Coalition for Affordable Drugs VIII, LLC,

Petitioner,

v.

The Trustees of the University of Pennsylvania,

Patent Owner

Case No. IPR2015-01835 (Patent 8,618,135 B2)
Case No. IPR2015-01836 (Patent 7,932,268 B2)

Inter Partes Review Hearing – December 1, 2016

Patent Owner's Demonstrative Exhibits

Grounds Instituted by Board for the ’135 and ’268 Patents

Patent	Claims	Grounds Instituted
’135 Patent	1-10	**Obvious over Pink Sheet 2004 & Chang**
’135 Patent	1-10	**Obvious over Stein & Chang**
’268 Patent	1-8	**Obvious over Pink Sheet 2004 & Chang**
’268 Patent	1-8	**Obvious over Stein & Chang**

Source: Institution Decision at 34 [33]

Petitioner Has Not Shown That the Claims of the '135 and '268 Patents Are Obvious

- **Petitioner fails to show a motivation to combine the Pink Sheet or Stein with Chang**
  - The prior art suggested that lomitapide could not be dosed safely in humans
  - The Pink Sheet and Stein provide no motivation to use lomitapide
  - Chang provides no motivation to use a stepwise regimen for lomitapide, let alone in the claimed amounts
  - Chang's unsupported statement about "similar efficacy" would not have motivated a POSA
  - General overlap in therapeutic class (*i.e.*, MTP inhibitors) is not sufficient to combine specific teachings regarding lomitapide and implitapide
- **A POSA would not have had a reasonable expectation of success**
  - No showing that lomitapide and implitapide had "similar efficacy"
  - Chang's rabbit data do not suggest similar dosing of lomitapide and implitapide
  - A POSA would have expected lomitapide and implitapide to have different PK/PD Properties

Source: POR at 1-6, 26-38, 38-44; MTA at 20-22 [20-21]; RMTA at 9-10

Objective Indicia of Non-Obviousness Confirm the Patentability of the Claims

- **Unexpected Results:** It was unexpected that increasing the dose of lomitapide would reduce side effects and thus allow patients to safely tolerate therapeutically effective doses
- **Long-felt Need:** JUXTAPID® met the long-felt need for effective treatment of HoFH
- **Failure of Others:** BMS abandoned lomitapide after a decade of research due to toxicity concerns; numerous other pharmaceutical companies (including Stein and PPD) also failed to develop an MTP inhibitor
- **Praise:** The successful use of Dr. Rader's idea was published in the *New England Journal of Medicine*
- **Licensing/Commercial Success:** Aegerion Pharmaceuticals licensed the patents from Penn, and FDA-approval of JUXTAPID® resulted in millions of dollars in sales, facilitating the growth of Aegerion

Source: POR at 56-64; MTA at 22-24; RMTA at 10-11

The Pink Sheet 2004 Provides No Motivation to Use Lomitapide

- **The Pink Sheet 2004 is a one-page article**
- **It describes the development strategy for implitapide and notes the protocol for Phase II proof-of-concept trials**
- **Pink Sheet 2004 *does not* disclose:**
  - Lomitapide
  - Any results or data for the proposed protocol
  - That any subject would be administered more than the lowest dose

Source: Ex. 1013, Pink Sheet 2004, p. 2; POPR at 40-41 [38-39]; POR at 10-12, 26-40, 49

Stein Provides No Motivation to Use Lomitapide

- **Stein is a slide deck presented by Dr. Evan Stein for PPD, Inc.**
- **It describes a development plan for implitapide**
- **Stein *<u>does not</u>* disclose:**
  - Lomitapide
  - Any results or data for the proposed protocol
  - That any subject would be administered more than the lowest dose

Source: Ex. 1005, Butler Aff., p. 4; Ex. 1014, Stein, pp. 1, 37; POPR at 26-30 [24-28], 48-49 [46-47]; POR at 10-12, 26-38, 49; RMTA at 9

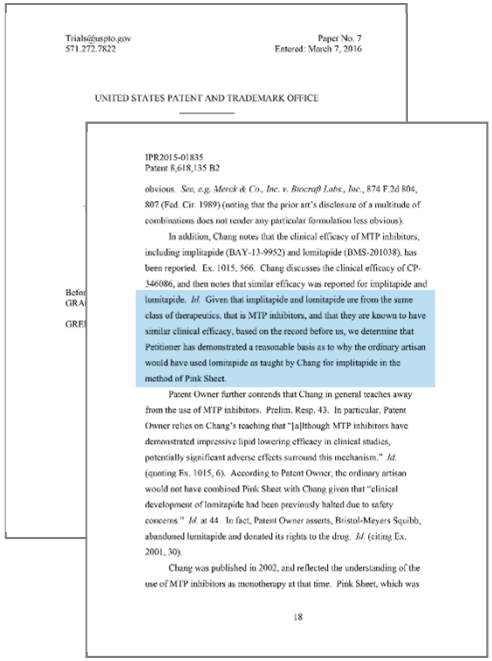
Chang Provides No Information Regarding the Human Dosing of Lomitapide

Chang does not disclose:

- **Any human data to support its "similar efficacy" statement**
- **Any dose of lomitapide used in humans**
- **PK/PD data for humans (or animals)**
- **The lomitapide therapeutic window in humans (or animals)**
- **That MTP inhibitors should be dosed similarly**
- **Rabbit data suggesting that lomitapide and implitapide can be dosed similarly**

Source: POR at 12-13, 31-35

The Board's Decision on Motivation to Combine Was Based on an Incomplete Record



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Paper No. 7
Entered: March 7, 2016

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

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

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

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

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"Given that implitapide and lomitapide are from the same class of therapeutics, that is MTP inhibitors, and that they are known to have similar clinical efficacy, based on the record before us, we determine that Petitioner has demonstrated a reasonable basis as to why the ordinary artisan would have used lomitapide as taught by Chang for implitapide in the method of Pink Sheet."

However:

- **Sharing the same therapeutic class is not sufficient to show motivation**
- **Unsupported statement of "similar efficacy" would not have motivated a POSA to select lomitapide for a dose specific step-wise regimen**

Source: Institution Decision at 18

Chang's Statement About "Similar Efficacy" Is Unsupported and Would Not Have Motivated a POSA

- **Chang does not disclose a scientific basis for its statement that lomitapide exhibited "similar efficacy" to other MTP inhibitors**
- **Only one reference is cited to support Chang's proposition on "similar efficacy"** (Footnote 43, Pink Sheet 2000)
- **Pink Sheet 2000 provides no information regarding the efficacy of lomitapide or any other MTP inhibitor**
- **Pink Sheet 2000 provides no information regarding any doses of lomitapide used in humans**

Source: Ex. 1015, Chang, p. 5, 8; Ex. 2011, Pink Sheet 2000, p. 1; POPR at 46-47 [44-45]; POR at 12-13, 31 [13]

Chang's Animal Data Would Not Motivate a POSA to Develop Lomitapide for Human Use

- **Chang's source of lomitapide animal data is the 1998 Wetterau paper (Ex. 1018), which was published before BMS withdrew lomitapide from the clinic**
- **The WHHL rabbit study cited by Chang was a single experiment in which five rabbits were administered one dose of lomitapide over two weeks**
- **Petitioner's experts agree that the WHHL rabbit model cannot quantitatively predict human efficacy**
- **Chang states that lomitapide showed significant liver toxicity in humans that was not observed in several animal species**

Source: Ex. 1015, Chang, pp. 4-6, Ex. 1018, Wetterau, pp. 2-4; Ex. 2021, Mayersohn Tr., 112:9-113:5; Ex. 2022, Zusman Tr., 92:9-93:9; POR at 27, 32-33, 36-37; RMTA at 4, 7-8

Drugs in the Same Therapeutic Class Are Not Necessarily Dosed Using the Same Regimen

- **Drugs in the same therapeutic class work on the same biological target but have different chemical structures**
- **Differences in structure often cause differences in key PK/PD properties such as potency, off-target toxicity, absorption, and metabolism**
- **A POSA would not expect compounds with different structures to have the same PK/PD properties**
- **If two compounds have dissimilar PK/PD properties, they will not be dosed using the same regimen**

Source: POR at 17-18, 41-44

A POSA Would Have No Motivation to Select Lomitapide For Use in the Stein and Pink Sheet 2004 Regimen

- **A POSA would be discouraged from developing lomitapide after BMS withdrew the compound from the clinic due to liver toxicity**
- **A POSA would expect off-target toxicities based on lomitapide's chemical structure**
- **In view of these toxicities, a POSA would not have considered the use of lomitapide as a combination therapy with statins and/or targeted HoFH treatment**
- **There were more promising MTP inhibitors available in the literature**

Source: POR at 12-13, 26-35

A POSA Would Have Had No Reasonable Expectation of Success in Using the Stein/Pink Sheet 2004 Dosing Regimen with Lomitapide

- **A POSA would have expected lomitapide and implitapide to have different PK/PD properties and thus to be dosed differently because they have different chemical structures**
- **No comparative human (or animal) PK/PD data existed for implitapide and lomitapide, so a POSA could not reasonably make any predictions regarding lomitapide dosing**
- **Stein and Pink Sheet 2004 describe a proposed dosing regimen—no evidence it would work even with implitapide**
- **No human dosing data available for lomitapide—a POSA could not know whether the doses proposed by Stein would be efficacious and/or toxic with lomitapide**

Source: POR 38-44; MTA at 20-22 [20-21]; RMTA at 9-10

Testimony Supporting Nonobviousness

Patent Owner Declarant	Key Testimony
Frank Sacks, M.D. (Harvard Medical School)	**The claimed lomitapide dosing regimen was not obvious, garnered praise, and satisfied a long-felt, unmet need**
Thomas A. Baillie, Ph.D (University of Washington, ex Merck)	**Nonobviousness in light of structural differences of implitapide and lomitapide and the effect on PK/PD properties and dosing; unexpected results; failure of others**
S. David Kimball, Ph.D. (Rutgers, ex BMS)	**Nonobviousness in light of structural differences of implitapide and lomitapide and the effect on off-target toxicity and PK/PD properties**
Daniel J. Rader, M.D. (University of Pennsylvania)	**Sole inventor of both patents; describes the events that led to the discovery of the invention, conception and reduction to practice**
Richard E. Gregg, M.D. (ex. BMS)	**Describes the early clinical work on lomitapide at BMS and the discontinuation of the program**

Source: POR at 13-14

Pink Sheet 2004 Is a One-Page News Article on Planned Implitapide Study

"The Pink Sheet"

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

February 16, 2004 "The Pink Sheet" 17

Bayer/PPD Implitapide Development Follows *Zetia* Model As Statin Add-On

PPD will adopt Merck/Schering-Plough's *Zetia* model in developing Bayer's implitapide as an add-on therapy in the lipid-lowering market, PPD subsidiary MRL International CEO Evan Stein, MD/PhD, said.

"We're not looking to compete with the statin market." While "no new agent is going to replace statin therapy...we've seen ezetimibe, Zetia, come onto the market and obtain a significant market share," Stein said during PPD's investor day Feb. 5.

PPD is conducting *Phase II* proof-of-concept studies on the use of implitapide (BAY-13-9952) as an add-on to statin therapy. The contract research organization licensed the microsomal triglyceride transfer protein inhibitor from Bayer.

Implitapide could mark Bayer's return to the lipid-lowering market after the 2001 Baycol withdrawal.

PPD is hoping to demonstrate implitapide's safety and efficacy in homozygous and severe heterozygous familial hypercholesterolemia "where even high-dose statins are ineffective or inadequate," Stein said. The drug is also being studied for hypertriglyceridemia.

The studies, which will enroll approximately 200 patients, are expected to position the drug as a way to improve upon statin therapy, much in the same way that Zetia is marketed, Stein said.

"The addition here of another 18% to 24% [LDL reduction] would allow us to build on current therapy," he said. Zetia's success "provides an equal opportunity for other drugs that can produce 18% to 24% LDL reduction safely in a single-dose pill on top of all existing therapy."

When used as an add-on to a statin, Zetia has a statistically significant effect on reducing LDL cholesterol. For example, across all *Lipitor* (atorvastatin) doses the combination reduces LDL levels 56% versus 44% with the statin alone.

Some analysts have questioned the pace of Zetia's uptake, however; new and total prescription share in December was 5.2% and 4.9%, a little over a year on the market ("The Pink Sheet" Feb. 2, 2004, p. 11).

Patients initially 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.

Zetia is similarly targeted. By contrast, Merck expects the *Zetia/Zocor* fixed-dose combination pending at FDA to compete directly with single-agent statins for patients who are diagnosed with high cholesterol but not treated ("The Pink Sheet" Dec. 22, 2003, p. 23).

PPD suggested implitapide could eventually be used as a triple combination therapy with Zetia and a statin. In that case, Stein estimated that LDL-cholesterol reductions could range between 66%-72%.

PPD expects Bayer will be interested in buying back rights to implitapide after seeing the *Phase II* results. "If they meet, I think, even a reasonable hurdle, Bayer will be pretty keen to take it," Stein maintained.

Implitapide would mark Bayer's return to the lipid-lowering market; the company withdrew the statin *Baycol* (cerivastatin) in 2001 due to reports of rhabdomyolysis, including deaths ("The Pink Sheet" Aug. 13, 2001, p. 4).

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

"None of them were looking at LDL reductions or cholesterol reductions" as low as the 20% range, he said. "They didn't consider that viable in terms of marketing. There was no Zetia on the market, so there was no model for them."

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.♦♦

Unauthorized photocopying is prohibited by law. See page one.

CFAD Ex. 1013 (2 of 2)

PPD is conducting *Phase II* proof-of-concept studies on the use of implitapide (BAY-13-9952) as an add-on to statin therapy.

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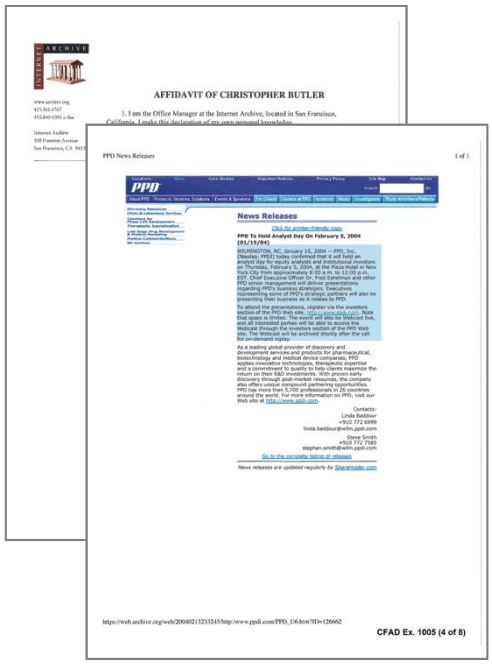
Source: Ex. 1013, Pink Sheet 2004, p. 2; POPR at 40-41 [38-39]; POR at 11-12, 38-40

The Stein Presentation Was Directed to Analysts and Investors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PPD News Releases

News Releases

CFAD Ex. 1005 (4 of 8)

"WILMINGTON, NC, January 15, 2004 -- PPD, Inc. (Nasdaq: PPDI) today confirmed that it will hold an analyst day for equity analysts and institutional investors on Thursday, February 5, 2004, at the Plaza Hotel in New York City from approximately 8:00a.m. to 12:00 p.m. EST. Chief Executive Officer Dr. Fred Eshelman and other PPD senior management will deliver presentations regarding PPD's business strategies. Executives representing some of PPD's strategic partners will also be presenting their business as it relates to PPD.

To attend the presentations, register via the investors section of the PPD Web site, http://www.ppdl.com. Note that space is limited. The event will also be Webcast live, and all interested parties will be able to access the Webcast through the investors section of the PPD Web site. The Webcast will be archived shortly after the call for on-demand replay."

Source: Ex. 1005, Butler Aff., p. 4; POPR at 28 [26]

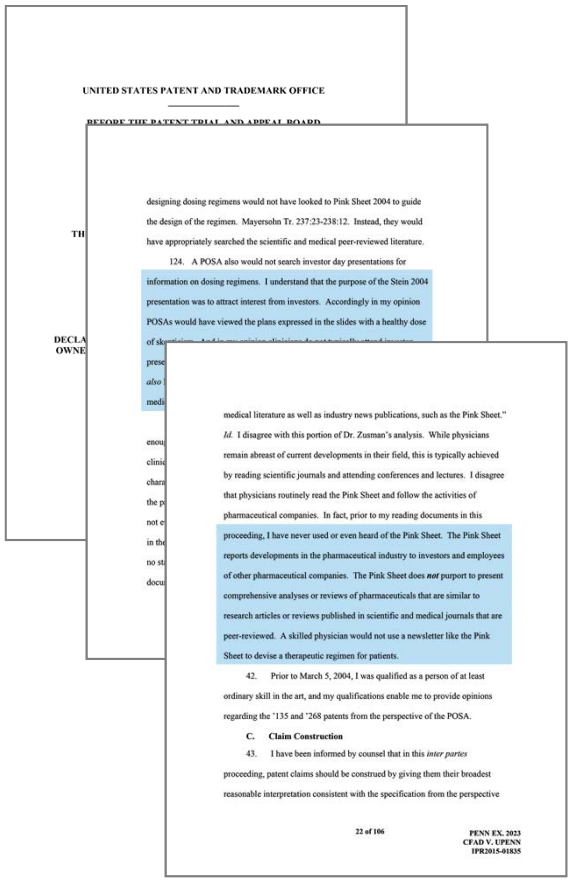
The Stein Presentation Was Limited to Implitapide

Source: Ex. 1014, Stein, p. 1; POPR at 26-30 [24-28]; POR at 10-11

Stein Contains Limited Information Regarding the Proposed Dosing of Implitapide

Source: Ex. 1014, Stein, p. 37; POPR at 48-49 [46-47]; POR at 35; RMTA at 9

Dr. Sacks: A POSA Would Not Use Stein or Pink Sheet 2004 to Design a Human Dosing Regimen



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designing dosing regimens would not have looked to Pink Sheet 2004 to guide the design of the regimen. Mayersohn Tr. 237:23-238:12. Instead, they would have appropriately searched the scientific and medical peer-reviewed literature.

124. A POSA also would not search investor day presentations for information on dosing regimens. I understand that the purpose of the Stein 2004 presentation was to attract interest from investors. Accordingly in my opinion POSAs would have viewed the plans expressed in the slides with a healthy dose

medical literature as well as industry news publications, such as the Pink Sheet." *Id.* I disagree with this portion of Dr. Zusman's analysis. While physicians remain abreast of current developments in their field, this is typically achieved by reading scientific journals and attending conferences and lectures. I disagree that physicians routinely read the Pink Sheet and follow the activities of pharmaceutical companies. In fact, prior to my reading documents in this proceeding, I have never used or even heard of the Pink Sheet. The Pink Sheet reports developments in the pharmaceutical industry to investors and employees of other pharmaceutical companies. The Pink Sheet does ***not*** purport to present comprehensive analyses or reviews of pharmaceuticals that are similar to research articles or reviews published in scientific and medical journals that are peer-reviewed. A skilled physician would not use a newsletter like the Pink Sheet to devise a therapeutic regimen for patients.

42. Prior to March 5, 2004, I was qualified as a person of at least ordinary skill in the art, and my qualifications enable me to provide opinions regarding the '135 and '268 patents from the perspective of the POSA.

C. **Claim Construction**

43. I have been informed by counsel that in this *inter partes* proceeding, patent claims should be construed by giving them their broadest reasonable interpretation consistent with the specification from the perspective

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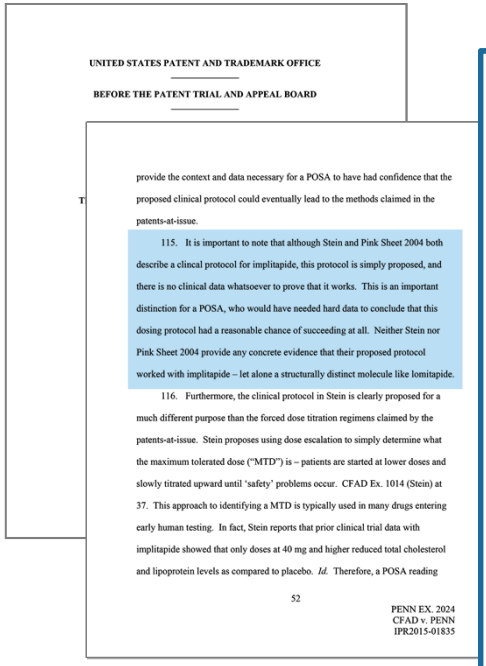
"I understand that the purpose of the Stein 2004 presentation was to attract interest from investors. Accordingly in my opinion POSAs would have viewed the plans expressed in the slides with a healthy dose of skepticism. And in my opinion clinicians do not typically attend investor presentations for purposes of obtaining information on dosing regimens. *See also* Mayersohn Tr. at 192:5-9. A POSA would instead look to peer-reviewed medical literature."

"The Pink Sheet reports developments in the pharmaceutical industry to investors and employees of other pharmaceutical companies. The Pink Sheet does *not* purport to present comprehensive analyses or reviews of pharmaceuticals that are similar to research articles or reviews published in scientific and medical journals that are peer-reviewed. A skilled physician would not use a newsletter like the Pink Sheet to devise a therapeutic regimen for patients."

Source: Ex. 2023, Sacks Decl., ¶ 124, ¶ 41; POR at 9-12

Stein and Pink Sheet 2004 Describe a Protocol for Implitapide and No Data Demonstrating That It Will Work



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provide the context and data necessary for a POSA to have had confidence that the proposed clinical protocol could eventually lead to the methods claimed in the patents-at-issue.

