23-32). To the extent the Board has any doubts about the motivation of the skilled artisan or their expectation of success from Pink Sheet 2004, Stein 2004 necessarily puts those doubts to rest.

The following claim chart shows an element-by-element comparison between the '135 patent claims and the combination of Stein 2004 and Chang (bold emphasis added). There are no non-obvious differences to the skilled artisan:

U.S. 8,618,135	Stein 2004 in view of Chang
Claim 1. A method of treating a subject suffering hyperlipidemia or hypercholesterolemia, the method comprising	"Phase I, Multiple-Day Dose Escalation Study of Implitapide (BAY 13-9952) . . . Evaluation of the safety and tolerability of increasing doses of implitapide administered for 10 days to hyperlipidemic patients" CFAD Ex. 1014:27-28. *See also id.* at 29-32. "[I]nhibition of MTP should reduce plasma lipids by preventing triglyceride-rich, apoB-containing lipoprotein assembly in the liver and intestine." CFAD Ex. 1015:563. "The lipid lowering and anti-atherosclerosis effects of MTP inhibitors have been consistently observed and broadly demonstrated across all series evaluated using a wide variety of representative animal models." *Id.* at 564.
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	"Three studies with virtually identical design: All are ≅39 weeks duration with dose titration schedule every 5 weeks **based on safety and tolerability** at 4 weeks . . . Starting dose is 10 mg daily with escalation by 5 mg every 5 weeks to maximum of 40 mg." CFAD Ex. 1014:38. *See id.*, 28-29, 32 (reporting implitapide Phase I and Phase II trial results (efficacy at listed doses)).
wherein a first dose level is from about 2 to about 13	"Starting dose is 10 mg daily with escalation by 5 mg every 5 weeks to maximum of 40 mg." *Id.* at 38;

U.S. 8,618,135	Stein 2004 in view of Chang
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	*see also id.* at 37. [*i.e.* 10 mg/day for 5 weeks; 15 mg/day for 5 weeks; 20 mg/day for 5 weeks; 25 mg/day for 5 weeks; 30 mg/day for 5 weeks; 35 mg/day for 5 weeks; and 40 mg/day for 5 weeks] "Challenge to find 'Therapeutic' window, i.e. efficacy without toxicity. . . . Potential to control both fat malabsorption and GI side effects with lower doses." *Id.* at 21; *see id.* at 31.
wherein the MTP inhibitor is represented by:  [lomitapide] or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof, and	Chang reports CP-346086 lowers human and animal plasma cholesterol and triglycerides in in dose-dependent manner. CFAD Ex. 1015:564-66. "Similar efficacy was reported for BAY-13-9952 [implitapide], 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 [lomitapide] also showed similar efficacy in phase I and phase II clinical trials."** *Id.* at 566; *see also id.* at Fig. 2.
wherein each dose level is administered to the subject for about 1 to about 5 weeks.	"Three studies with virtually identical design: All are ≅39 weeks duration with dose titration schedule every 5 weeks based on safety and tolerability at 4 weeks . . . Starting dose is 10 mg daily with escalation by 5 mg **every 5 weeks** to maximum of 40 mg." CFAD Ex. 1014:38 (emphasis added).
Claim 2. The method of claim 1 wherein the disorder is severe hypercholesterolemia.	"Potential for very large reductions VLDL and LDL, Chylos and remnants . . . May still have role in HoFH, HeFH, FCH and hyperchylomicronemia" *Id.* at 21; *see also id.* at 19-26. "With the goal of developing a therapy for treating patients with **dyslipidemia that extends beyond primary hypercholesterolemia,** the pharmaceutical industry has targeted inhibition of microsomal triglyceride transfer protein (MTP) as a mechanism for reducing not only plasma total and LDL

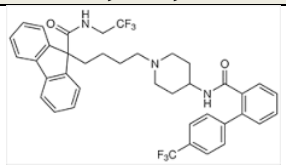
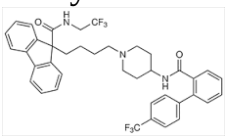
<table>
<tr><th>U.S. 8,618,135</th><th>Stein 2004 in view of Chang</th></tr>
<tr><td></td><td>cholesterol, but also plasma very low density lipoprotein (VLDL) cholesterol and triglycerides." CFAD Ex. 1015:562; see also id. at 563.</td></tr>
<tr><td>Claim 3. The method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and lipoprotein B are reduced by at least 15%, compared to control levels.</td><td>See CFAD Ex. 1014:28-29, 32 (reporting implitapide Phase I and Phase II trial results).