115. It is important to note that although Stein and Pink Sheet 2004 both describe a clincal protocol for implitapide, this protocol is simply proposed, and there is no clinical data whatsoever to prove that it works. This is an important distinction for a POSA, who would have needed hard data to conclude that this dosing protocol had a reasonable chance of succeeding at all. Neither Stein nor Pink Sheet 2004 provide any concrete evidence that their proposed protocol worked with implitapide – let alone a structurally distinct molecule like lomitapide.

116. Furthermore, the clinical protocol in Stein is clearly proposed for a much different purpose than the forced dose titration regimens claimed by the patents-at-issue. Stein proposes using dose escalation to simply determine what the maximum tolerated dose ("MTD") is – patients are started at lower doses and slowly titrated upward until 'safety' problems occur. CFAD Ex. 1014 (Stein) at 37. This approach to identifying a MTD is typically used in many drugs entering early human testing. In fact, Stein reports that prior clinical trial data with implitapide showed that only doses at 40 mg and higher reduced total cholesterol and lipoprotein levels as compared to placebo. *Id.* Therefore, a POSA reading

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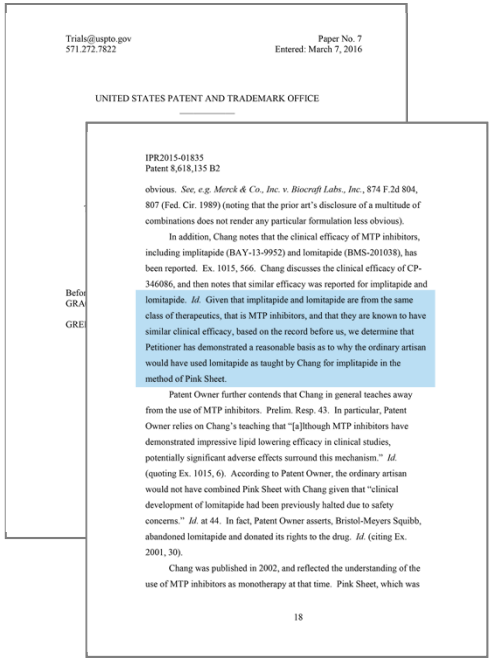
Source: Ex. 2024, Baillie Decl., ¶ 115; POR at 38-44

A POSA Would Not Have Based a Lomitapide Dosing Regimen on Stein or Pink Sheet 2004

- **The disclosures of Stein and Pink Sheet 2004 are not directed to medical professionals**
- **Stein and Pink Sheet 2004 disclose *a proposal* to conduct a standard dose-finding regimen for *implitapide***
- **Stein and Pink Sheet 2004 provide no data to suggest that the proposed regimen would be successful**

Source: POR at 10-12, 26-38, 49

The Board's Institution Decision Was Based on An Incomplete Record Regarding Similar Clinical Efficacy



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

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

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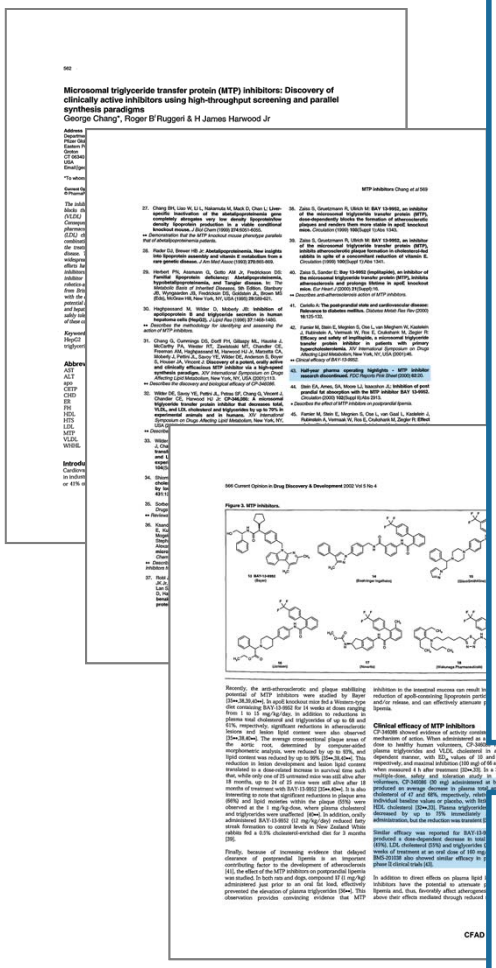
Source: Institution Decision at 18

Chang's "Similar Efficacy" Statement Is Unsupported



"**. . . CP-346086 (30 mg) administered at bedtime, produced an average decrease in plasma total and LDL cholesterol of 47 and 68%, respectively, . . . Plasma triglycerides were also decreased by up to 75% . . .**

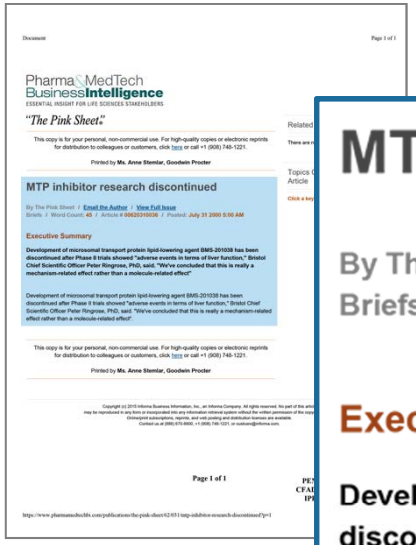
Similar efficacy was reported for BAY-13-9952, which produced a dose-dependent decrease in total cholesterol (45%), LDL cholesterol (55%) and triglycerides (29%) after 4 weeks of treatment at an oral dose of 160 mg/day.

BMS-201038 also showed similar efficacy in phase I and phase II clinical trials [43]."

"**43. Half-year pharma operating highlights - MTP inhibitor research discontinued. *FOG Reports Pink Sheet (2000) 62:20.*"

Source: Ex. 1015, Chang, p. 5, 8; POPR at 46-47 [44-45]; POR at 12-13 [13]

Pink Sheet 2000 (Ref. 43) Does Not Disclose Any Dosing Information for Lomitapide



MTP inhibitor research discontinued

By The Pink Sheet / Email the Author / View Full Issue
Briefs / Word Count: 45 / Article # 00620310036 / Posted: July 31 2000 5:00 AM

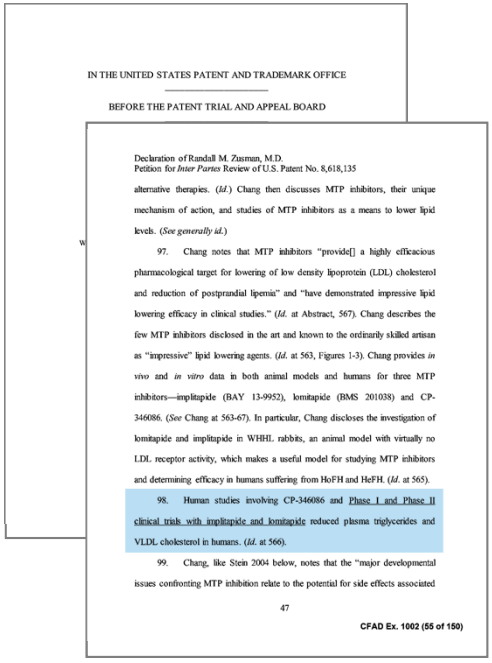
Executive Summary

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

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

Source: Ex. 2011, Pink Sheet 2000, p. 1; POPR at 46-47 [44-45]; POR at 13, 31

Dr. Zusman Relied on Chang's "Similar Efficacy" Statement In His Declaration



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Declaration of Randall M. Zusman, M.D.
Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135

alternative therapies. (*Id.*) Chang then discusses MTP inhibitors, their unique mechanism of action, and studies of MTP inhibitors as a means to lower lipid levels. (*See generally id.*)

97. Chang notes that MTP inhibitors "provide[] a highly efficacious pharmacological target for lowering of low density lipoprotein (LDL) cholesterol and reduction of postprandial lipemia" and "have demonstrated impressive lipid lowering efficacy in clinical studies." (*Id.* at Abstract, 567). Chang describes the few MTP inhibitors disclosed in the art and known to the ordinarily skilled artisan as "impressive" lipid lowering agents. (*Id.* at 563, Figures 1-3). Chang provides *in vivo* and *in vitro* data in both animal models and humans for three MTP inhibitors—implitapide (BAY 13-9952), lomitapide (BMS 201038) and CP-346086. (*See* Chang at 563-67). In particular, Chang discloses the investigation of lomitapide and implitapide in WHHL rabbits, an animal model with virtually no LDL receptor activity, which makes a useful model for studying MTP inhibitors and determining efficacy in humans suffering from HoFH and HeFH. (*Id.* at 565).

98. Human studies involving CP-346086 and Phase I and Phase II clinical trials with implitapide and lomitapide reduced plasma triglycerides and VLDL cholesterol in humans. (*Id.* at 566).

99. Chang, like Stein 2004 below, notes that the "major developmental issues confronting MTP inhibition relate to the potential for side effects associated

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"Human studies involving CP-346086 and Phase I and Phase II clinical trials with implitapide and lomitapide reduced plasma triglycerides and VLDL cholesterol in humans. (*Id.* at 566)."

Source: Ex. 1002, Zusman Decl., ¶ 98

Dr. Zusman Did Not Consider Pink Sheet 2000 (Ref. 43) Before Submitting His Declaration to the Board

Q. You have not seen the reference that Chang cites to in his paper reference 43, correct?

A. No, I have not.

Q. So you did not rely on reference 43 in forming or offering your opinions in this proceeding, correct?

A. No, I did not, . . .

Source: Ex. 2022, Zusman Tr., 98:16-22; POR at 31

Petitioner's Expert Dr. Zusman Conceded That Liver Toxicity Would Discourage a POSA from Developing a Drug

- **Dr. Zusman testified that the FDA was "extraordinarily sensitized" to liver toxicity and was thus reluctant to approve hepatoxic compounds.** (Tr. at 171:17-172:6)
- **Dr. Zusman conceded that if a drug caused a twofold increase in liver enzyme levels, it might be "too hot to handle", and would have discouraged a POSA from developing it.** (Tr. at 172:16-24)
- **Dr. Zusman admitted that a POSA's concerns regarding liver toxicity would apply to MTP inhibitors generally.** (Tr. at 174:11-175:8)

Ex. 2022, Zusman Tr., 171:17-172:6, 172:16-24, 174:11-175:8; POR at 2, 27-28; MTA at 18

Petitioner's Experts Concede that the Prior Art Does Not Identify Any Dose of Lomitapide Used in Humans

Dr. Mayersohn:

Q. And as of 2004–2005, the prior art did not teach doses of lomitapide in humans that caused adverse events to a degree sufficient to cause Bristol-Myers to discontinue the drug, correct?

A. Well, it's the same question you've been asking. No, there is no information in that abstract or that announcement.

* * *

Q. Yeah, I was asking if the specific dose that had been put into a human body was reported in the prior art.

A. And the answer to the best of my knowledge was no.

Dr. Zusman:

Q. . . . . But as far as your declaration in this proceeding, you have not identified a reference nor do you state in your declaration what dose was used in the Phase 1 and Phase 2 clinical trials for lomitapide?

A. I can't recollect that reference right now, no, I cannot.

Source: Ex. 2021 Mayersohn Tr., 170:18-171:2 (objection omitted), 173:7-11; Ex. 2022, Zusman Tr., 97:6-12; POR at 28, 31, 34, 41

Dr. Zusman Conceded that the Prior Art Does Not Identify a Non-Toxic Dose for Lomitapide in Humans

Q. But Dr. Zusman, sitting here today, you don't know what lower dose you could go to for lomitapide based on reading Chang.

A. Based on only reading Chang, that's correct.

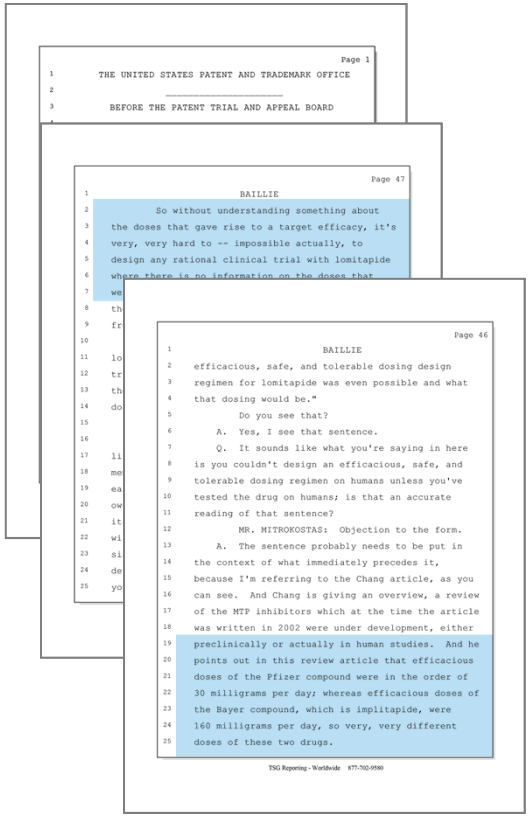
* * *

Q. . . . And so reading Chang, a person of ordinary skill in the art doesn't know what, quote, lower dose they would need to go to in order to reduce or eliminate these liver toxicities, correct, with lomitapide?

A. Not precisely what dose one might employ.

Source: Ex. 2022, Zusman Tr., 111:8-13 (objection omitted), 111:22-112:3; POR at 34

Chang Provides No Guidance on Dosing Lomitapide to Humans



THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BAILLIE

So without understanding something about the doses that gave rise to a target efficacy, it's very, very hard to -- impossible actually, to design any rational clinical trial with lomitapide where there is no information on the doses that

BAILLIE

efficacious, safe, and tolerable dosing design regimen for lomitapide was even possible and what that dosing would be."

Do you see that?

A. Yes, I see that sentence.

Q. It sounds like what you're saying in here is you couldn't design an efficacious, safe, and tolerable dosing regimen on humans unless you've tested the drug on humans; is that an accurate reading of that sentence?

MR. MITROKOSTAS: Objection to the form.

A. The sentence probably needs to be put in the context of what immediately precedes it, because I'm referring to the Chang article, as you can see. And Chang is giving an overview, a review of the MTP inhibitors which at the time the article was written in 2002 were under development, either preclinically or actually in human studies. And he points out in this review article that efficacious doses of the Pfizer compound were in the order of 30 milligrams per day; whereas efficacious doses of the Bayer compound, which is implitapide, were 160 milligrams per day, so very, very different doses of these two drugs.

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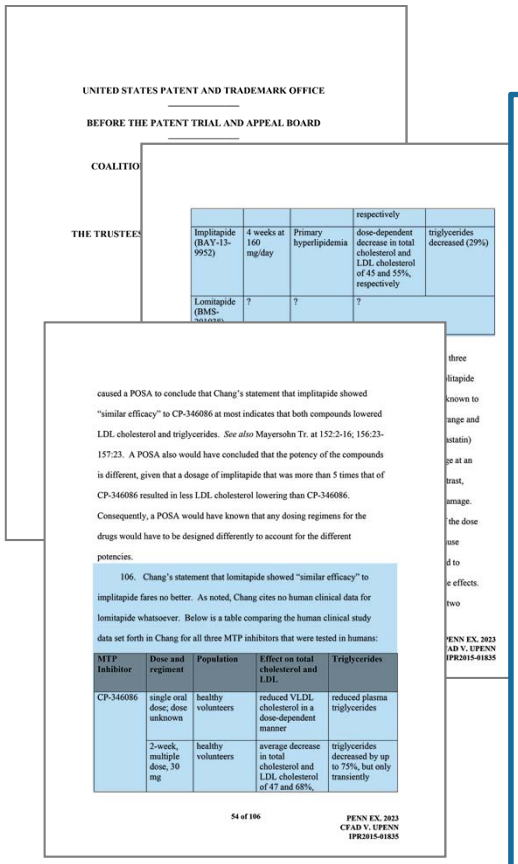
". . . he points out in this review article that efficacious doses of the Pfizer compound were in the order of 30 milligrams per day; whereas efficacious doses of the Bayer compound, which is implitapide, were 160 milligrams per day, so very, very different doses of these two drugs.

So without understanding something about the doses that gave rise to a target efficacy, it's very, very hard to -- impossible actually, to design any rational clinical trial with lomitapide where there is no information on the doses that were giving rise to a pharmacological effect."

Source: Ex. 1048 [1056], Baillie Tr., 46:19-47:7; POR at 12-13

Dr. Sacks: Chang's Disclosures Regarding Lomitapide are Limited



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			respectively	
Implitapide (BAY-13-9952)	4 weeks at 160 mg/day	Primary hyperlipidemia	dose-dependent decrease in total cholesterol and LDL cholesterol of 45 and 55%, respectively	triglycerides decreased (29%)
Lomitapide (BMS-	?	?	?	

caused a POSA to conclude that Chang's statement that implitapide showed "similar efficacy" to CP-346086 at most indicates that both compounds lowered LDL cholesterol and triglycerides. *See also* Mayersohn Tr. at 152:2-16; 156:23-157:23. A POSA also would have concluded that the potency of the compounds is different, given that a dosage of implitapide that was more than 5 times that of CP-346086 resulted in less LDL cholesterol lowering than CP-346086. Consequently, a POSA would have known that any dosing regimens for the drugs would have to be designed differently to account for the different potencies.

106. Chang's statement that lomitapide showed "similar efficacy" to implitapide fares no better. As noted, Chang cites no human clinical data for lomitapide whatsoever. Below is a table comparing the human clinical study data set forth in Chang for all three MTP inhibitors that were tested in humans:

MTP Inhibitor	Dose and regiment	Population	Effect on total cholesterol and LDL	Triglycerides
CP-346086	single oral dose; dose unknown	healthy volunteers	reduced VLDL cholesterol in a dose-dependent manner	reduced plasma triglycerides
	2-week, multiple dose, 30 mg	healthy volunteers	average decrease in total cholesterol and LDL cholesterol of 47 and 68%,	triglycerides decreased by up to 75%, but only transiently

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MTP Inhibitor	Dose and Regimen	Population	Effect on total cholesterol and LDL	Triglycerides
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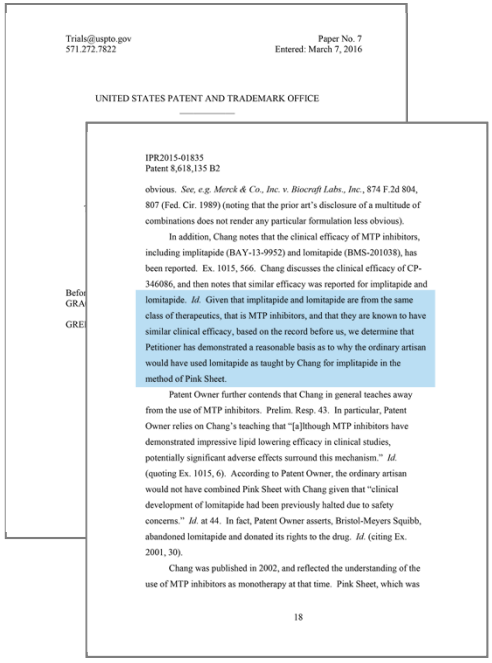
	2-week, multiple dose, 30 mg	healthy volunteers	average decrease in total cholesterol and LDL cholesterol of 47 and 68%, respectively	triglycerides decreased by up to 75%, but only transiently
Implitapide (BAY-13-9952)	4 weeks at 160 mg/day	Primary hyperlipidemia	dose-dependent decrease in total cholesterol and LDL cholesterol of 45 and 55%, respectively	triglycerides decreased (29%)
Lomitapide (BMS-201038)	?	?	?	

Source: Ex. 2023, Sack Decl., ¶ 106; POR at 12-13, 29-33

The Board's Institution Decision Was Based on an Incomplete Record Regarding Dosing of Drugs in the Same Therapeutic Class



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Paper No. 7
Entered: March 7, 2016

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

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

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

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

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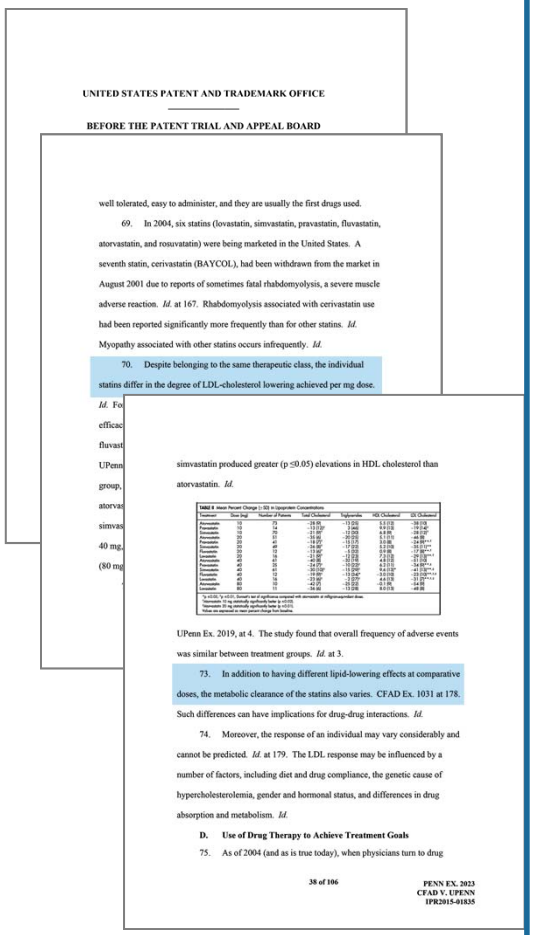
"Given that implitapide and lomitapide are from the same class of therapeutics, that is MTP inhibitors, and that they are known to have similar clinical efficacy, based on the record before us, we determine that Petitioner has demonstrated a reasonable basis as to why the ordinary artisan would have used lomitapide as taught by Chang for implitapide in the method of Pink Sheet."