"Similar efficacy was reported for BAY-13-9952 [implitapide], 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 [lomitapide] also showed similar efficacy in phase I and phase II clinical trials." CFAD Ex. 1015:566.</td></tr>
<tr><td>Claim 4. The method of claim 1 wherein one or more of Total Cholesterol, LDL, … (TG), VLDL,… (Lp(a)), and lipoprotein B are reduced by at least 25%, compared to control levels.</td><td>See CFAD Ex. 1014:28-29, 32 (reporting implitapide Phase I and Phase II trial results).

<table><tr><th>Dose (mg/day)</th><th>LDL-C</th><th>Total-C</th><th>apoB</th></tr><tr><td>20 mg</td><td>-10%</td><td>-12%</td><td>-2%</td></tr><tr><td>40 mg</td><td>-31%</td><td>-22%</td><td>-17%</td></tr><tr><td>80 mg</td><td>-32%</td><td>-27%</td><td>-28%</td></tr><tr><td>160 mg</td><td>-61%</td><td>-54%</td><td>-55%</td></tr></table></td></tr>
<tr><td>Claim 5. The method of claim 1 wherein the MTP inhibitor is administered orally.</td><td>Similar efficacy was reported for BAY-13-9952 [implitapide], 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." CFAD Ex. 1015:566.</td></tr>
<tr><td>Claim 6. The method of claim 1 wherein said increasing dose levels further comprise a fourth dose level.</td><td>"Three studies with virtually identical design: All are ≅39 weeks duration with dose titration schedule every 5 weeks based on safety and tolerability at 4 weeks . . . Starting dose is 10 mg daily with escalation by 5 mg every 5 weeks to maximum of 40 mg." CFAD Ex. 1014:38.

[i.e. 10 mg/day for 5 weeks; 15 mg/day for 5 weeks; 20 mg/day for 5 weeks; 25 mg/day for 5 weeks; 30 mg/day for 5 weeks; 35 mg/day for 5 weeks; and 40</td></tr>
</table>

U.S. 8,618,135	Stein 2004 in view of Chang
	mg/day for 5 weeks]
Claim 7. The method of claim 1 wherein said increasing dose levels further comprise a fourth and a fifth dose level.	*See* Claim 6, *supra*.
Claim 8. The method of claim 7, wherein said fourth dose level is from about 20 to about 60 mg/day, and said fifth dose level is from about 30 to about 75 mg/day.	*See* Claim 6, *supra*.
Claim 9. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising	*See* Claim 1, *supra*.
administering to the subject an effective amount of an MTP inhibitor,	*See* Claim 1, *supra*.
wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor	*See* Claim 1, *supra*.
wherein a first dose level is from about 2 to about 13 mg/day, administered to the subject for about 2 weeks; a second dose level is from about 5 to about 30 mg/day, administered to the subject for about 2 weeks to about 4 weeks; and a third dose level is from about 10 to about 50 mg/day, administered to the subject for about 2 weeks to about 4 weeks; and	"Proposed MTP Development plan…Start at low doses, 10 mg and dose titrate by 5mg based on 'safety' every 5 weeks…" CFAD Ex. 1014:37. "Three studies … with dose titration schedule every 5 weeks based on safety and tolerability at 4 weeks… Starting dose is 10 mg daily with escalation by 5 mg **every 5 weeks** to maximum of 40 mg." CFAD Ex. 1014:38.
wherein the MTP inhibitor is represented by:	*See* Claim 1, *supra*.

U.S. 8,618,135	Stein 2004 in view of Chang
 [lomitapide], or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof.	
Claim 10. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising	*See* Claim 1, *supra*.
administering to the subject an effective amount of an MTP inhibitor,	*See* Claim 1, *supra*.
wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor	*See* Claim 1, *supra*.
wherein a first dose level is from about 2 to about 13 mg/day, administered to the subject for about 1 to about 12 weeks; a second dose level is from about 5 to about 30 mg/day, administered to the subject for about 4 weeks; and a third dose level is from about 10 to about 50 mg/day, administered to the subject for about 4 weeks; and	"Three studies with virtually identical design: All are ≅39 weeks duration with dose titration schedule every 5 weeks based on safety and tolerability at 4 weeks . . . Starting dose is 10 mg daily with escalation by 5 mg **every 5 weeks** to maximum of 40 mg." CFAD Ex. 1014:38. *See also* Claim 9, *supra*.
wherein the MTP inhibitor is represented by:  [lomitapide], or a pharmaceutically acceptable	*See* Claim 1, *supra*.