Source: Institution Decision at 18

Therapeutic Class Does Not Determine Dosing Regimen



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well tolerated, easy to administer, and they are usually the first drugs used.

69. In 2004, six statins (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin) were being marketed in the United States. A seventh statin, cerivastatin (BAYCOL), had been withdrawn from the market in August 2001 due to reports of sometimes fatal rhabdomyolysis, a severe muscle adverse reaction. *Id.* at 167. Rhabdomyolysis associated with cerivastatin use had been reported significantly more frequently than for other statins. *Id.* Myopathy associated with other statins occurs infrequently. *Id.*

70. Despite belonging to the same therapeutic class, the individual statins differ in the degree of LDL-cholesterol lowering achieved per mg dose.

simvastatin produced greater ($p \leq 0.05$) elevations in HDL cholesterol than atorvastatin. *Id.*

UPenn Ex. 2019, at 4. The study found that overall frequency of adverse events was similar between treatment groups. *Id.* at 3.

73. In addition to having different lipid-lowering effects at comparative doses, the metabolic clearance of the statins also varies. CFAD Ex. 1031 at 178. Such differences can have implications for drug-drug interactions. *Id.*

74. Moreover, the response of an individual may vary considerably and cannot be predicted. *Id.* at 179. The LDL response may be influenced by a number of factors, including diet and drug compliance, the genetic cause of hypercholesterolemia, gender and hormonal status, and differences in drug absorption and metabolism. *Id.*

D. Use of Drug Therapy to Achieve Treatment Goals

75. As of 2004 (and as is true today), when physicians turn to drug

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"Despite belonging to the same therapeutic class, the individual statins differ in the degree of LDL-cholesterol lowering achieved per mg dose."

* * *

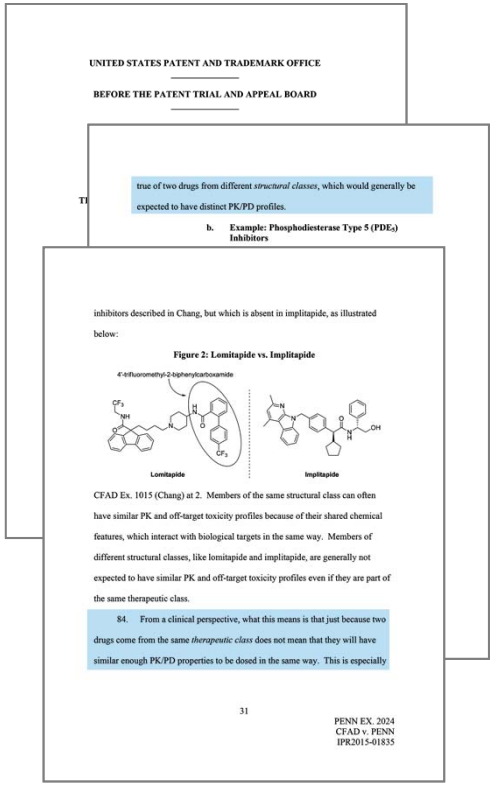
". . . individual drugs in the same class (whether statins or MTP inhibitors) will have a unique profile, including that they differ in potency, time of day when they must be taken, their dosage range, their lipophilicity/hydrophobicity (which affects the side effect profile) and their compatibility with other drugs."

* * *

". . . a dose range for a member of a class of drugs and its toxicity profile cannot be used directly for another member of the same class; dose ranges and toxicity profiles can differ substantially and critically."

Source: Ex. 2023, Sacks Decl., ¶¶ 70, 73, 96-97; POR at 17, 42

Members of the Same Therapeutic Class Do Not Necessarily Have the Same PK/PD Properties



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true of two drugs from different *structural classes*, which would generally be expected to have distinct PK/PD profiles.

b. Example: Phosphodiesterase Type 5 (PDE_5) Inhibitors

inhibitors described in Chang, but which is absent in implitapide, as illustrated below:

Figure 2: Lomitapide vs. Implitapide

4'-trifluoromethyl-2-biphenylcarboxamide

Lomitapide Implitapide

CFAD Ex. 1015 (Chang) at 2. Members of the same structural class can often have similar PK and off-target toxicity profiles because of their shared chemical features, which interact with biological targets in the same way. Members of different structural classes, like lomitapide and implitapide, are generally not expected to have similar PK and off-target toxicity profiles even if they are part of the same therapeutic class.

84. From a clinical perspective, what this means is that just because two drugs come from the same *therapeutic class* does not mean that they will have similar enough PK/PD properties to be dosed in the same way. This is especially

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"From a clinical perspective, what this means is that just because two drugs come from the same *therapeutic class* does not mean that they will have similar enough PK/PD properties to be dosed in the same way. This is especially true of two drugs from different *structural classes*, which would generally be expected to have distinct PK/PD profiles."

Source: Ex. 2024, Baillie Decl., ¶ 84; POR at 17, 42

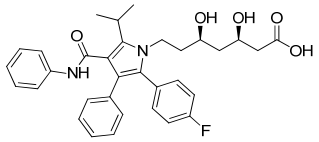
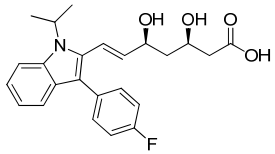
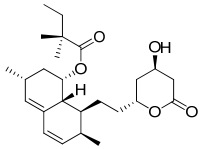
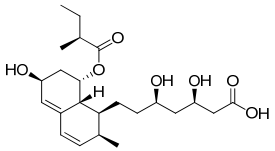
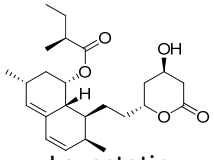
Dr. Baillie: Each Drug In a Therapeutic Class Has To Be Evaluated on Its Own Merits

Q. I guess my point is today we've talked a lot about developing a dosing regimen, and I'm trying to understand what the role is of drugs in the same therapeutic class in determining that dosing regimen.

A. Well, I would argue that there is very little influence of dosing regimens in other members of a therapeutic class. As I mentioned earlier, every compound has to be considered on its own merits. Every individual molecule will have its own PK properties. Every individual molecule will have its own pharmacodynamic properties. And since the PK/PD profile really is the primary determinant of clinical dose, you can't assume that you can translate PK/PD relationships for one molecule in the same therapeutic class to another.

Source: Ex. 1048 [1056], Baillie Tr., 47:10-48:2; POR at 38-44

Drugs in the Same Therapeutic Class Often Do Not Have the Same Potency – Statins

Drug	LDL Reduction		
	10 mg	20 mg	40 mg
 Atorvastatin	38%	46%	51%
 Fluvastatin	n/d	17%	23%
 Simvastatin	28%	35%	41%
 Pravastatin	19%	24%	34%
 Lovastatin	n/d	29%	31%

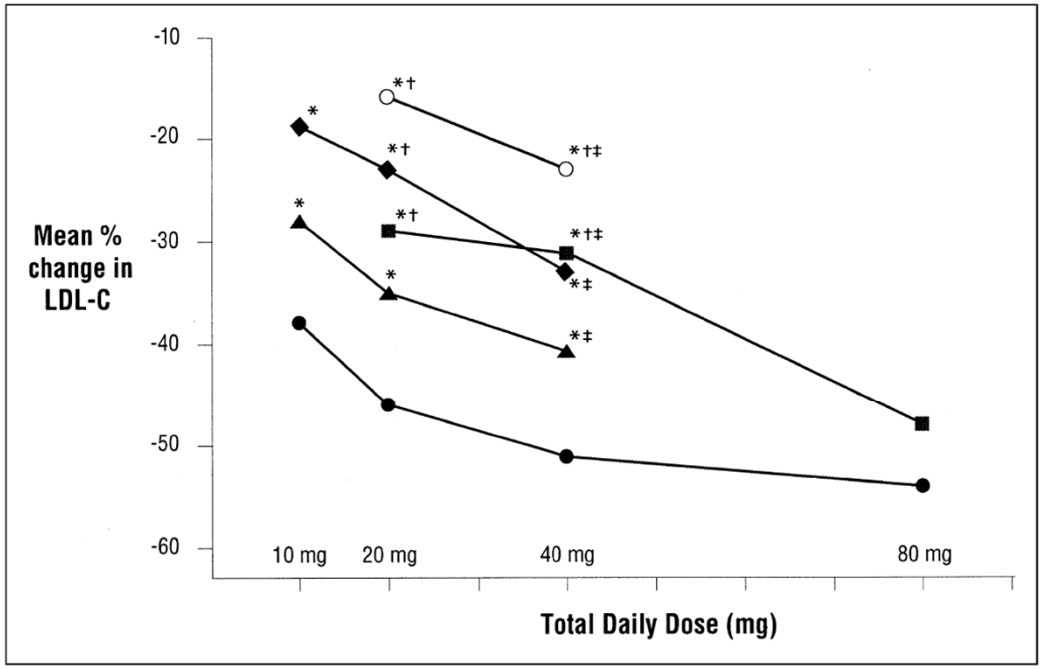
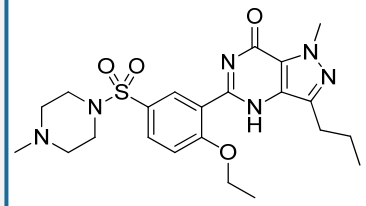
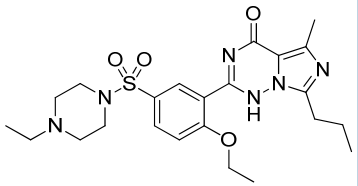
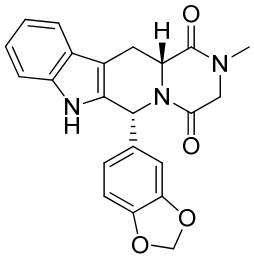
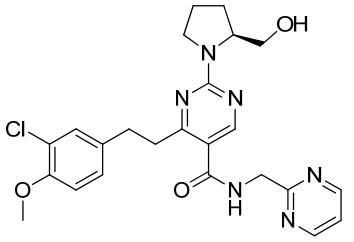


FIGURE 1. Percent reduction in low-density lipoprotein cholesterol (LDL-C) after 8 weeks of treatment with atorvastatin (●), simvastatin (▲), pravastatin (◆), lovastatin (■), and fluvastatin (○). *p ≤0.01 versus atorvastatin at mg equivalent doses; †p ≤0.02 versus atorvastin 10 mg; ‡p ≤ versus atorvastin 20 mg.

Source: Ex. 2019, Jones, at 3-4; Ex. 2023, Sacks Decl., at ¶¶ 70-74; Ex. 2025, Kimball Decl., at ¶¶ 78-80; POR at 17

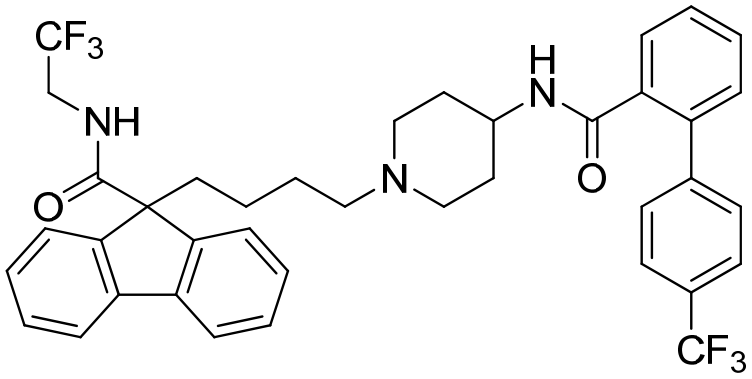
Drugs in the Same Therapeutic Class Often Do Not Have Interchangeable Dosing Regimens – PDE_5 Inhibitors

Figure 4: PK/PD Properties of PDE_5 Inhibitors

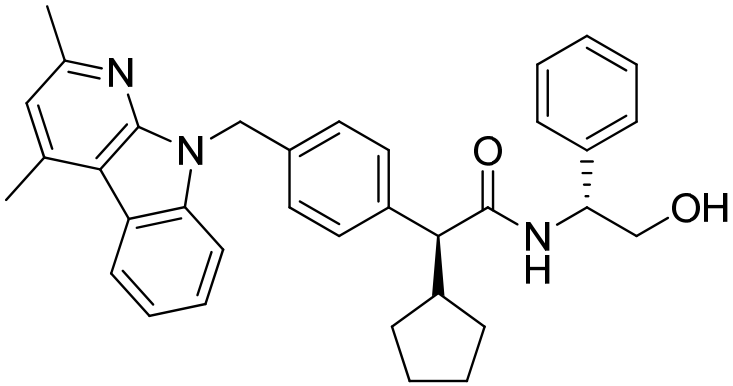
Drug	Viagra® (Sildenafil)	Levitra® (Vardenafil)	Cialis® (Tadalafil)	Stendra® (Avanafil)
Structure				
Biological half-life ($T_{1/2}$)	4 hrs	4–5 hrs	17.5 hrs	5 hrs
Absorption Time (T_{max})	0.5–2.0 hrs	0.5–2.0 hrs	0.5–6.0 hrs	0.50–0.75 hrs
Off-Target PDE Inhibition	PDE_1, PDE_6	PDE_1, PDE_6	PDE_{11}	n/a
Common Side Effects	Headache, flushing, nasal congestion, nasal pharyngitis, visual abnormalities	Headache, flushing, nasal congestion, nasal pharyngitis, visual abnormalities	Headache, flushing, nasal congestion, nasal pharyngitis, back pain, myalgia	Headache, flushing, nasal congestion, nasal pharyngitis
Dosing Frequency	As needed	As needed	Daily OR as needed	As needed

Source: Ex. 2024, Baillie Decl., at ¶¶ 85-90; POR at 42

Lomitapide and Implitapide Have Different Chemical Structures



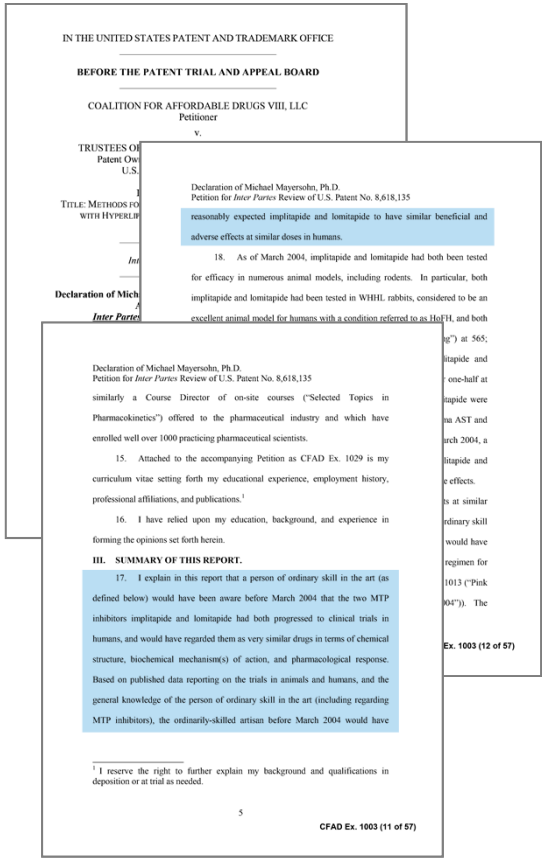
Lomitapide



Implitapide

Source: Ex. 2024 (Baillie Decl.) at ¶¶ 99-100; Ex. 2025 (Kimball Decl.) at ¶¶ 101-03; POR at 42-44

Petitioner's Expert Characterized Lomitapide and Implitapide As "Very Similar Drugs in Terms of Chemical Structure . . ."



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VIII, LLC
Petitioner
v.

Declaration of Michael Mayersohn, Ph.D.
Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135

reasonably expected implitapide and lomitapide to have similar beneficial and adverse effects at similar doses in humans.

18. As of March 2004, implitapide and lomitapide had both been tested for efficacy in numerous animal models, including rodents. In particular, both implitapide and lomitapide had been tested in WHHL rabbits, considered to be an excellent animal model for humans with a condition referred to as HoFH, and both

Ex. 1003 (12 of 57)

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similarly a Course Director of on-site courses ("Selected Topics in Pharmacokinetics") offered to the pharmaceutical industry and which have enrolled well over 1000 practicing pharmaceutical scientists.

15. Attached to the accompanying Petition as CFAD Ex. 1029 is my curriculum vitae setting forth my educational experience, employment history, professional affiliations, and publications.[1]

16. I have relied upon my education, background, and experience in forming the opinions set forth herein.

III. SUMMARY OF THIS REPORT.

17. I explain in this report that a person of ordinary skill in the art (as defined below) would have been aware before March 2004 that the two MTP inhibitors implitapide and lomitapide had both progressed to clinical trials in humans, and would have regarded them as very similar drugs in terms of chemical structure, biochemical mechanism(s) of action, and pharmacological response. Based on published data reporting on the trials in animals and humans, and the general knowledge of the person of ordinary skill in the art (including regarding MTP inhibitors), the ordinarily-skilled artisan before March 2004 would have

[1] I reserve the right to further explain my background and qualifications in deposition or at trial as needed.

5

CFAD Ex. 1003 (11 of 57)

"I explain in this report that a person of ordinary skill in the art (as defined below) would have been aware before March 2004 that the two MTP inhibitors implitapide and lomitapide had both progressed to clinical trials in humans, and would have regarded them as very similar drugs in terms of chemical structure, biochemical mechanism(s) of action, and pharmacological response."

Source: Ex. 1003 (Mayersohn Decl.) at ¶ 17

Dr. Mayersohn Lacks Expertise to Evaluate Chemical Structures

Q. So in forming your opinions, did you compare the chemical structure of lomitapide and implitapide?

A. No. I'm not a medicinal chemist. I don't have the ability to do that.

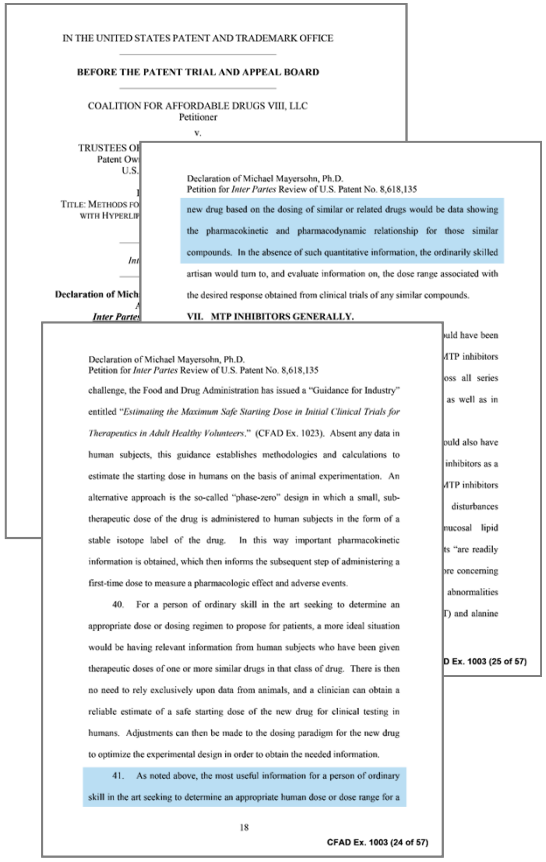
* * *

Q. What about these two structures is very similar?

A. They've got a lot of rings, a bunch of nitrogens. They're highly saturated. But beyond that, I can't comment.

Source: Ex. 2021, Mayersohn Tr., 74:15-19, 78:10-14; POR at 43

Dr. Mayersohn: PK/PD Data Is the Most Useful Information to a POSA in Designing a Dosing Regimen



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VIII, LLC
Petitioner
v.

Declaration of Michael Mayersohn, Ph.D.
Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135

new drug based on the dosing of similar or related drugs would be data showing the pharmacokinetic and pharmacodynamic relationship for those similar compounds. In the absence of such quantitative information, the ordinarily skilled artisan would turn to, and evaluate information on, the dose range associated with the desired response obtained from clinical trials of any similar compounds.

VII. MTP INHIBITORS GENERALLY.

CFAD Ex. 1003 (25 of 57)

Declaration of Michael Mayersohn, Ph.D.
Petition for *Inter Partes* Review of U.S. Patent No. 8,618,135

challenge, the Food and Drug Administration has issued a "Guidance for Industry" entitled "*Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*." (CFAD Ex. 1023). Absent any data in human subjects, this guidance establishes methodologies and calculations to estimate the starting dose in humans on the basis of animal experimentation. An alternative approach is the so-called "phase-zero" design in which a small, sub-therapeutic dose of the drug is administered to human subjects in the form of a stable isotope label of the drug. In this way important pharmacokinetic information is obtained, which then informs the subsequent step of administering a first-time dose to measure a pharmacologic effect and adverse events.

40. For a person of ordinary skill in the art seeking to determine an appropriate dose or dosing regimen to propose for patients, a more ideal situation would be having relevant information from human subjects who have been given therapeutic doses of one or more similar drugs in that class of drug. There is then no need to rely exclusively upon data from animals, and a clinician can obtain a reliable estimate of a safe starting dose of the new drug for clinical testing in humans. Adjustments can then be made to the dosing paradigm for the new drug to optimize the experimental design in order to obtain the needed information.

41. As noted above, the most useful information for a person of ordinary skill in the art seeking to determine an appropriate human dose or dose range for a

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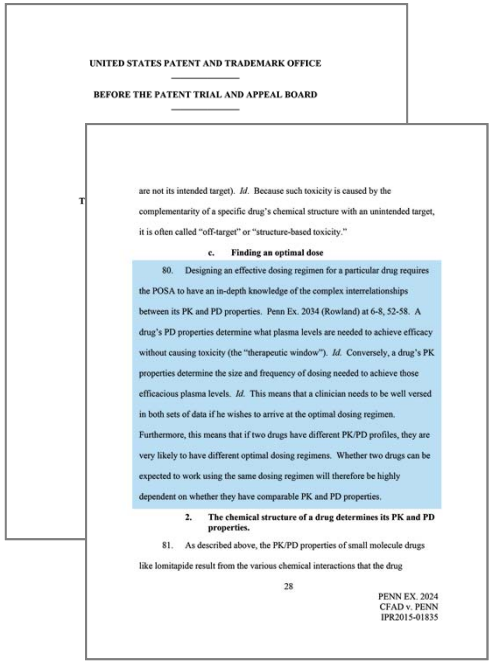
CFAD Ex. 1003 (24 of 57)

"As noted above, the most useful information for a person of ordinary skill in the art seeking to determine an appropriate human dose or dose range for a new drug based on the dosing of similar or related drugs would be data showing the pharmacokinetic and pharmacodynamic relationship for those similar compounds."

Source: Ex. 1003, Mayersohn Decl., ¶ 41; POR at 16, 41

Dr. Baillie: Designing a Dosing Regimen Requires Knowledge of a Drug's PK and PD Properties



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

are not its intended target). *Id.* Because such toxicity is caused by the complementarity of a specific drug's chemical structure with an unintended target, it is often called "off-target" or "structure-based toxicity."

c. Finding an optimal dose

80. Designing an effective dosing regimen for a particular drug requires the POSA to have an in-depth knowledge of the complex interrelationships between its PK and PD properties. Penn Ex. 2034 (Rowland) at 6-8, 52-58. A drug's PD properties determine what plasma levels are needed to achieve efficacy without causing toxicity (the "therapeutic window"). *Id.* Conversely, a drug's PK properties determine the size and frequency of dosing needed to achieve those efficacious plasma levels. *Id.* This means that a clinician needs to be well versed in both sets of data if he wishes to arrive at the optimal dosing regimen. Furthermore, this means that if two drugs have different PK/PD profiles, they are very likely to have different optimal dosing regimens. Whether two drugs can be expected to work using the same dosing regimen will therefore be highly dependent on whether they have comparable PK and PD properties.

2. The chemical structure of a drug determines its PK and PD properties.

81. As described above, the PK/PD properties of small molecule drugs like lomitapide result from the various chemical interactions that the drug

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"Designing an effective dosing regimen for a particular drug requires the POSA to have an in-depth knowledge of the complex interrelationships between its PK and PD properties. . . . Whether two drugs can be expected to work using the same dosing regimen will therefore be highly dependent on whether they have comparable PK and PD properties."

Source: Ex. 2024, Baillie Decl., ¶ 80; POR at 15-16

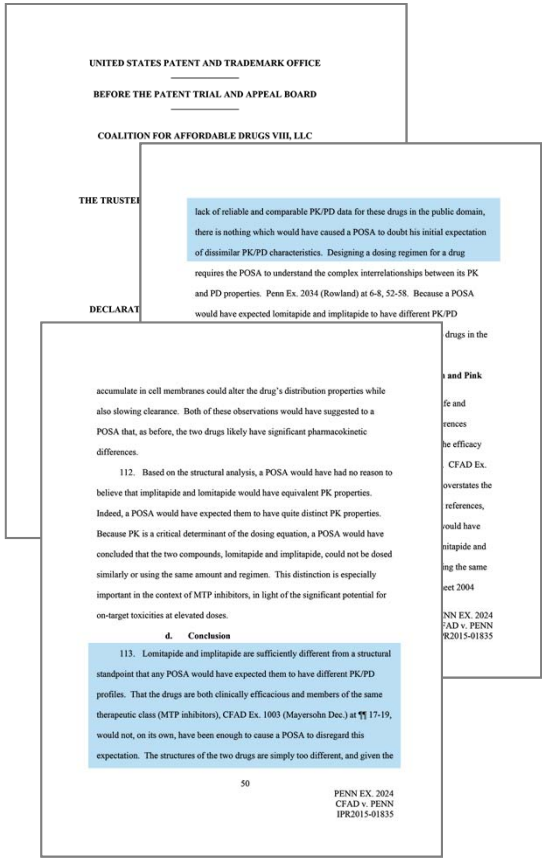
Dr. Zusman: The Prior Art Provides No PK/PD Data for Lomitapide

Q. . . . . Dr. Zusman, the prior art that you're aware of provides no PK or PD data for lomitapide, correct?

A. Not that I'm personally aware of today.

Source: Ex. 2022, Zusman Tr., 175:10-13; POR at 41

Dr. Baillie: The Structural Differences Between Lomitapide and Implitapide Suggest Different PK/PD Properties



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VIII, LLC

THE TRUSTEE

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lack of reliable and comparable PK/PD data for these drugs in the public domain, there is nothing which would have caused a POSA to doubt his initial expectation of dissimilar PK/PD characteristics. Designing a dosing regimen for a drug requires the POSA to understand the complex interrelationships between its PK and PD properties. Penn Ex. 2034 (Rowland) at 6-8, 52-58. Because a POSA would have expected lomitapide and implitapide to have different PK/PD

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accumulate in cell membranes could alter the drug's distribution properties while also slowing clearance. Both of these observations would have suggested to a POSA that, as before, the two drugs likely have significant pharmacokinetic differences.

112. Based on the structural analysis, a POSA would have had no reason to believe that implitapide and lomitapide would have equivalent PK properties. Indeed, a POSA would have expected them to have quite distinct PK properties. Because PK is a critical determinant of the dosing equation, a POSA would have concluded that the two compounds, lomitapide and implitapide, could not be dosed similarly or using the same amount and regimen. This distinction is especially important in the context of MTP inhibitors, in light of the significant potential for on-target toxicities at elevated doses.

d. Conclusion

113. Lomitapide and implitapide are sufficiently different from a structural standpoint that any POSA would have expected them to have different PK/PD profiles. That the drugs are both clinically efficacious and members of the same therapeutic class (MTP inhibitors), CFAD Ex. 1003 (Mayersohn Dec.) at ¶¶ 17-19, would not, on its own, have been enough to cause a POSA to disregard this expectation. The structures of the two drugs are simply too different, and given the

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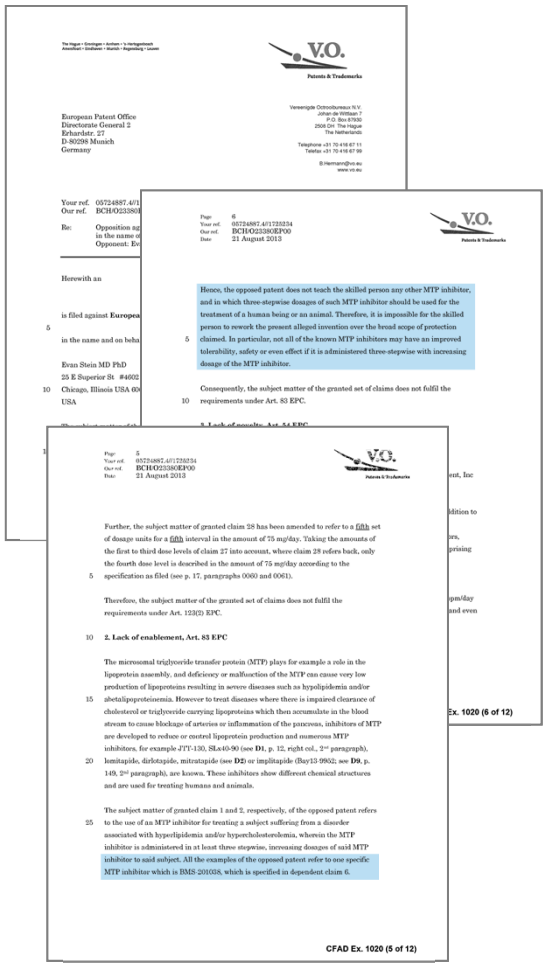
NN EX. 2024
FAD v. PENN
R2015-01835

"Lomitapide and implitapide are sufficiently different from a structural standpoint that any POSA would have expected them to have different PK/PD profiles. . . . given the lack of reliable and comparable PK/PD data for these drugs in the public domain, there is nothing which would have caused a POSA to doubt his initial expectation of dissimilar PK/PD characteristics."

Source: Ex. 2024, Baillie Decl., ¶¶ 113; POR at 44

Dr. Evan Stein: MTP Inhibitors Do Not Necessarily Have Interchangeable Dosing Regimens



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

Consequently, the subject matter of the granted set of claims does not fulfil the requirements under Art. 83 EPC.

Further, the subject matter of granted claim 28 has been amended to refer to a fifth set of dosage units for a fifth interval in the amount of 75 mg/day. Taking the amounts of the first to third dose levels of claim 27 into account, where claim 28 refers back, only the fourth dose level is described in the amount of 75 mg/day according to the specification as filed (see p. 17, paragraphs 0060 and 0061).

Therefore, the subject matter of the granted set of claims does not fulfil the requirements under Art. 123(2) EPC.

2. Lack of enablement, Art. 83 EPC

The microsomal triglyceride transfer protein (MTP) plays for example a role in the lipoprotein assembly, and deficiency or malfunction of the MTP can cause very low production of lipoproteins resulting in severe diseases such as hypolipidemia and/or abetalipoproteinemia. However to treat diseases where there is impaired clearance of cholesterol or triglyceride carrying lipoproteins which then accumulate in the blood stream to cause blockage of arteries or inflammation of the pancreas, inhibitors of MTP are developed to reduce or control lipoprotein production and numerous MTP inhibitors, for example JTT-130, SLx40-90 (see **D1**, p. 12, right col., 2nd paragraph), lomitapide, dirlotapide, mitratapide (see **D2**) or implitapide (Bay13-9952; see **D9**, p. 149, 2nd paragraph), are known. These inhibitors show different chemical structures and are used for treating humans and animals.

The subject matter of granted claim 1 and 2, respectively, of the opposed patent refers to the use of an MTP inhibitor for treating a subject suffering from a disorder associated with hyperlipidemia and/or hypercholesterolemia, wherein the MTP inhibitor is administered in at least three stepwise, increasing dosages of said MTP inhibitor to said subject. All the examples of the opposed patent refer to one specific MTP inhibitor which is BMS-201038, which is specified in dependent claim 6.

CFAD Ex. 1020 (5 of 12)

"All the examples of the opposed patent refer to one specific MTP inhibitor which is BMS-201038, which is specified in dependent claim 6. Hence, the opposed patent does not teach the skilled person any other MTP inhibitor, and in which three-stepwise dosages of such MTP inhibitor should be used for the treatment of a human being or an animal. Therefore, it is impossible for the skilled person to rework the present alleged invention over the broad scope of protection claimed. In particular, not all of the known MTP inhibitors may have an improved tolerability, safety or even effect if it is administered three-stepwise with increasing dosage of the MTP inhibitor."

Source: Ex. 1020, Stein Opposition, pp. 5-6; POPR at 45-46 [43-44]; POR at 43-44

A POSA Would Not Substitute One Drug for Another In the Same Dosing Regimen Without Supporting Data

Dr. Baillie:

Q. Okay. So if you -- if a POSA had substituted lomitapide for implitapide in Stein's protocol, would the aforementioned biological adaptation occur?

A. Well, I mean, I think that's – that's very speculative because a POSA would never have thought about doing such a thing. I mean, why would you take a protocol for one molecule and think that a different molecule, that that same protocol would be appropriate? I think that it is scientifically inappropriate to do such a thing in the absence of the necessary data that we discussed this morning.

Source: Ex. 1048 [1056], Baillie Tr., 100:21-101:10; POR at 41-42

A POSA Would Not Substitute One Drug for Another In the Same Dosing Regimen Without Supporting Data

Dr. Kimball:

Q. "In the case of two drugs with very different chemical structures, for example, lomitapide and implitapide, a POSA would not have been confident in dosing them using the same regimen because he would expect the two drugs to have very different pharmacokinetic properties." Do you see that?

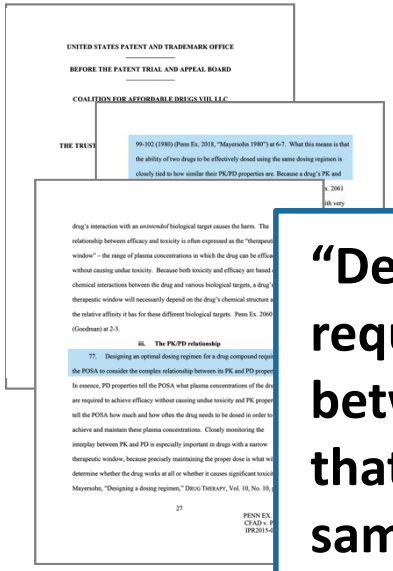
A. I do.

Q. You don't cite to any article there. Is that just general knowledge?

A. That's general knowledge and the fact that I never heard of an example where you could cut and paste protocol from one drug onto another in clinical trials. It's too much at risk.

Source: Ex. 1056 [1052], Kimball Tr., 137:17-138:8; POR at 41-42

Dr. Kimball: Designing a Dosing Regimen Requires Knowledge of a Drug's PK and PD Properties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BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VIII, LLC

THE TRUST

99-102 (1980) (Penn Ex. 2018, "Mayersohn 1980") at 6-7. What this means is that the ability of two drugs to be effectively dosed using the same dosing regimen is closely tied to how similar their PK/PD properties are. Because a drug's PK and

drug's interaction with an *unintended* biological target causes the harm. The relationship between efficacy and toxicity is often expressed as the "therapeu window" – the range of plasma concentrations in which the drug can be effic without causing undue toxicity. Because both toxicity and efficacy are based chemical interactions between the drug and various biological targets, a drug's therapeutic window will necessarily depend on the drug's chemical structure the relative affinity it has for these different biological targets. Penn Ex. 2060 (Goodman) at 2-3.

iii. The PK/PD relationship

77. Designing an optimal dosing regimen for a drug compound requi the POSA to consider the complex relationship between its PK and PD proper In essence, PD properties tell the POSA what plasma concentrations of the dru are required to achieve efficacy without causing undue toxicity and PK proper tell the POSA how much and how often the drug needs to be dosed in order to achieve and maintain these plasma concentrations. Closely monitoring the interplay between PK and PD is especially important in drugs with a narrow therapeutic window, because precisely maintaining the proper dose is what wi determine whether the drug works at all or whether it causes significant toxici Mayersohn, "Designing a dosing regimen," DRUG THERAPY, Vol. 10, No. 10,

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"Designing an optimal dosing regimen for a drug compound requires the POSA to consider the complex relationship between its PK and PD properties. . . . What this means is that the ability of two drugs to be effectively dosed using the same dosing regimen is closely tied to how similar their PK/PD properties are."

Ex. 2025, Kimball Decl., ¶ 77; POR at 15-16

A Drug's Chemical Structure Determines Its PK/PD Properties

"As described above, the PK/PD properties of small molecule drugs like lomitapide result from the various chemical interactions that the drug undergoes within the human body . . . In the end, the strength of these chemical interactions (and therefore the strength of the resulting biological effects) depends on how compatible the drug's chemical structure is with that of the molecular entities with which it interacts. What this means is that the chemical structure of a drug will ultimately determine its biological properties (i.e. PK/PD profile), and that structural differences between drugs will translate to differences in biological performance.

Source: Ex. 2024 (Baillie Decl.) at ¶ 81; POR at 16, 42

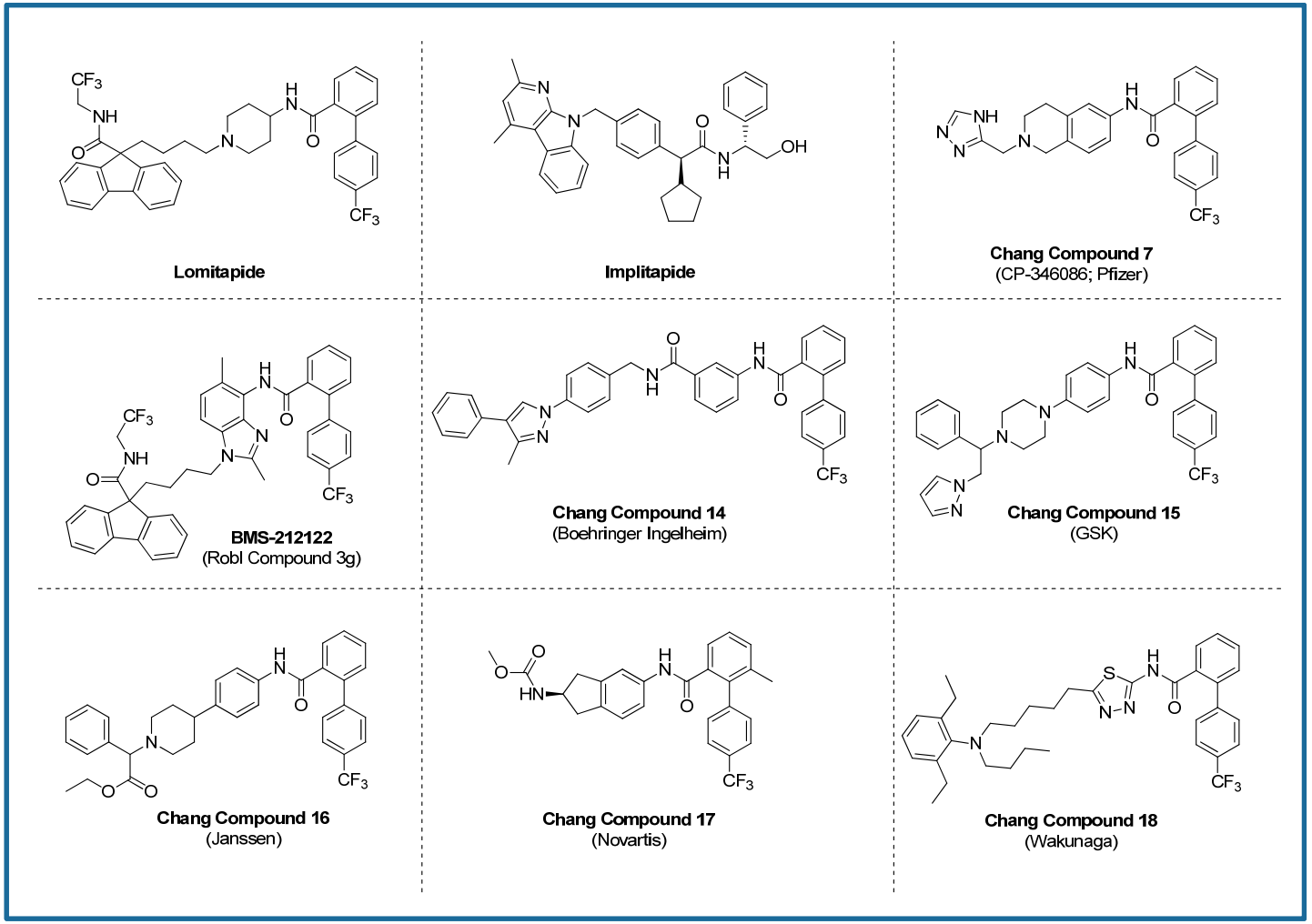
Dr. Baillie: A POSA Would Not Expect Lomitapide And Implitapide to Be Interchangeable

Q. Now, if a person of ordinary skill in the art was following Stein's regimen with lomitapide, wouldn't they start off with starting dose of 10 milligrams daily of lomitapide?

A. If they were to use the identical dosing protocol with lomitapide that Stein had proposed in this study for implitapide, that's correct. Although, I don't see what the rationale for picking the 10-milligram starting dose would be for a different drug.