U.S. 8,618,135	Stein 2004 in view of Chang
salt thereof or the piperidine N-oxide thereof.	

(*See* Zusman, ¶¶ 187-260, 262 (confirming each element, and that the skilled artisan's general knowledge renders dose escalation timing obvious)).

As described in the chart above, Stein 2004 teaches a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor (implitapide), wherein said administration comprises at least three (actually up to seven) step-wise increasing dose levels of the MTP inhibitors. (*See* CFAD Ex. 1014:27-32, 37-38; Zusman ¶¶ 103-05, 194, 197-98, 200). The first dose level taught therein 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 (CFAD Ex. 1014:37-38; Zusman ¶¶ 201-02), and each dose level is administered to the subject for about 1 to about 5 weeks (CFAD Ex. 1014:37-38; Zusman ¶¶ 201-02). Lipid-lowering drugs generally were titrated upwards at intervals of 2 to 4 weeks, or longer. (Zusman, ¶ 47). Thus, the claimed intervals fall into the known dose titration ranges already used to evaluate safety/tolerability. *See Galderma*, 737 F.3d at 737-38 (obviousness of prior art range).

Stein 2004 does not specifically disclose the MTP inhibitor represented by [lomitapide], or a pharmaceutically acceptable salt or piperidine N-oxide thereof.

Chang teaches a method of treating a subject suffering from hyperlipidemia or hypercholesterolemia using MTP inhibitors specifically including lomitapide. (CFAD Ex. 1015:564-66; Zusman, ¶¶ 195-96, 199, 203-04).

The sole difference between Chang and the claimed subject matter is that Chang did not expressly teach using lomitapide in an escalated-dose regimen. (Zusman, ¶¶ 194-99, 203-04). But Stein 2004 teaches the escalating-dose regimen not found in Chang. (*Id.* at ¶¶ 200-02, 205). The Stein 2004 dosing regimen increases the dose by the 5 week mark, which meets the "about 1 to about 5 weeks", "about four weeks", and "about 1 to about 12 weeks" limitations in claims 1, 9 and 10. (Zusman, ¶¶ 252-53, 259). Petitioner incorporates by reference the remaining discussion in Section X.A.1.

2. Motivation to Combine Stein 2004 with Chang.

The motivation to combine Stein 2004 with Chang corresponds to the motivation to combine set forth in Ground One. (*See* Zusman, ¶¶ 206-16; Mayersohn, ¶¶ 19, 46-48, 63-65, 68-70). Therefore, Petitioner incorporates by reference the analysis in Section X.B.2 about Chang's teachings, the Pink Sheet 2004 teachings also found in Stein 2004, and the motivation to combine them. But *additional* Stein 2004 teachings *further motivate* the skilled artisan.

For example, Stein 2004 reports that the U.S. "lipid lowering market is now the largest therapeutic segment at ≅ $16 to $18 billion." (CFAD Ex. 1014:7). Stein

also reports that market growth, while slowing, remained "in the double digits", and "[a]s a class statins are by far the largest component with each percentage of market share worth ≅ $160,000,000 per year." (*Id.*) Stein 2004 also clarified the nature of the market opportunity for MTP inhibitors as adjunctive therapy: "New therapeutic agents will be additive or complementary not competitive with statins or even existing agents." (*Id.*) The size of this potential market would surely have motivated the skilled artisan–as would Dr. Stein's proposed solution to managing side-effects by using known dosing techniques.

Stein 2004 also provides additional detail about the clinical need for MTP inhibitors not explicitly noted in Pink Sheet 2004. Stein teaches there is "[s]till large potential unmet need for additional, for [sic] even moderately effective (15-20%), LDLC lowering agents," (*Id.* at 45), and taught how to satisfy that need. (*Id.* at 22-43). The presentation touts the clinical potential for MTP inhibitors *as a class*, and motivates the ordinarily-skilled artisan to investigate further: "MTP inhibition offers the widest potential for reducing production of the atherogenic lipoproteins including chylomicrons, VLDL, IDL, and LDL." (*Id.* at 45).

Stein 2004 also would encourage the skilled artisan to reasonably expect success by teaching that applying stepwise escalating dosing will achieve the desired clinical targets with lower doses. Stein 2004 confirmed the "**[i]nitial 'hurdles' and expectations are modest and based on existing scientific data.**" (*Id.* at 44)

(emphasis added). Significantly, given Chang's expressed concerns about an appropriate therapeutic index and marketing hurdles for MTP inhibitors, the skilled artisan would understand from Stein 2004 that the MTP inhibitor need only produce a modest result to justify pursuit. (Zusman, ¶¶ 105, 210-14).

All of these teachings in Stein 2004, as well as the detailed implitapide trial data in the presentation (CFAD Ex. 1014:23-32), provide additional motivation to the ordinarily-skilled artisan to pursue other MTP inhibitors which could work according to the plan Stein proposed for implitapide. As noted above, that search would quickly lead to Chang and to lomitapide. (Zusman, ¶¶ 93-95, 144).

3. Reasonable Expectation of Success With Lomitapide.

The analysis of the skilled artisan's reasonable expectation of success when substituting lomitapide for implitapide in the stepwise escalating dosing regimen taught by Stein 2004 in view of Chang correlates to the Pink Sheet 2004/Chang combination analysis. (*See id.* at ¶¶ 217-21; Mayersohn, ¶¶ 18-19, 48, 54, 65). Petitioner incorporates by reference here the "reasonable expectation of success" analysis in Section X.A.3 above. But *further* Stein 2004 teachings confirm the reasonable expectation of success, including the implitapide trial data (CFAD Ex. 1014:23-32) and Dr. Stein's teachings that the success required need only be modest to justify pursuing MTP inhibitors. (*Id.* at 44; Zusman, ¶¶ 105, 210-14).

Given the above, there are no non-obvious differences between the claims and

the prior art. Further, as discussed below, the alleged secondary considerations of nonobviousness asserted during the '135 prosecution cannot undermine or refute the strong showing of obviousness. From the perspective of one of ordinary skill in the art, claims 1-10 were obvious when filed. They are invalid.

C. Secondary Considerations Presented During Prosecution Do Not Rebut the *Prima Facie* Case of Unpatentability.

An obviousness analysis must consider "secondary considerations" evidence when presented. *See Graham v. John Deere*, 383 U.S. at 17-18. Petitioner submits **no** substantial evidence of secondary considerations exists, but nevertheless addresses Patentee's arguments raised during prosecution.

With Petitioner having presented a strong *prima facie* case of obviousness (Sections IV-X.B. above), Patentee has the burden to produce secondary considerations evidence with nexus to the claims to refute that case. *See In re Dillon*, 919 F.2d 688, 692-93 (Fed Cir. 1990) (*en banc*). Patentee cannot do so here. *See Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (secondary considerations "simply cannot overcome a strong *prima facie* case of obviousness"); *accord Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007); *Allergan v. Sandoz*, 726 F.3d 1286, 1293 (Fed. Cir. 2013).

First, "where the inventions represented no more than 'the predictable use of prior art elements according to their established functions,' the secondary considerations are inadequate to establish nonobviousness as a matter of law."

Wyers, 616 F.3d at 1246 (*quoting KSR*, 550 U.S. at 417). The prior art here taught each element of the '135 patent claims, and their predictable and expected results. *See Senju*, 780 F.3d at 1353 (routine experimental work was obvious).

Second, the patentee argued during prosecution that the alleged "failure of others" to solve the side-effects problem, "unexpected results" from the claimed stepwise dosing regimen, and alleged "industry skepticism" were objective evidence of the nonobviousness of the '135 patent claims. (*See* CFAD Ex. 1009:7-9; *see also* CFAD Ex. 1010:1-2). None withstand scrutiny.

No failure of others. Dr. Stein's solution for MTP inhibitor dosing—escalating step-wise dosing—was already published. This alone is fatal to patentee's argument, because it precludes any nexus to the '135 patent claims. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006); *see also Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327-28 (Fed. Cir. 2008) (nexus required to give substantial weight to secondary considerations evidence).