Source: Ex. 1048 [1056], Baillie Tr., 96:9-18; POR at 41-42

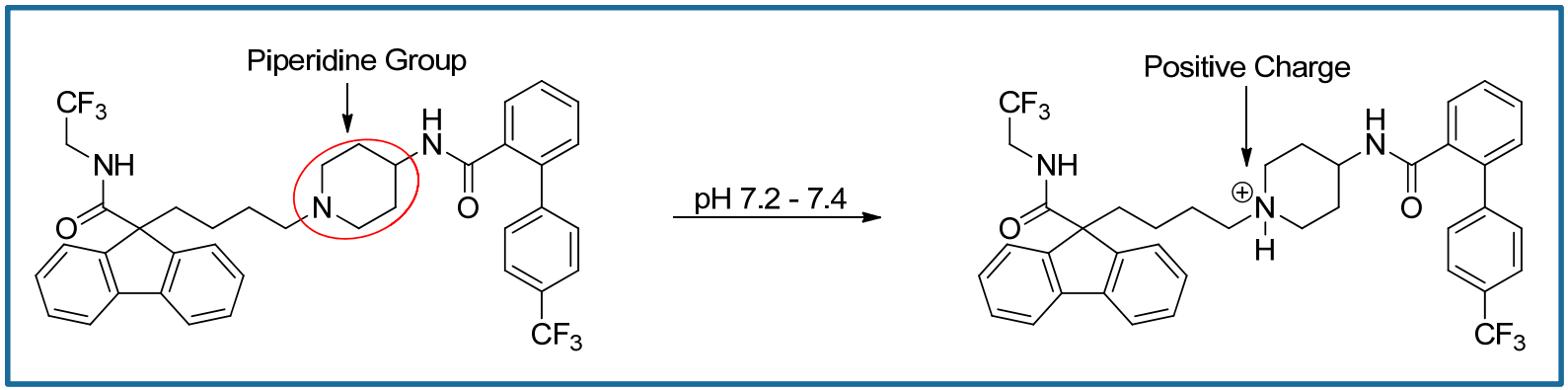
The Prior Art Disclosed a Large Number of MTP Inhibitors



Source: Ex. 2024 (Baillie Decl.) at ¶¶ 99-100, Ex. 2025 (Kimball Decl.) at ¶¶ 101-03; POR at 42-44

Lomitapide's Structure Suggests a Potential for Off-Target Toxicity

- **Lomitapide is a Cationic Amphiphilic Drug ("CAD"), it is both lipophilic and carries a positive charge at physiological pH**



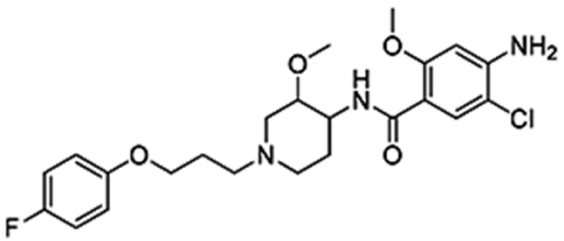
- **CADs are associated with several membrane-related toxicities such as phospholipidosis and hERG blockade**

Source: Ex. 2024 (Baillie Decl.) at ¶¶ 101-02, 107; Ex. 2025 (Kimball Decl.) at ¶¶ 85-93, 107-11, POR at 17-18

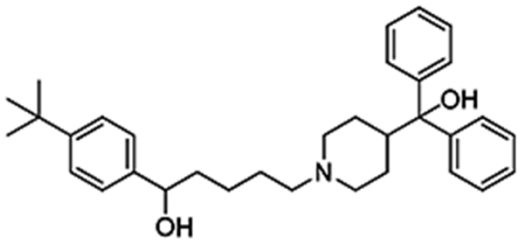
hERG Blockade Causes Potentially Fatal Arrythmias

". . . when hERG function is interrupted (*e.g.*, via drug binding), a patient's heart rate can become erratic and potentially fatal arrhythmias can occur."

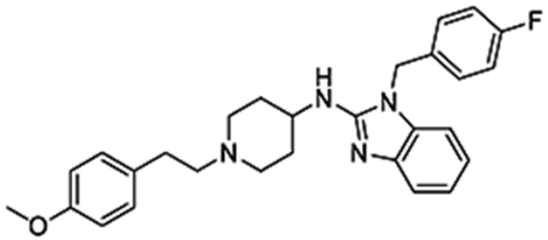
Drugs Withdrawn from Market Due to hERG Toxicity:



Cisapride
(PROPULSID, withdrawn 2000)



Terfenadine
(SELDANE, withdrawn 1997)

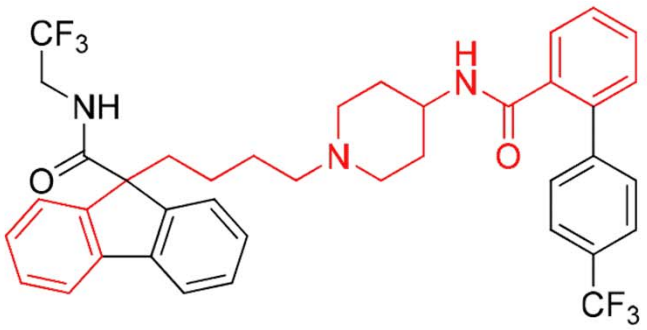


Astemizole
(HISMANAL, withdrawn 1999)

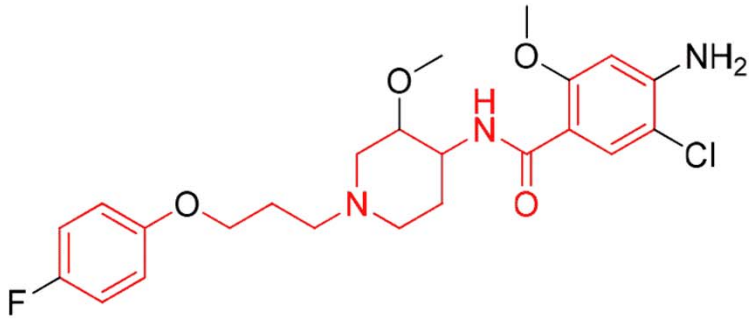
Source: Ex. 2025, Kimball Decl., ¶¶ 87-89; POR at 18

Lomitapide Shows Striking Similarity to Known hERG Channel Blockers

"The potential for hERG inhibition here is particularly concerning due both to the seriousness of the resulting side effect . . . and to the striking structural similarity between lomitapide and cisapride, a known hERG channel blocker:"



Lomitapide



Cisapride

Source: Ex. 2025, Kimball Decl., ¶ 117; POR at 29

Dr. Kimball: Lomitapide Was Developed Prior to the Widespread Understanding of hERG Toxicity

Q. Okay. Do you know or have any idea whether BMS was vigilant to identify whether lomitapide was a CAD or had a chemical structure which substantially overlapped with known hERG inhibitors?

A. I have no specific knowledge of that. It was prior to this understanding or would have likely been.

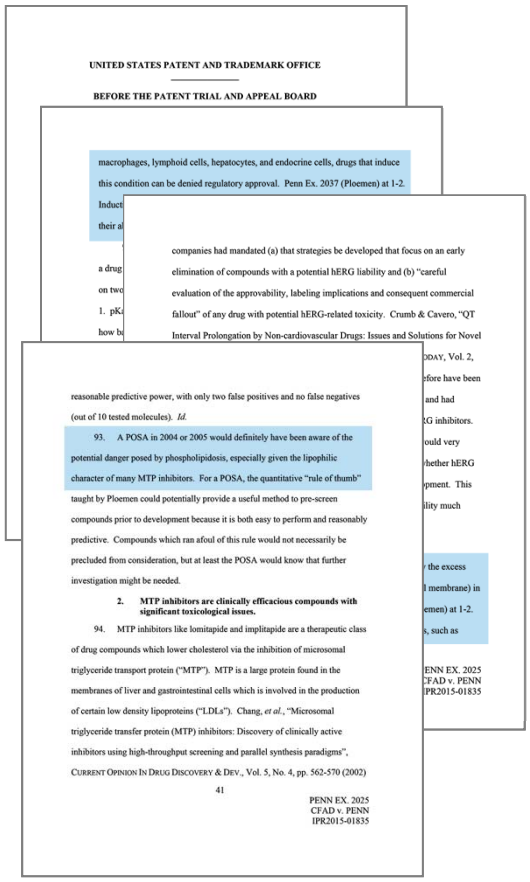
* * *

Q. Would it be surprising to you if BMS did not take those into consideration?

A. At the time that this drug was put into clinical development, the issue of hERG was not understood.

Source: Ex. 1056 [1052], Kimball Tr., 71:18-25, 72:8-14 (objection omitted); POR at 17-18

Phospholipidosis Is a Membrane-Related Toxicity Associated with CADs



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macrophages, lymphoid cells, hepatocytes, and endocrine cells, drugs that induce this condition can be denied regulatory approval. Penn Ex. 2037 (Ploemen) at 1-2.

companies had mandated (a) that strategies be developed that focus on an early elimination of compounds with a potential hERG liability and (b) "careful evaluation of the approvability, labeling implications and consequent commercial fallout" of any drug with potential hERG-related toxicity. Crumb & Cavero, "QT Interval Prolongation by Non-cardiovascular Drugs: Issues and Solutions for Novel

reasonable predictive power, with only two false positives and no false negatives (out of 10 tested molecules). *Id.*

93. A POSA in 2004 or 2005 would definitely have been aware of the potential danger posed by phospholipidosis, especially given the lipophilic character of many MTP inhibitors. For a POSA, the quantitative "rule of thumb" taught by Ploemen could potentially provide a useful method to pre-screen compounds prior to development because it is both easy to perform and reasonably predictive. Compounds which ran afoul of this rule would not necessarily be precluded from consideration, but at least the POSA would know that further investigation might be needed.

2. MTP inhibitors are clinically efficacious compounds with significant toxicological issues.

94. MTP inhibitors like lomitapide and implitapide are a therapeutic class of drug compounds which lower cholesterol via the inhibition of microsomal triglyceride transport protein ("MTP"). MTP is a large protein found in the membranes of liver and gastrointestinal cells which is involved in the production of certain low density lipoproteins ("LDLs"). Chang, *et al.*, "Microsomal triglyceride transfer protein (MTP) inhibitors: Discovery of clinically active inhibitors using high-throughput screening and parallel synthesis paradigms", CURRENT OPINION IN DRUG DISCOVERY & DEV., Vol. 5, No. 4, pp. 562-570 (2002)

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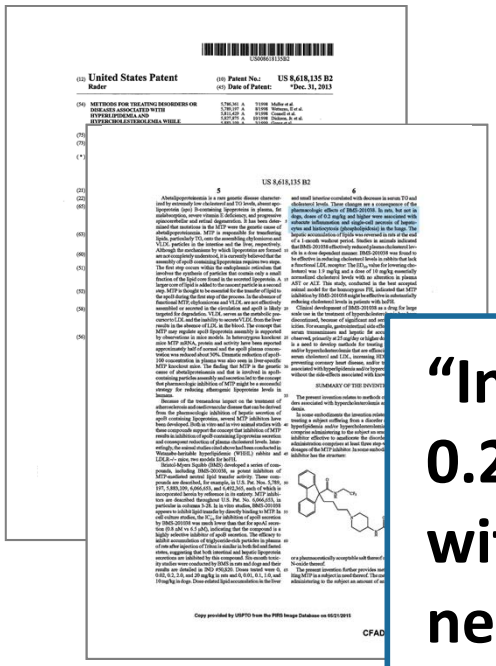
"Phospholipidosis is a type of cellular toxicity caused by the excess accumulation of phospholipids (which are normally found in the cell membrane) in a cell's lysosomes. . . . Induction of phospholipidosis is classically associated with CAD molecules due to their ability to accumulate within and thus disturb cell membranes."

"A POSA in 2004 or 2005 would definitely have been aware of the potential danger posed by phospholipidosis, especially given the lipophilic character of many MTP inhibitors."

Source: Ex. 2025, Kimball Decl., ¶¶ 91, 93; POR at 18

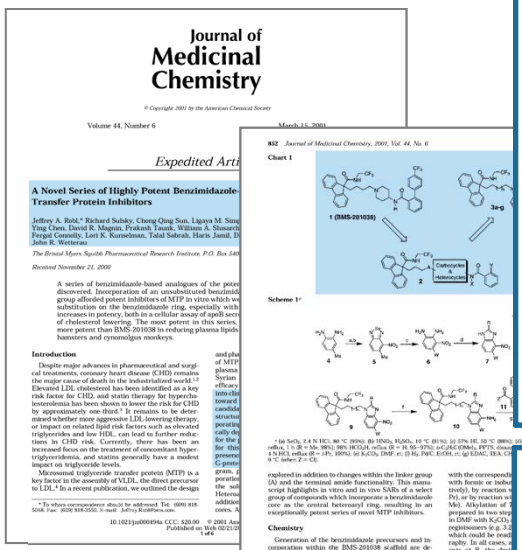
Lomitapide Caused Phospholipidosis in Rats



“In rats, but not in dogs, doses of 0.2 mg/kg and higher were associated with subacute inflammation and single-cell necrosis of hepatocytes and histiocytosis (phospholipidosis) in the lungs.”

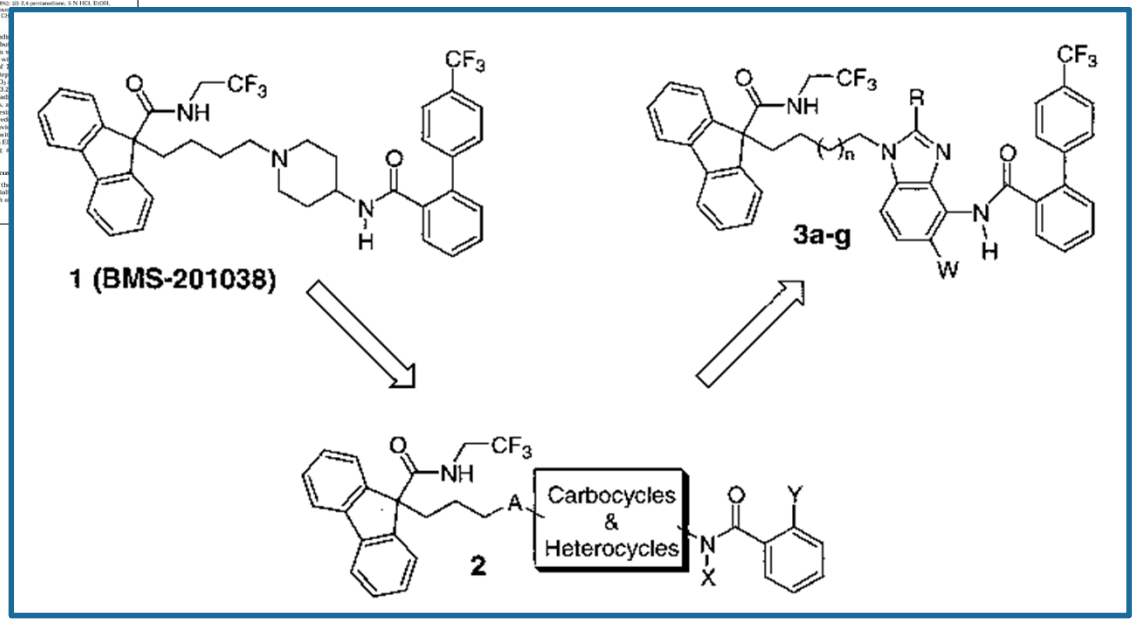
Source: Ex. 1001, (’135 Patent) at 6:3-6

BMS Modified Lomitapide's Structure to Create an Improved MTP Inhibitor


Journal of Medicinal Chemistry

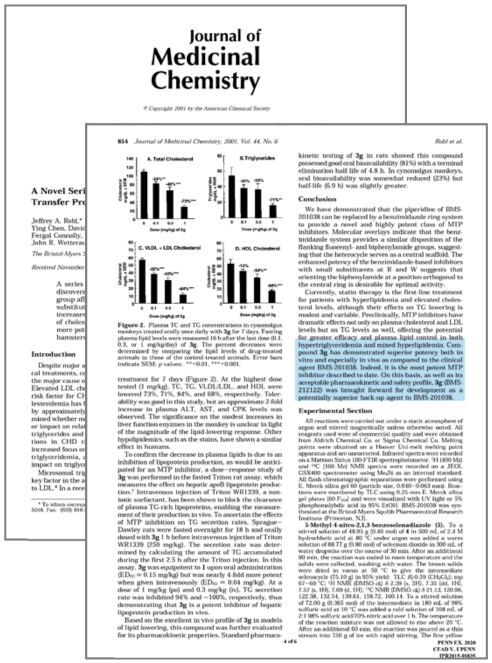
A Novel Series of Highly Potent Benzimidazole-Transfer Protein Inhibitors

"Our focus was subsequently directed toward the identification of a suitable back-up clinical candidate to BMS-201038. A substantial amount of structure-activity studies (SAR) were performed incorporating various carbocycles and heterocycles, generically depicted by structure 2 (Chart 1), as replacements for the piperidine ring in BMS-201038."



Source: Ex. 2020, Robl, pp. 1-2; POR at 30

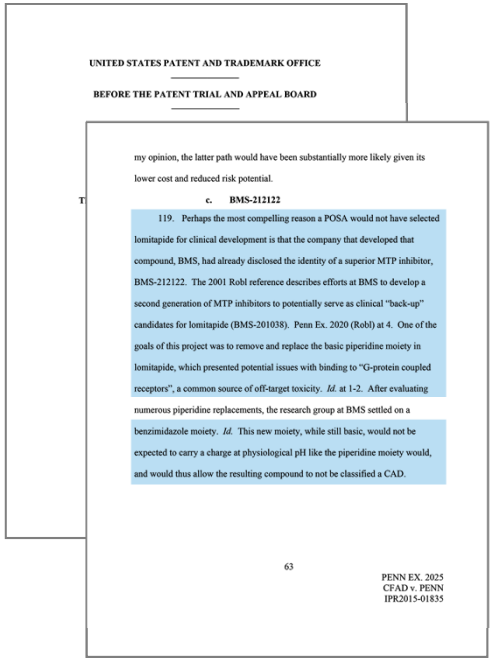
BMS' Modification of Lomitapide Produced A Potentially Superior MTP Inhibitor



"Compound 3g has demonstrated superior potency both in vitro and especially in vivo as compared to the clinical agent BMS-201038. Indeed, it is the most potent MTP inhibitor described to date. On this basis, as well as its acceptable pharmacokinetic and safety profile, 3g (BMS-212122) was brought forward for development as a potentially superior back-up agent to BMS-201038."

Source: Ex. 2020, Robl, p. 4; POR at 30

Dr. Kimball: BMS Modified Lomitapide to Avoid Off-Target Toxicity



UNITED STATES PATENT AND TRADEMARK OFFICE

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my opinion, the latter path would have been substantially more likely given its lower cost and reduced risk potential.

c. BMS-212122

119. Perhaps the most compelling reason a POSA would not have selected lomitapide for clinical development is that the company that developed that compound, BMS, had already disclosed the identity of a superior MTP inhibitor, BMS-212122. The 2001 Robl reference describes efforts at BMS to develop a second generation of MTP inhibitors to potentially serve as clinical "back-up" candidates for lomitapide (BMS-201038). Penn Ex. 2020 (Robl) at 4. One of the goals of this project was to remove and replace the basic piperidine moiety in lomitapide, which presented potential issues with binding to "G-protein coupled receptors", a common source of off-target toxicity. *Id.* at 1-2. After evaluating numerous piperidine replacements, the research group at BMS settled on a benzimidazole moiety. *Id.* This new moiety, while still basic, would not be expected to carry a charge at physiological pH like the piperidine moiety would, and would thus allow the resulting compound to not be classified a CAD.

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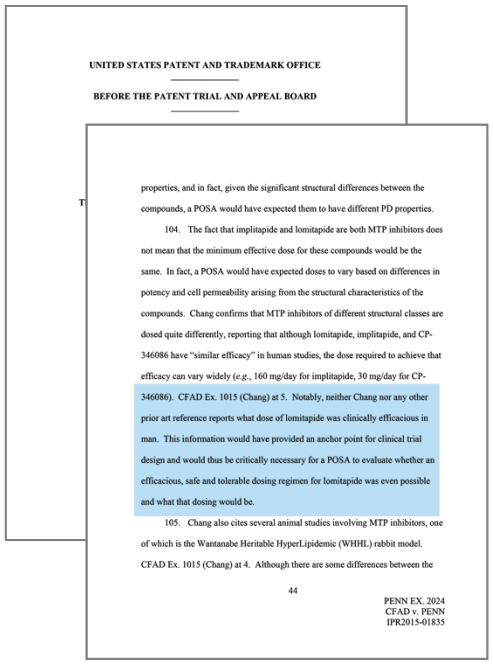
"Perhaps the most compelling reason a POSA would not have selected lomitapide for clinical development is that the company that developed that compound, BMS, had already disclosed the identity of a superior MTP inhibitor, BMS-212122."

"The 2001 Robl reference describes efforts at BMS to develop a second generation of MTP inhibitors to potentially serve as clinical 'back-up' candidates for lomitapide (BMS-201038). . . . One of the goals of this project was to remove and replace the basic piperidine moiety in lomitapide, which presented potential issues with binding to 'G-protein coupled Receptors,' a common source of off-target toxicity."

"This new moiety, while still basic, would not be expected to carry a charge at physiological pH like the piperidine moiety would, and would thus allow the resulting compound to not be classified a CAD."

Source: Ex. 2025, Kimball Decl., ¶ 119; POR at 30

The Prior Art Does Not Identify a Clinically Effective Dose for Lomitapide



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properties, and in fact, given the significant structural differences between the compounds, a POSA would have expected them to have different PD properties.

104. The fact that implitapide and lomitapide are both MTP inhibitors does not mean that the minimum effective dose for these compounds would be the same. In fact, a POSA would have expected doses to vary based on differences in potency and cell permeability arising from the structural characteristics of the compounds. Chang confirms that MTP inhibitors of different structural classes are dosed quite differently, reporting that although lomitapide, implitapide, and CP-346086 have "similar efficacy" in human studies, the dose required to achieve that efficacy can vary widely (*e.g.*, 160 mg/day for implitapide, 30 mg/day for CP-346086). CFAD Ex. 1015 (Chang) at 5. Notably, neither Chang nor any other prior art reference reports what dose of lomitapide was clinically efficacious in man. This information would have provided an anchor point for clinical trial design and would thus be critically necessary for a POSA to evaluate whether an efficacious, safe and tolerable dosing regimen for lomitapide was even possible and what that dosing would be.