Patentee's related argument that "scientists and investigators of the failed [circa-1990s BMS lomitapide] trial, did not appear to arrive at any solution to these adverse events" is also wrong. (CFAD Ex. 1009:8; CFAD Ex. 1010:1). Those "others" were dosing lomitapide in the hope of competing commercially with statin drugs as *monotherapy*. (*See* Zusman, ¶ 266; CFAD Ex. 1001, col. 8:27-30 (BMS decided side effects "made it unlikely that BMS-201038 could be developed as a

drug for large scale use in the treatment of hypercholesterolemia"); *see also* CFAD Ex. 1013:2 ("'None of them were looking at LDL reductions or cholesterol reductions' as low as the 20% range, [Stein] said. 'They didn't consider that viable in terms of marketing.'"). BMS's decision to discontinue lomitapide development for economic reasons does not demonstrate scientific or technological obstacles to (or the nonobviousness of) the claimed invention. *See Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1013 (Fed. Cir. 1983). Indeed, patentee's proposed solutions—dose-escalation of lomitapide in combination therapy, treatment of HoFH and other niche diseases, therapeutic improvements in the 15-25% range, etc.—merely copy Stein's prior art solutions. (*See* CFAD Ex. 1001, col. 7:49-60; col. 10:35-42; col.11:33 – 13:62; *Cf.* CFAD Ex. 1013:2; CFAD Ex. 1014:7, 33-38; Zusman, ¶¶ 76-78, 267; Mayersohn, ¶¶ 72-73).

No unexpected results. The Sasiela Declaration asserts reduced side effects from the claimed escalating dosing regimen was a "surprising" and "unexpected result." (*See* CFAD Ex. 1010:2-3). To the contrary, this was the natural result flowing from applying Stein's escalating-dose method to lomitapide. (Zusman, ¶¶ 74-76, 265). Before March 2004, ordinarily-skilled artisans would reasonably expect reduced side-effects to result from using lower initial doses of anti-cholesterol drugs, including MTP inhibitors, in an escalating dosing regimen. (*See id.* at ¶¶ 74-76, 265; CFAD Ex. 1014:31, 36-38; CFAD Ex. 1013:2; CFAD Ex.

1021). This is especially so given the known dose dependency of the cholesterol-lowering effects of MTP inhibitors, and their gastrointestinal and hepatic side-effects. (*See* Zusman, ¶ 265; CFAD Ex. 1015:564-67).

No skepticism. Patentee argued skilled artisans were allegedly "skeptical" about the benefits of step-wise dosing for MTP inhibitors as shown by alleged teaching away in the references cited by the Examiner. (*See* CFAD Ex. 1009:7-9). Any purported skepticism was resolved by the publication of the Pink Sheet 2004 or Stein 2004 references. *See Hoffman-LaRoche, Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1330-31 (Fed. Cir. 2013). Indeed, Dr. Stein's active pursuit and promotion of a step-wise, escalating dosing regimen for MTP inhibitors in phase II clinical trials of implitapide confirms a *lack* of skepticism in the art. (Zusman, ¶ 268; CFAD Ex. 1014: 31, 36-38; CFAD Ex. 1013:2). To obtain informed consent and ethically conduct Phase II clinical trials, researchers must reasonably expect some positive clinical benefit. *See* 21 C.F.R. § 50.25 (2001); 45 C.F.R. § 46.116 (2001).

Finally, Patentee did not argue "commercial success" before the Examiner; no lomitapide products were then sold. Any such argument now would fail for at least these reasons: (a) there can be no nexus between the '135 patent claims and any alleged commercial success of success of Juxtapid®–lomitapide, its uses, and escalating step-wise dosing were all known in the prior art; (b) BMS blocking patents on lomitapide (as a compound) have protected Juxtapid® from competing

lomitapide products; and (c) Juxtapid® has enjoyed regulatory market exclusivity since its 2012 approval. *See Merck & Co.*, 395 F.3d at 1377 (finding commercial success "not significantly probative" where others were "legally barred" from "commercially testing the [prior art] ideas."). But regardless of the commercial opportunity, the core of the obviousness analysis remains in the science. Marketing challenges or the absence of an attractive commercial opportunity are not evidence of non-obviousness. Businessmen not pursuing a path "for economic reasons is not the same as saying that it could not be done because skilled persons in the art felt that there was some technological incompatibility that prevented" the invention. *Orthopedic Equip. Co.*, 702 F.2d at 1013.

XI. CONCLUSION.

The prior art and evidence presented show a substantial likelihood that each of the challenged claims of the '135 patent are invalid under 35 U.S.C. § 103. Petitioner therefore requests that the Board grant this Petition for *inter partes* review and find the claims of the '135 patent are invalid.

Respectfully submitted,

Dated: August 28, 2015

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I, Dr. Gregory J. Gonsalves, hereby certify that on this 28th day of August, 2015, I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135 (and accompanying exhibits 1001 - 1041) in its entirety by U.S. Express Mail, on the following:

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