105. Chang also cites several animal studies involving MTP inhibitors, one of which is the Wantanabe Heritable HyperLipidemic (WHHL) rabbit model. CFAD Ex. 1015 (Chang) at 4. Although there are some differences between the

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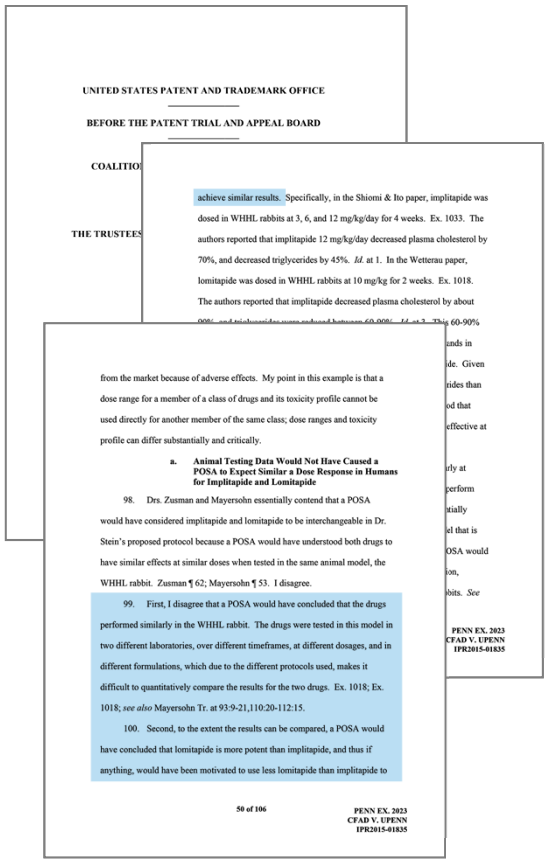
"**Notably, neither Chang nor any other prior art reference reports what dose of lomitapide was clinically efficacious in man.** This information would have provided an anchor point for clinical trial design and would thus be **critically necessary for a POSA to evaluate whether an efficacious, safe and tolerable dosing regimen for lomitapide was even possible** and what that dosing would be."

Source: Ex. 2024, Baillie Decl., ¶ 104; POR at 21-23, 26-35

Chang's Rabbit Data Do Not Suggest Dosing Lomitapide and Implitapide Similarly



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achieve similar results. Specifically, in the Shiomi & Ito paper, implitapide was dosed in WHHL rabbits at 3, 6, and 12 mg/kg/day for 4 weeks. Ex. 1033. The authors reported that implitapide 12 mg/kg/day decreased plasma cholesterol by 70%, and decreased triglycerides by 45%. *Id.* at 1. In the Wetterau paper, lomitapide was dosed in WHHL rabbits at 10 mg/kg for 2 weeks. Ex. 1018. The authors reported that implitapide decreased plasma cholesterol by about

from the market because of adverse effects. My point in this example is that a dose range for a member of a class of drugs and its toxicity profile cannot be used directly for another member of the same class; dose ranges and toxicity profile can differ substantially and critically.

a. Animal Testing Data Would Not Have Caused a POSA to Expect Similar a Dose Response in Humans for Implitapide and Lomitapide

98. Drs. Zusman and Mayersohn essentially contend that a POSA would have considered implitapide and lomitapide to be interchangeable in Dr. Stein's proposed protocol because a POSA would have understood both drugs to have similar effects at similar doses when tested in the same animal model, the WHHL rabbit. Zusman ¶ 62; Mayersohn ¶ 53. I disagree.

99. First, I disagree that a POSA would have concluded that the drugs performed similarly in the WHHL rabbit. The drugs were tested in this model in two different laboratories, over different timeframes, at different dosages, and in different formulations, which due to the different protocols used, makes it difficult to quantitatively compare the results for the two drugs. Ex. 1018; Ex. 1018; *see also* Mayersohn Tr. at 93:9-21,110:20-112:15.

100. Second, to the extent the results can be compared, a POSA would have concluded that lomitapide is more potent than implitapide, and thus if anything, would have been motivated to use less lomitapide than implitapide to

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"First, I disagree that a POSA would have concluded that the drugs performed similarly in the WHHL rabbit. The drugs were tested in this model in two different laboratories, over different timeframes, at different dosages, and in different formulations, which due to the different protocols used, makes it difficult to quantitatively compare the results for the two drugs. Ex. 1018; Ex. 1018; see also Mayersohn Tr. at 93:9-21,110:20-112:15.

. . . Second, to the extent the results can be compared, a POSA would have concluded that lomitapide is more potent than implitapide, and thus if anything, would have been motivated to use less lomitapide than implitapide to achieve similar results."

Source: Ex. 2023, Sacks Decl., ¶¶ 99-100; POR at 33

Wetterau Reports a Single Dose, Two-Week Study in Five Rabbits

SCIENCE VOL 282 23 OCTOBER 1998

Fig. 4. Effect of compound **9** on plasma lipid levels in WHHL rabbits (a negative percentage indicates a decrease). Five rabbits were treated orally for 14 days with compound **9** (10 mg/kg). Plasma (**A**) total cholesterol and (**B**) triglyceride levels were measured 18 hours after the last dose. Prebleed, solid bars; 14-day treatment, hatched bars.

Source: Ex. 1018, Wetterau, p. 3; RMTA at 8

Petitioner's Expert Dr. Zusman: The WHHL Rabbit Model Cannot Qualitatively Predict Human Efficacy

Q. You don't contend that the efficacy on a dosage basis seen in the WHHL rabbit model would be identical to what you would expect in a human patient, right?

A. No. I don't believe that would be the case.

Q. Right. And WHHL rabbits don't necessarily have the same rate of absorption, metabolism, distribution and excretion as human patients, correct?

A. That's correct.

Source: Ex. 2022, Zusman Tr., 92:9-93:9 (Objection Omitted); RMTA at 4, 7

Petitioner's Expert Dr. Mayersohn: The WHHL Rabbit Model Cannot Qualitatively Predict Human Efficacy

A. So you want me to predict what's going to happen to humans based on rabbits?

Q. Right.

A. My prediction would be they would both be effective in reducing the lipids we're concerned about but perhaps not to the same extent.

Q. …Is there something in these two rabbit studies that suggests to you that the two drugs, in fact, would not have the same extent of reduction in humans?

A. No, they could. I think importantly when it comes to that point, when you're testing in humans, you will optimize the dosing regimen to determine what is best for the human. So these data, while they're very useful, do not represent the endpoint with regard to development of the drug in the human.

Source: Ex. 2021, Mayersohn Tr., 112:9-113:5; RMTA at 7

Humans Taking Lomitapide Experienced Liver Toxicity Not Observed in Animal Models

Microsomal triglyceride transfer protein (MTP) inhibitors: Discovery of clinically active inhibitors using high-throughput screening and parallel synthesis paradigms

George Chang*, Roger B'Ruggeri & H James Harwood Jr

CFAD Ex. 1015 (6 of 9)

It is important to note, however, that although hepatic lipid levels were markedly increased with treatment, hamsters administered BMS-201038 (6 mg/kg/day) for 3 weeks showed minimal change in liver weight, and plasma ALT and AST levels did not rise significantly during the treatment period [24••]. Similarly, WHHL rabbits treated with BMS-201038 (10 mg/kg/day) for 2 weeks showed no alteration in plasma AST or ALT levels, despite normalization of plasma lipids [24••].

In this regard, it is important to note that plasma ALT and AST levels were increased 3-fold above normal in 12 to 27% of patients receiving 80 mg/day and 160 mg/day doses of BAY-13-9952 [42••]. Similar AST and ALT elevations, of a magnitude sufficient to halt the development of BMS-201038, were also reported [43].

Source: Ex. 1015, Chang, p. 6; POR at 27, 36-37

The Rabbit Data Cited by Chang Suggests that Lomitapide Is More Potent than Implitapide

	Wetterau (Ex. 1018)	Shiomi (Ex. 1033)
Study Sponsor	BMS	Bayer
Compound	Lomitapide	Implitapide
Dose	10 mg/kg	3, 6, 12 mg/kg
Study Duration	2 weeks	4 weeks
Total Cholesterol Reduction (Avg.)	89%	70% (12 mg/kg)
Triglyceride Reduction (Avg.)	81%	45% (12 mg/kg)

Source: Ex. 1015 (Chang) at 4; Ex. 1018 (Wetterau) at 3; Ex. 1033 (Shiomi) at 1-3; POR at 32-33

Dr. Zusman: No Way to Predict the Outcome of a Lomitapide Dosing Regimen Without a Clinical Trial

Q. . . . But the person would actually have to design and then conduct the clinical trial before they could reasonably predict what the outcome is going to be of this dosing regimen with lomitapide.

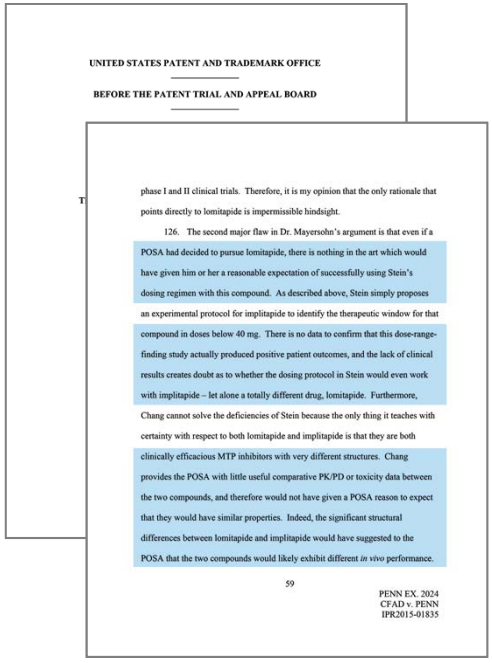
A. That's correct. One would actually have to do the trial to acquire the information.

Q. . . . And as of March 2004, there was no trial that had been disclosed or discussed in literature that provided that person of ordinary skill in the art with that information.

A. That is my understanding.

Source: Ex. 2022, Zusman Tr., 178:16-179:3; POR at 4, 40, 54

A POSA Would Have No Reasonable Expectation of Success



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phase I and II clinical trials. Therefore, it is my opinion that the only rationale that points directly to lomitapide is impermissible hindsight.

126. The second major flaw in Dr. Mayersohn's argument is that even if a POSA had decided to pursue lomitapide, there is nothing in the art which would have given him or her a reasonable expectation of successfully using Stein's dosing regimen with this compound. As described above, Stein simply proposes an experimental protocol for implitapide to identify the therapeutic window for that compound in doses below 40 mg. There is no data to confirm that this dose-range-finding study actually produced positive patient outcomes, and the lack of clinical results creates doubt as to whether the dosing protocol in Stein would even work with implitapide – let alone a totally different drug, lomitapide. Furthermore, Chang cannot solve the deficiencies of Stein because the only thing it teaches with certainty with respect to both lomitapide and implitapide is that they are both clinically efficacious MTP inhibitors with very different structures. Chang provides the POSA with little useful comparative PK/PD or toxicity data between the two compounds, and therefore would not have given a POSA reason to expect that they would have similar properties. Indeed, the significant structural differences between lomitapide and implitapide would have suggested to the POSA that the two compounds would likely exhibit different *in vivo* performance.

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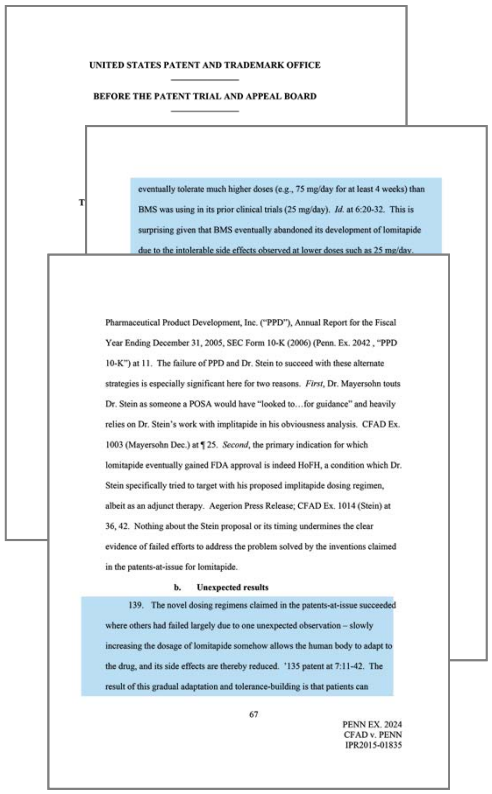
". . . there is nothing in the art which would have given him or her a reasonable expectation of successfully using Stein's dosing regimen with this compound."

"There is no data to confirm that this dose-range-finding study actually produced positive patient outcomes, and the lack of clinical results creates doubt as to whether the dosing protocol in Stein would even work with implitapide – let alone a totally different drug, lomitapide."

"Chang provides the POSA with little useful comparative PK/PD or toxicity data between the two compounds, and therefore would not have given a POSA reason to expect that they would have similar properties. Indeed, the significant structural differences between lomitapide and implitapide would have suggested to the POSA that the two compounds would likely exhibit different *in vivo* performance."

Source: Ex. 2024, Baillie Decl., ¶ 126; POR at 41-44

The Claimed Dosing Regimen Produced Unexpected Results



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eventually tolerate much higher doses (e.g., 75 mg/day for at least 4 weeks) than BMS was using in its prior clinical trials (25 mg/day). *Id.* at 6:20-32. This is surprising given that BMS eventually abandoned its development of lomitapide due to the intolerable side effects observed at lower doses such as 25 mg/day.

Pharmaceutical Product Development, Inc. ("PPD"), Annual Report for the Fiscal Year Ending December 31, 2005, SEC Form 10-K (2006) (Penn. Ex. 2042 , "PPD 10-K") at 11. The failure of PPD and Dr. Stein to succeed with these alternate strategies is especially significant here for two reasons. *First*, Dr. Mayersohn touts Dr. Stein as someone a POSA would have "looked to…for guidance" and heavily relies on Dr. Stein's work with implitapide in his obviousness analysis. CFAD Ex. 1003 (Mayersohn Dec.) at ¶ 25. *Second*, the primary indication for which lomitapide eventually gained FDA approval is indeed HoFH, a condition which Dr. Stein specifically tried to target with his proposed implitapide dosing regimen, albeit as an adjunct therapy. Aegerion Press Release; CFAD Ex. 1014 (Stein) at 36, 42. Nothing about the Stein proposal or its timing undermines the clear evidence of failed efforts to address the problem solved by the inventions claimed in the patents-at-issue for lomitapide.

b. Unexpected results

139. The novel dosing regimens claimed in the patents-at-issue succeeded where others had failed largely due to one unexpected observation – slowly increasing the dosage of lomitapide somehow allows the human body to adapt to the drug, and its side effects are thereby reduced. '135 patent at 7:11-42. The result of this gradual adaptation and tolerance-building is that patients can

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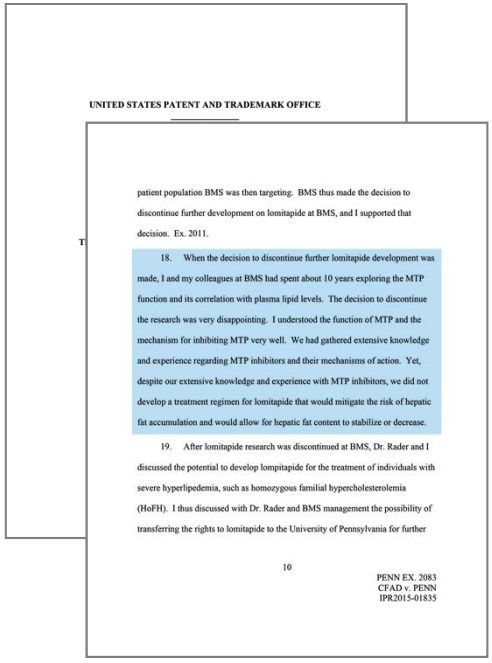
"The novel dosing regimens claimed in the patents-at-issue succeeded where others had failed largely due to one unexpected observation – slowly increasing the dosage of lomitapide somehow allows the human body to adapt to the drug, and its side effects are thereby reduced. The result of this gradual adaptation and tolerance-building is that patients can eventually tolerate much higher doses (e.g., 75 mg/day for at least 4 weeks) than BMS was using in its prior clinical trials (25 mg/day). This is surprising given that BMS eventually abandoned its development of lomitapide due to the intolerable side effects observed at lower doses such as 25 mg/day."

Source: Ex. 2024, Baillie Decl., ¶ 139 (citations omitted); POR at 56-59; MTA at 16, 22

BMS Failed to Develop an Acceptable Regimen for Lomitapide



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patient population BMS was then targeting. BMS thus made the decision to discontinue further development on lomitapide at BMS, and I supported that decision. Ex. 2011.

18. When the decision to discontinue further lomitapide development was made, I and my colleagues at BMS had spent about 10 years exploring the MTP function and its correlation with plasma lipid levels. The decision to discontinue the research was very disappointing. I understood the function of MTP and the mechanism for inhibiting MTP very well. We had gathered extensive knowledge and experience regarding MTP inhibitors and their mechanisms of action. Yet, despite our extensive knowledge and experience with MTP inhibitors, we did not develop a treatment regimen for lomitapide that would mitigate the risk of hepatic fat accumulation and would allow for hepatic fat content to stabilize or decrease.

19. After lomitapide research was discontinued at BMS, Dr. Rader and I discussed the potential to develop lomitapide for the treatment of individuals with severe hyperlipedemia, such as homozygous familial hypercholesterolemia (HoFH). I thus discussed with Dr. Rader and BMS management the possibility of transferring the rights to lomitapide to the University of Pennsylvania for further

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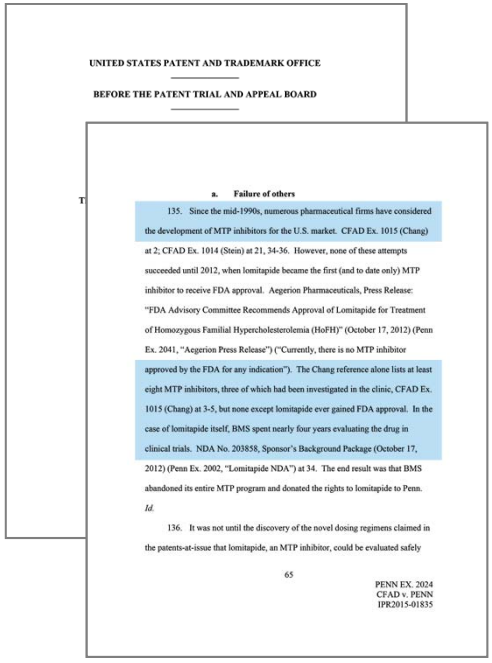
"When the decision to discontinue further lomitapide development was made, I and my colleagues at BMS had spent about 10 years exploring the MTP function and its correlation with plasma lipid levels. The decision to discontinue the research was very disappointing. . . . despite our extensive knowledge and experience with MTP inhibitors, we did not develop a treatment regimen for lomitapide that would mitigate the risk of hepatic fat accumulation and would allow for hepatic fat content to stabilize or decrease."

Source: Ex. 2083, Gregg Decl., ¶ 18; POR at 21-23, 61

Dr. Baillie: Numerous Companies Tried and Failed To Develop an MTP Inhibitor for Human Use



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a. Failure of others

135. Since the mid-1990s, numerous pharmaceutical firms have considered the development of MTP inhibitors for the U.S. market. CFAD Ex. 1015 (Chang) at 2; CFAD Ex. 1014 (Stein) at 21, 34-36. However, none of these attempts succeeded until 2012, when lomitapide became the first (and to date only) MTP inhibitor to receive FDA approval. Aegerion Pharmaceuticals, Press Release: "FDA Advisory Committee Recommends Approval of Lomitapide for Treatment of Homozygous Familial Hypercholesterolemia (HoFH)" (October 17, 2012) (Penn Ex. 2041, "Aegerion Press Release") ("Currently, there is no MTP inhibitor approved by the FDA for any indication"). The Chang reference alone lists at least eight MTP inhibitors, three of which had been investigated in the clinic, CFAD Ex. 1015 (Chang) at 3-5, but none except lomitapide ever gained FDA approval. In the case of lomitapide itself, BMS spent nearly four years evaluating the drug in clinical trials. NDA No. 203858, Sponsor's Background Package (October 17, 2012) (Penn Ex. 2002, "Lomitapide NDA") at 34. The end result was that BMS abandoned its entire MTP program and donated the rights to lomitapide to Penn. *Id.*

136. It was not until the discovery of the novel dosing regimens claimed in the patents-at-issue that lomitapide, an MTP inhibitor, could be evaluated safely

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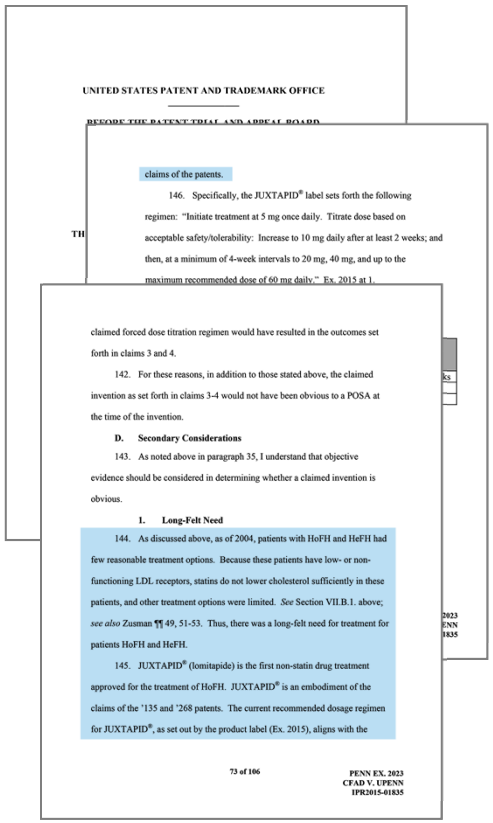
"Since the mid-1990s, numerous pharmaceutical firms have considered the development of MTP inhibitors for the U.S. market. . . . The Chang reference alone lists at least eight MTP inhibitors, three of which had been investigated in the clinic, CFAD Ex. 1015 (Chang) at 3-5, but none except lomitapide ever gained FDA approval. In the case of lomitapide itself, BMS spent nearly four years evaluating the drug in clinical trials."

Source: Ex. 2024, Baillie Decl., ¶ 135; POR at 21-22, 61; MTA at 23-24

Dr. Sacks: Dr. Rader's Invention Met a Long-Felt Need



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claims of the patents.

146. Specifically, the JUXTAPID® label sets forth the following regimen: "Initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: Increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily." Ex. 2015 at 1.

claimed forced dose titration regimen would have resulted in the outcomes set forth in claims 3 and 4.

142. For these reasons, in addition to those stated above, the claimed invention as set forth in claims 3-4 would not have been obvious to a POSA at the time of the invention.

D. Secondary Considerations

143. As noted above in paragraph 35, I understand that objective evidence should be considered in determining whether a claimed invention is obvious.

1. Long-Felt Need

144. As discussed above, as of 2004, patients with HoFH and HeFH had few reasonable treatment options. Because these patients have low- or non-functioning LDL receptors, statins do not lower cholesterol sufficiently in these patients, and other treatment options were limited. *See* Section VII.B.1. above; *see also* Zusman ¶¶ 49, 51-53. Thus, there was a long-felt need for treatment for patients HoFH and HeFH.

145. JUXTAPID® (lomitapide) is the first non-statin drug treatment approved for the treatment of HoFH. JUXTAPID® is an embodiment of the claims of the '135 and '268 patents. The current recommended dosage regimen for JUXTAPID®, as set out by the product label (Ex. 2015), aligns with the

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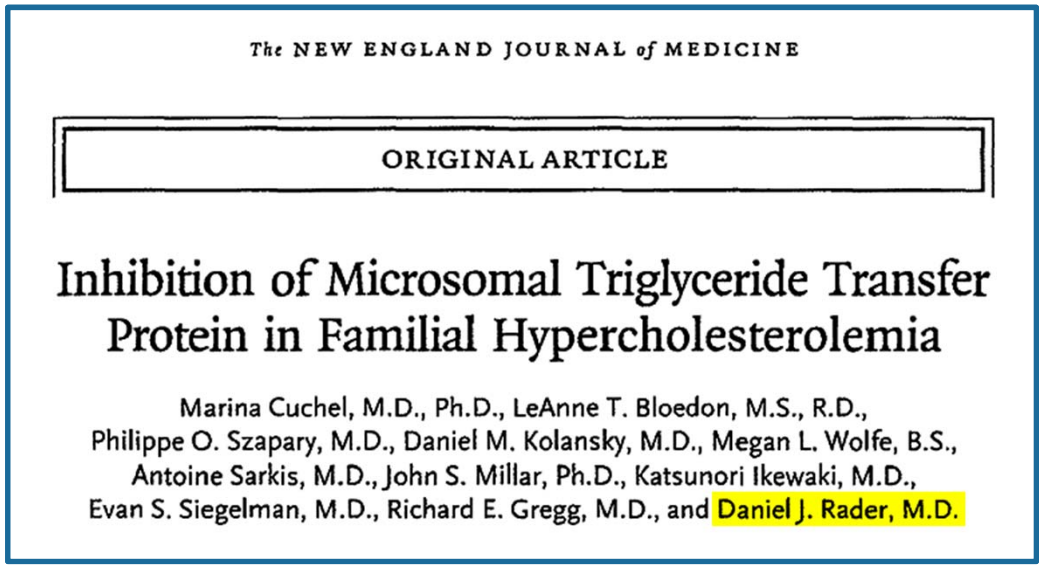
". . . patients with HoFH and HeFH had few reasonable treatment options. Because these patients have low- or nonfunctioning LDL receptors, statins do not lower cholesterol sufficiently in these patients, and other treatment options were limited. . . . Thus, there was a long-felt need for treatment for patients HoFH and HeFH."

". . . JUXTAPID® (lomitapide) is the first non-statin drug treatment approved for the treatment of HoFH. . . . The current recommended dosage regimen for JUXTAPID®, as set out by the product label (Ex. 2015), aligns with claims of the patents."

Source: Ex. 2023, Sacks Decl., ¶¶ 144-145; POR at 59-60; MTA at 23

Dr. Rader's Groundbreaking Work Was Published in the *New England Journal of Medicine*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhibition of Microsomal Triglyceride Transfer Protein in Familial Hypercholesterolemia

Marina Cuchel, M.D., Ph.D., LeAnne T. Bloedon, M.S., R.D., Philippe O. Szapary, M.D., Daniel M. Kolansky, M.D., Megan L. Wolfe, B.S., Antoine Sarkis, M.D., John S. Millar, Ph.D., Katsunori Ikewaki, M.D., Evan S. Siegelman, M.D., Richard E. Gregg, M.D., and Daniel J. Rader, M.D.

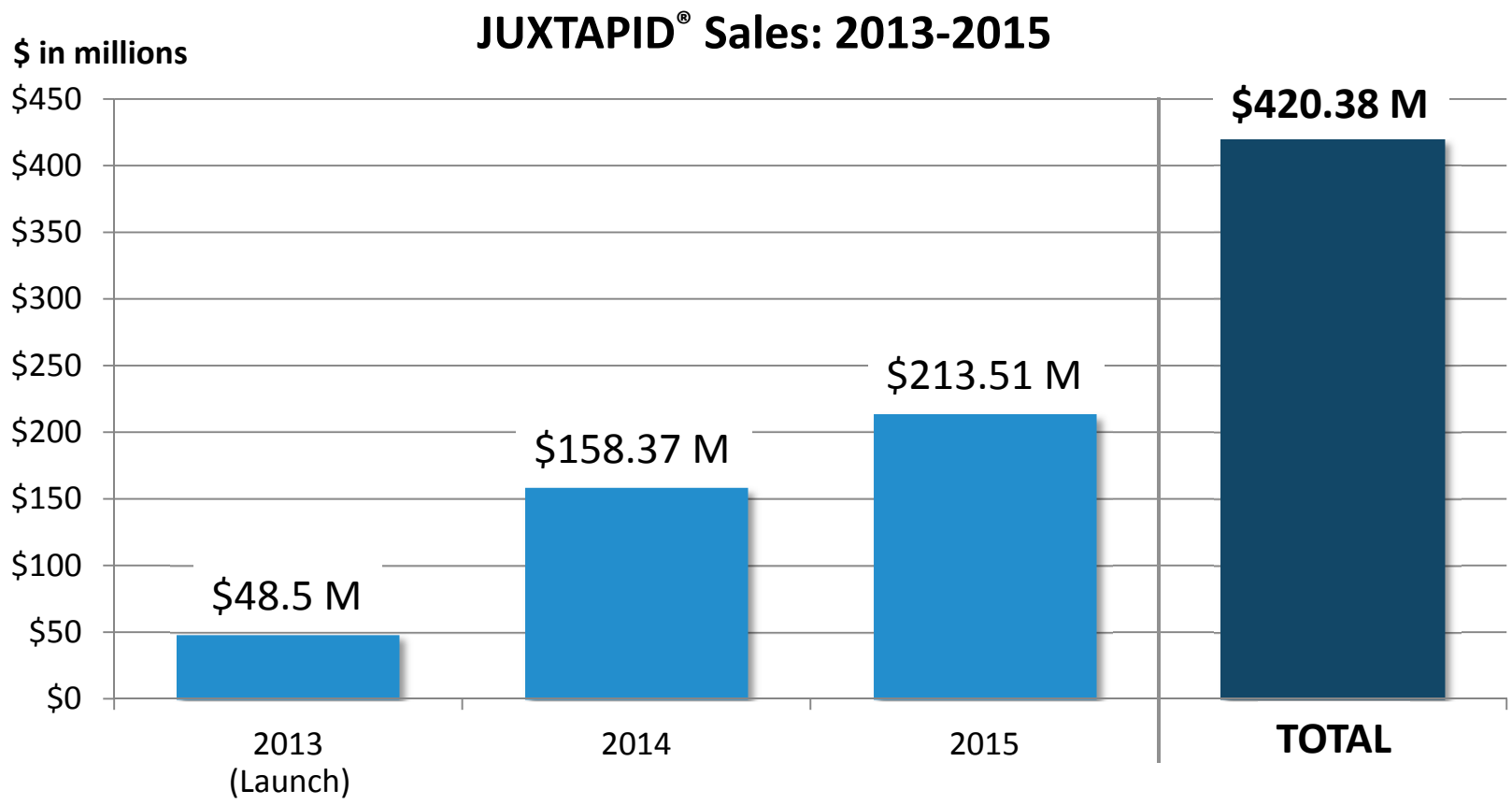
Dr. Mayersohn:

Q. So a competitive journal like the New England Journal of Medicine, do they only publish results that they consider groundbreaking or new?

A. They tend to, yeah.

Source: Ex. 2004, Cuchel I, p. 1; Ex. 2021, Mayersohn Tr., 203:20-24; POR at 62; MTA at 24

JUXTAPID® Is a Commercial Success



Source: Ex. 2012 (Aegerion 2014 10-K) at 95; Ex. 2075 (Aegerion 2015 10-K) at 222; POR at 62-64; MTA at 24

The JUXTAPID® Label Requires a Dosing Regimen Covered by the Claims

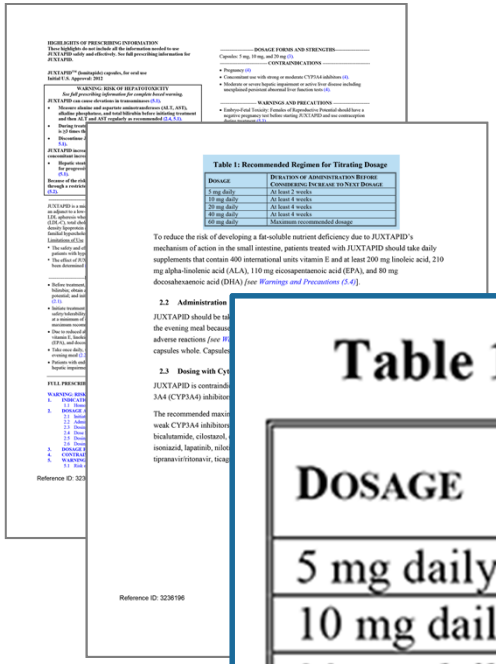


Table 1: Recommended Regimen for Titrating Dosage

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

Source: Ex. 2015, Juxtapid Label, p. 5; POPR at 54-55 [52-53]

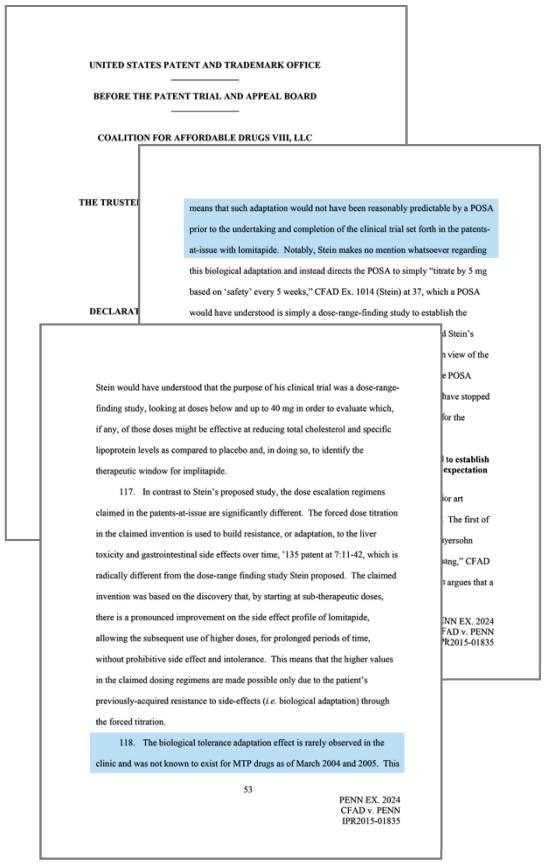
Dr. Baillie: Dr. Rader's Dosing Regimen Promoted Unexpected Biological Adaptation

Q. So my question is, do you know if a POSA followed Stein's proposed regimen with lomitapide, would the POSA have never arrived at the claimed invention because he would have stopped dosing upon observing undue toxicity?

A. I think what I was really getting at here is the adaptation to the toxicity, because for the vast majority of drugs, when you see toxicity at a particular dose regardless of what it is, you would not have the expectation that staying with that dose or even more, escalating that dose is going to result in a diminution of the toxicity. You would only expect an exacerbation of the toxicity.

Source: Ex. 1048 [1056], Baillie Tr., 99:14-100:2; POR at 58-59

Dr. Baillie: Adaptation to Side Effect Is Rare and Was Unknown with MTP Inhibitors



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means that such adaptation would not have been reasonably predictable by a POSA prior to the undertaking and completion of the clinical trial set forth in the patents-at-issue with lomitapide. Notably, Stein makes no mention whatsoever regarding this biological adaptation and instead directs the POSA to simply "titrate by 5 mg based on 'safety' every 5 weeks," CFAD Ex. 1014 (Stein) at 37, which a POSA would have understood is simply a dose-range-finding study to establish the

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Stein would have understood that the purpose of his clinical trial was a dose-range-finding study, looking at doses below and up to 40 mg in order to evaluate which, if any, of those doses might be effective at reducing total cholesterol and specific lipoprotein levels as compared to placebo and, in doing so, to identify the therapeutic window for implitapide.

117. In contrast to Stein's proposed study, the dose escalation regimens claimed in the patents-at-issue are significantly different. The forced dose titration in the claimed invention is used to build resistance, or adaptation, to the liver toxicity and gastrointestinal side effects over time, '135 patent at 7:11-42, which is radically different from the dose-range finding study Stein proposed. The claimed invention was based on the discovery that, by starting at sub-therapeutic doses, there is a pronounced improvement on the side effect profile of lomitapide, allowing the subsequent use of higher doses, for prolonged periods of time, without prohibitive side effect and intolerance. This means that the higher values in the claimed dosing regimens are made possible only due to the patient's previously-acquired resistance to side-effects (*i.e.* biological adaptation) through the forced titration.

118. The biological tolerance adaptation effect is rarely observed in the clinic and was not known to exist for MTP drugs as of March 2004 and 2005. This

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"The biological tolerance adaptation effect is rarely observed in the clinic and was not known to exist for MTP drugs as of March 2004 and 2005. This means that such adaptation would not have been reasonably predictable by a POSA prior to the undertaking and completion of the clinical trial set forth in the patents-at-issue with lomitapide."

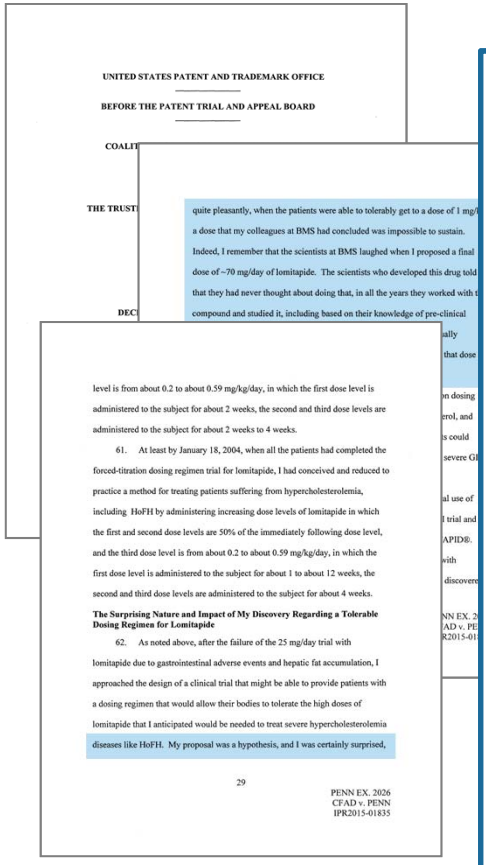
Source: Ex. 2024, Baillie Decl., ¶¶ 117-118; POR at 58

A Low-Fat Diet Was Not Responsible for Dr. Rader's Clinical Success with Lomitapide

- **Both BMS's and Dr. Rader's clinical trials utilized controlled, low fat diets**
- **BMS discovered that the incidence of lomitapide adverse events were *dose-dependent***
- **BMS encountered unacceptable toxicity at a single fixed doses of 25 mg/day**
- **Dr. Rader used his claimed forced titration regimen to successfully increase dose above 25 mg/day**
- **If diet alone were responsible for the decrease in adverse events, Dr. Rader's results should have been the same (or worse) than those seen by BMS**

Source: Ex. 2305 (Baillie Suppl. Decl.) at ¶¶ 71-75 [65-69]; RMTA at 10

BMS Scientists Doubted That Dr. Rader's Dosing Regimen Would Succeed



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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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quite pleasantly, when the patients were able to tolerably get to a dose of 1 mg/
a dose that my colleagues at BMS had concluded was impossible to sustain.
Indeed, I remember that the scientists at BMS laughed when I proposed a final
dose of ~70 mg/day of lomitapide. The scientists who developed this drug told
that they had never thought about doing that, in all the years they worked with t
compound and studied it, including based on their knowledge of pre-clinical
ally
that dose

level is from about 0.2 to about 0.59 mg/kg/day, in which the first dose level is administered to the subject for about 2 weeks, the second and third dose levels are administered to the subject for about 2 weeks to 4 weeks.

61. At least by January 18, 2004, when all the patients had completed the forced-titration dosing regimen trial for lomitapide, I had conceived and reduced to practice a method for treating patients suffering from hypercholesterolemia, including HoFH by administering increasing dose levels of lomitapide in which the first and second dose levels are 50% of the immediately following dose level, and the third dose level is from about 0.2 to about 0.59 mg/kg/day, in which the first dose level is administered to the subject for about 1 to about 12 weeks, the second and third dose levels are administered to the subject for about 4 weeks.

The Surprising Nature and Impact of My Discovery Regarding a Tolerable Dosing Regimen for Lomitapide

62. As noted above, after the failure of the 25 mg/day trial with lomitapide due to gastrointestinal adverse events and hepatic fat accumulation, I approached the design of a clinical trial that might be able to provide patients with a dosing regimen that would allow their bodies to tolerate the high doses of lomitapide that I anticipated would be needed to treat severe hypercholesterolemia diseases like HoFH. My proposal was a hypothesis, and I was certainly surprised,

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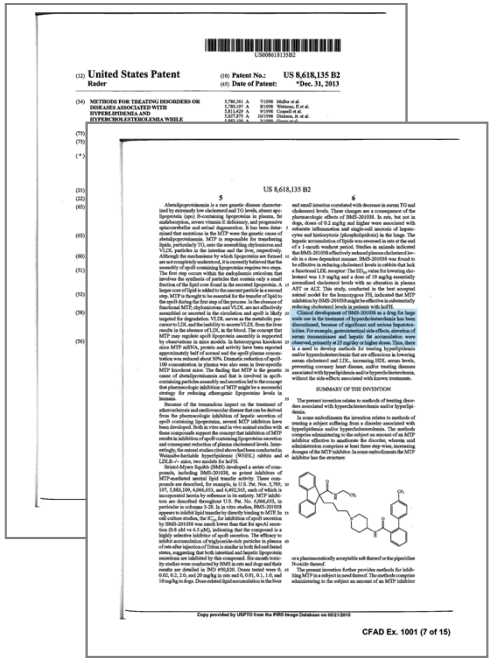
"My proposal was a hypothesis, and I was certainly surprised, quite pleasantly, when the patients were able to tolerably get to a dose of 1 mg/kg, a dose that my colleagues at BMS had concluded was impossible to sustain. Indeed, I remember that the scientists at BMS laughed when I proposed a final dose of ~70 mg/day of lomitapide. The scientists who developed this drug told me that they had never thought about doing that, in all the years they worked with the compound and studied it, including based on their knowledge of pre-clinical animal data and proprietary clinical data, and they told me it was virtually impossible that we could get up to doses of 60-80 mg/day and sustain that dose for any period of time without intolerable GI side effects."

Source: Ex. 2026, Rader Decl., ¶ 62; MTA at 11-14

BMS Discontinued Lomitapide Due to Unacceptable Toxicity



US008618135B2

(12) United States Patent
Rader

(10) Patent No.: US 8,618,135 B2
(45) Date of Patent: *Dec. 31, 2013

(54) METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE

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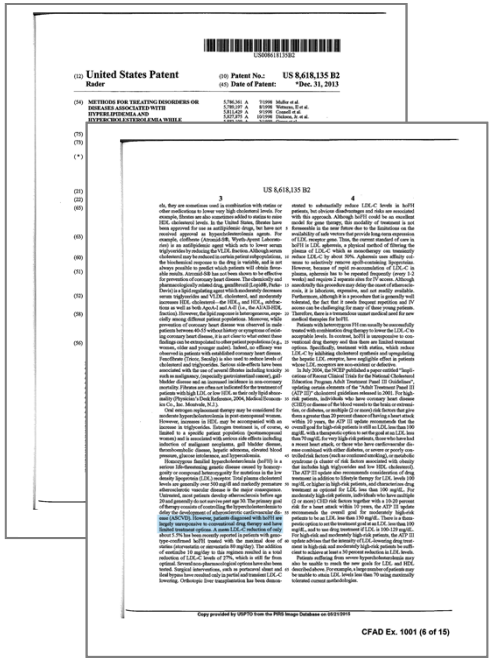
5 6

CFAD Ex. 1001 (7 of 15)

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

Source: Ex. 1001, ('135 Patent), 6:20-25; POPR at 1, 7

Standard Therapies Are Ineffective Against HoFH



US008618135B2

(12) **United States Patent**
Rader

(10) **Patent No.: US 8,618,135 B2**
(45) **Date of Patent: *Dec. 31, 2013**

(54) **METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE**

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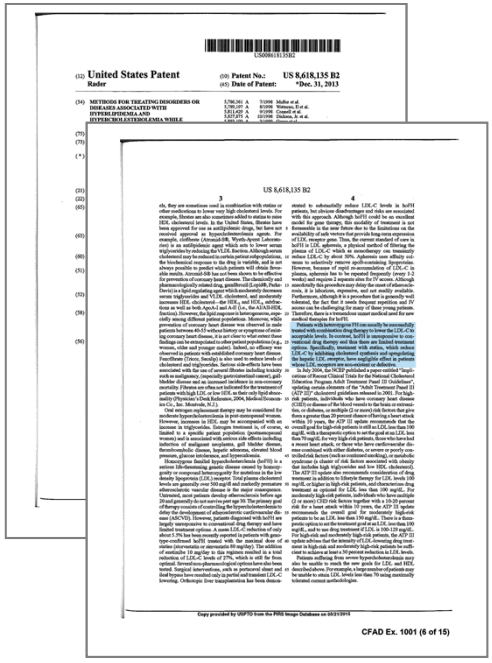
3 4

CFAD Ex. 1001 (6 of 15)

However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options.

Source: Ex. 1001, ('135 Patent), 3:56-58; POPR at 6

HoFH Patients Are Unresponsive to Statins



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CFAD Ex. 1001 (6 of 15)

In contrast, hoFH is unresponsive to conventional drug therapy and thus there are limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and unregulating the hepatic LDL receptor, have negligible effect in patients whose LDL receptors are non-existent or defective.

Source: Ex. 1001, ('135 Patent), 4:24-29; POPR at 5

Dependent Claims 3 and 4 Require Specific Levels of Lipid Reductions Not Taught by the Prior Art

Claim 3:

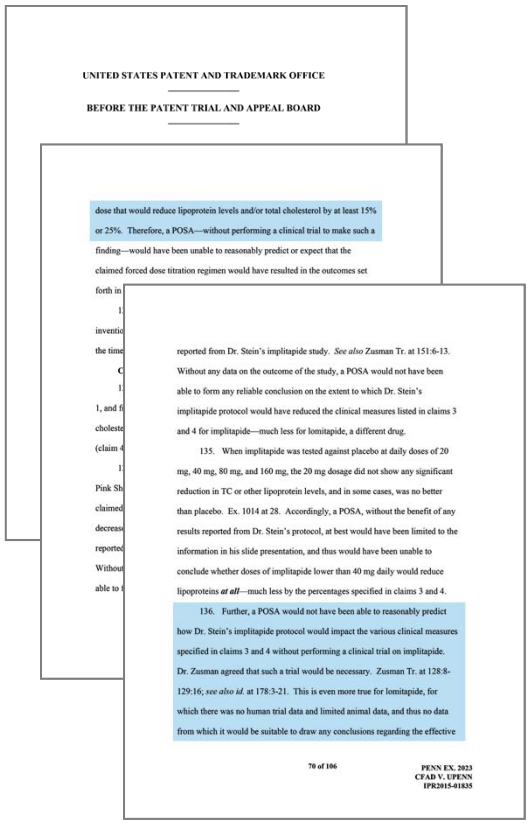
The method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-I, A-II, B, and E are reduced by at least 15%, compared to control levels.

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.

Source: Ex. 1001 ('135 Patent) at 20:3-11; Ex. 1001 ('268 Patent) at 20:26-33

A POSA Could Not Reasonably Predict The Claimed Lipid Reductions



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dose that would reduce lipoprotein levels and/or total cholesterol by at least 15% or 25%. Therefore, a POSA—without performing a clinical trial to make such a finding—would have been unable to reasonably predict or expect that the claimed forced dose titration regimen would have resulted in the outcomes set forth in

reported from Dr. Stein's implitapide study. *See also* Zusman Tr. at 151:6-13. Without any data on the outcome of the study, a POSA would not have been able to form any reliable conclusion on the extent to which Dr. Stein's implitapide protocol would have reduced the clinical measures listed in claims 3 and 4 for implitapide—much less for lomitapide, a different drug.

135. When implitapide was tested against placebo at daily doses of 20 mg, 40 mg, 80 mg, and 160 mg, the 20 mg dosage did not show any significant reduction in TC or other lipoprotein levels, and in some cases, was no better than placebo. Ex. 1014 at 28. Accordingly, a POSA, without the benefit of any results reported from Dr. Stein's protocol, at best would have been limited to the information in his slide presentation, and thus would have been unable to conclude whether doses of implitapide lower than 40 mg daily would reduce lipoproteins ***at all***—much less by the percentages specified in claims 3 and 4.

136. Further, a POSA would not have been able to reasonably predict how Dr. Stein's implitapide protocol would impact the various clinical measures specified in claims 3 and 4 without performing a clinical trial on implitapide. Dr. Zusman agreed that such a trial would be necessary. Zusman Tr. at 128:8-129:16; *see also id.* at 178:3-21. This is even more true for lomitapide, for which there was no human trial data and limited animal data, and thus no data from which it would be suitable to draw any conclusions regarding the effective

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". . . a POSA would not have been able to reasonably predict how Dr. Stein's implitapide protocol would impact the various clinical measures specified in claims 3 and 4 without performing a clinical trial on implitapide.

*** * ***

"This is even more true for lomitapide, for which there was no human trial data and limited animal data, and thus no data from which it would be suitable to draw any conclusions regarding the effective dose that would reduce lipoprotein levels and/or total cholesterol by at least 15% or 25%."

Source: Ex. 2023, Sacks Decl., ¶ 136; POR at 53-54

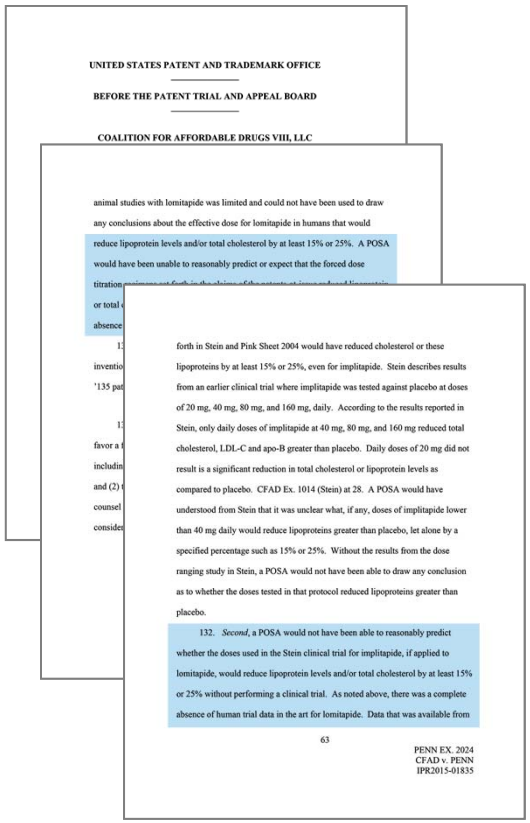
Dr. Zusman Agreed That a POSA Could Not Reasonably Predict the Claimed Lipid Reductions

Q. . . . And so a person of ordinary skill in the art with that information in hand can't reasonably predict whether giving a dose of lomitapide at 20 milligrams would reduce LDL by 15 percent without doing a clinical trial?

A. That's correct. You would have to obviously acquire the information.

Source: Ex. 2022, Zusman Tr., 178:3-11 (objection omitted); POR at 40

Dr. Baillie: Without Clinical Data, a POSA Could Not Know Exactly How Efficacious a Given Dose of Lomitapide Would Be



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animal studies with lomitapide was limited and could not have been used to draw any conclusions about the effective dose for lomitapide in humans that would reduce lipoprotein levels and/or total cholesterol by at least 15% or 25%. A POSA would have been unable to reasonably predict or expect that the forced dose titration

forth in Stein and Pink Sheet 2004 would have reduced cholesterol or these lipoproteins by at least 15% or 25%, even for implitapide. Stein describes results from an earlier clinical trial where implitapide was tested against placebo at doses of 20 mg, 40 mg, 80 mg, and 160 mg, daily. According to the results reported in Stein, only daily doses of implitapide at 40 mg, 80 mg, and 160 mg reduced total cholesterol, LDL-C and apo-B greater than placebo. Daily doses of 20 mg did not result is a significant reduction in total cholesterol or lipoprotein levels as compared to placebo. CFAD Ex. 1014 (Stein) at 28. A POSA would have understood from Stein that it was unclear what, if any, doses of implitapide lower than 40 mg daily would reduce lipoproteins greater than placebo, let alone by a specified percentage such as 15% or 25%. Without the results from the dose ranging study in Stein, a POSA would not have been able to draw any conclusion as to whether the doses tested in that protocol reduced lipoproteins greater than placebo.

132. *Second*, a POSA would not have been able to reasonably predict whether the doses used in the Stein clinical trial for implitapide, if applied to lomitapide, would reduce lipoprotein levels and/or total cholesterol by at least 15% or 25% without performing a clinical trial. As noted above, there was a complete absence of human trial data in the art for lomitapide. Data that was available from

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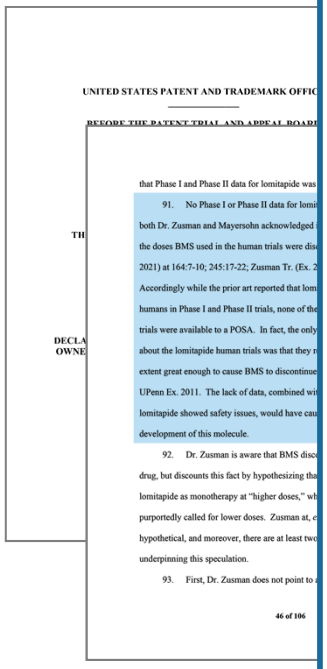
". . . a POSA would not have been able to reasonably predict whether the doses used in the Stein clinical trial for implitapide, if applied to lomitapide, would reduce lipoprotein levels and/or total cholesterol by at least 15% or 25% without performing a clinical trial. . . . there was a complete absence of human trial data in the art for lomitapide."

* * *

"A POSA would have been unable to reasonably predict or expect that the forced dose titration regimens set forth in the claims of the patents-at-issue reduced lipoprotein or total cholesterol levels by at least 15 % or 25% as compared to placebo in the absence of performing a clinical trial to make that finding."

Source: Ex. 2024, Baillie Decl., ¶ 132; POR at 53-54

The Only Prior Art Disclosure Regarding Lomitapide's Clinical Trials Was That BMS Discontinued Development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that Phase I and Phase II data for lomitapide was

91. No Phase I or Phase II data for lomi

both Dr. Zusman and Mayersohn acknowledged

the doses BMS used in the human trials were dis

2021) at 164:7-10; 245:17-22; Zusman Tr. (Ex. 2

Accordingly while the prior art reported that lom

humans in Phase I and Phase II trials, none of the

trials were available to a POSA. In fact, the only

about the lomitapide human trials was that they r

extent great enough to cause BMS to discontinue

UPenn Ex. 2011. The lack of data, combined wit

lomitapide showed safety issues, would have cau

development of this molecule.

92. Dr. Zusman is aware that BMS disc

drug, but discounts this fact by hypothesizing tha

lomitapide as monotherapy at "higher doses," wh

purportedly called for lower doses. Zusman at, e

hypothetical, and moreover, there are at least two

underpinning this speculation.

93. First, Dr. Zusman does not point to

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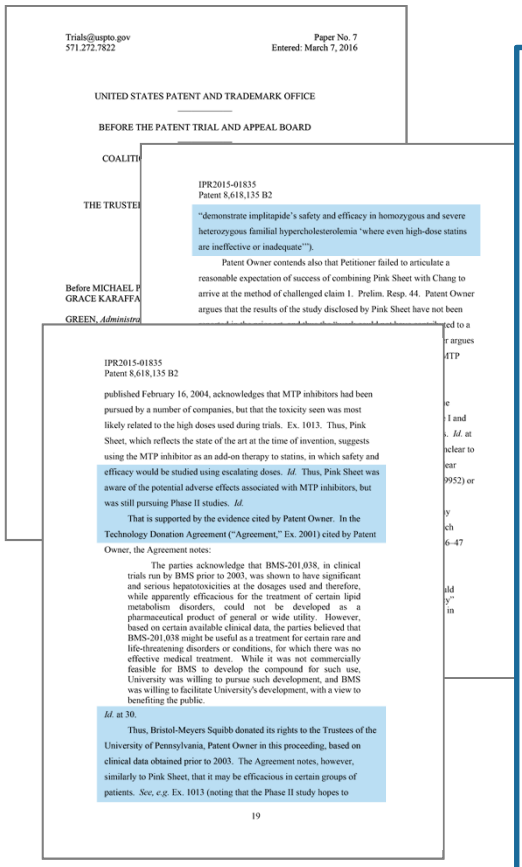
"No Phase I or Phase II data for lomitapide exists in the prior art. As both Dr. Zusman and Mayersohn acknowledged in their depositions, not even the doses BMS used in the human trials were disclosed. Mayersohn Tr. (Ex. 2021) at 164:7-10; 245:17-22; Zusman Tr. (Ex. 2022) at 96:18-97:12; 99:5-19. Accordingly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

Source: Ex. 2023, Sacks Decl., ¶ 91; POR at 28; MTA at 18

The Board Cited the Technology Donation Agreement (Ex. 2001)



Trials@uspto.gov
571.272.7822

Paper No. 7
Entered: March 7, 2016

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

Patent Owner contends also that Petitioner failed to articulate a reasonable expectation of success of combining Pink Sheet with Chang to arrive at the method of challenged claim 1. Prelim. Resp. 44. Patent Owner argues that the results of the study disclosed by Pink Sheet have not been

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

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

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

Id. at 30.

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

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"Thus, Pink Sheet was aware of the potential adverse effects associated with MTP inhibitors, but was still pursuing Phase II studies. . . . That is supported by the evidence cited by Patent Owner. In the Technology Donation Agreement ('Agreement,' Ex. 2001)

*** * ***

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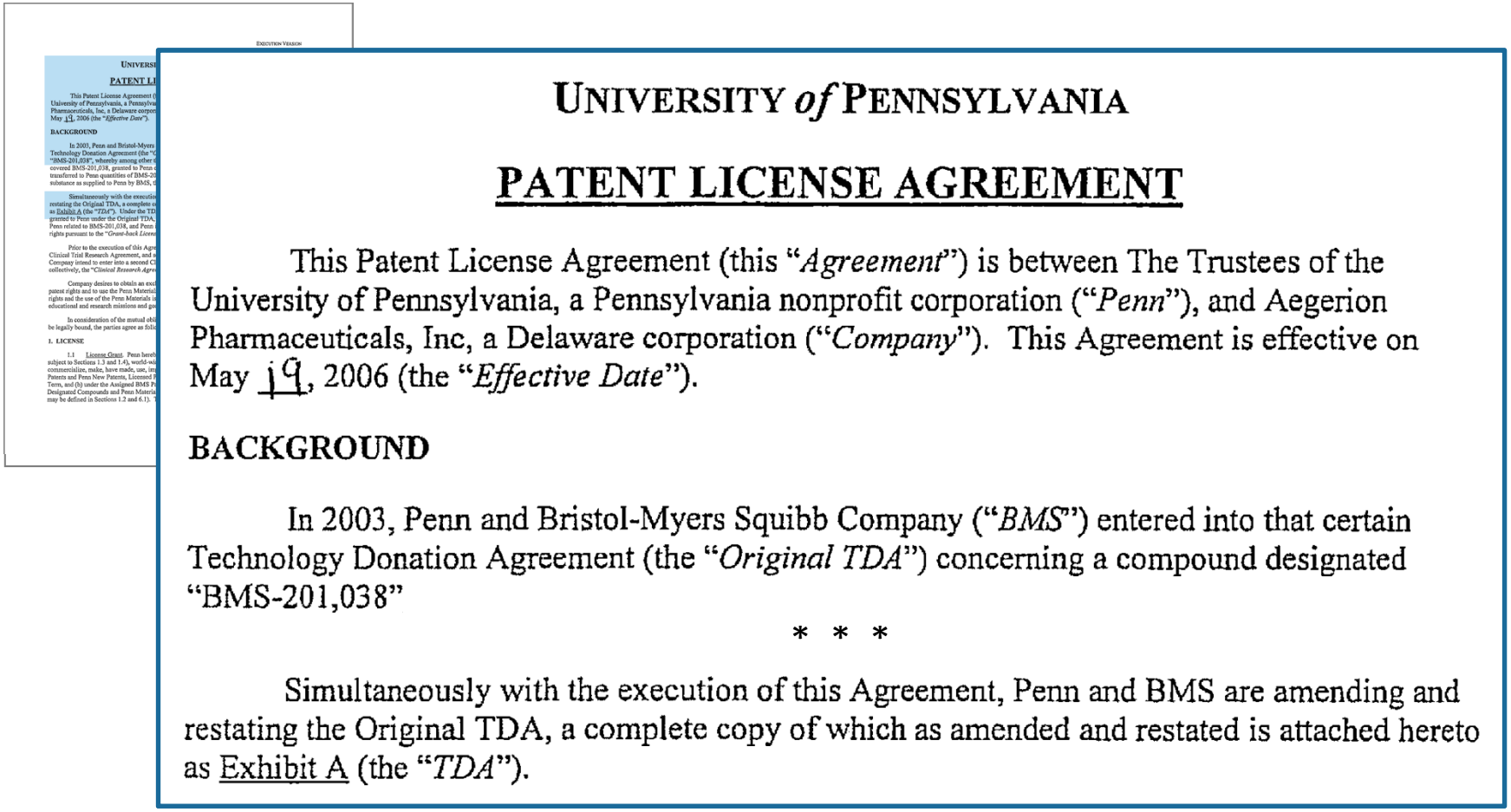
Source: Institution Decision at 19-20

Exhibit 2001 Is Not Prior Art



UNIVERSITY *of* PENNSYLVANIA

PATENT LICENSE AGREEMENT

This Patent License Agreement (this "*Agreement*") is between The Trustees of the University of Pennsylvania, a Pennsylvania nonprofit corporation ("*Penn*"), and Aegerion Pharmaceuticals, Inc, a Delaware corporation ("*Company*"). This Agreement is effective on May 19, 2006 (the "*Effective Date*").

BACKGROUND

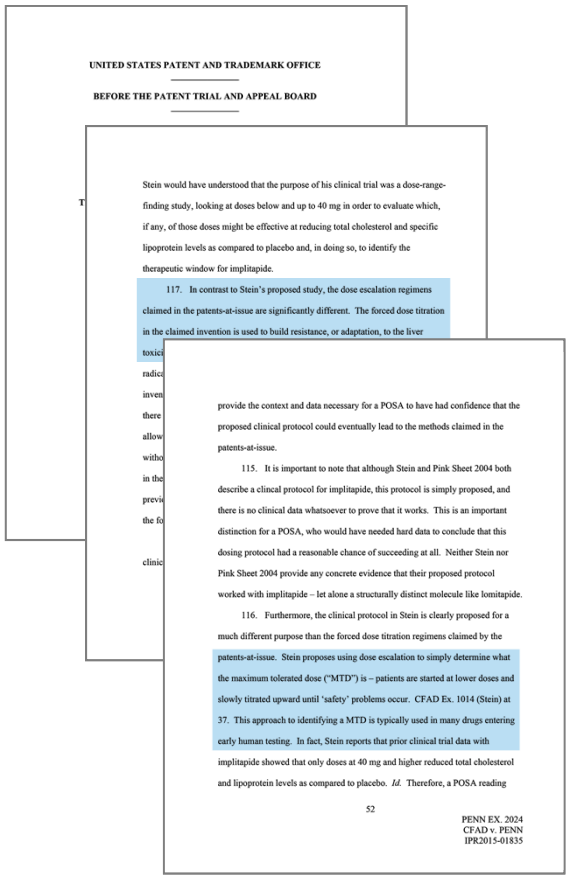
In 2003, Penn and Bristol-Myers Squibb Company ("*BMS*") entered into that certain Technology Donation Agreement (the "*Original TDA*") concerning a compound designated "BMS-201,038"

* * *

Simultaneously with the execution of this Agreement, Penn and BMS are amending and restating the Original TDA, a complete copy of which as amended and restated is attached hereto as Exhibit A (the "*TDA*").

Source: Ex. 2001, Tech Agreement at 1

Dr. Baillie: Stein and Pink Sheet 2004 Describe A Dose-Finding Study



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Stein would have understood that the purpose of his clinical trial was a dose-range-finding study, looking at doses below and up to 40 mg in order to evaluate which, if any, of those doses might be effective at reducing total cholesterol and specific lipoprotein levels as compared to placebo and, in doing so, to identify the therapeutic window for implitapide.

117. In contrast to Stein's proposed study, the dose escalation regimens claimed in the patents-at-issue are significantly different. The forced dose titration in the claimed invention is used to build resistance, or adaptation, to the liver

provide the context and data necessary for a POSA to have had confidence that the proposed clinical protocol could eventually lead to the methods claimed in the patents-at-issue.

115. It is important to note that although Stein and Pink Sheet 2004 both describe a clinical protocol for implitapide, this protocol is simply proposed, and there is no clinical data whatsoever to prove that it works. This is an important distinction for a POSA, who would have needed hard data to conclude that this dosing protocol had a reasonable chance of succeeding at all. Neither Stein nor Pink Sheet 2004 provide any concrete evidence that their proposed protocol worked with implitapide – let alone a structurally distinct molecule like lomitapide.

116. Furthermore, the clinical protocol in Stein is clearly proposed for a much different purpose than the forced dose titration regimens claimed by the patents-at-issue. Stein proposes using dose escalation to simply determine what the maximum tolerated dose ("MTD") is – patients are started at lower doses and slowly titrated upward until 'safety' problems occur. CFAD Ex. 1014 (Stein) at 37. This approach to identifying a MTD is typically used in many drugs entering early human testing. In fact, Stein reports that prior clinical trial data with implitapide showed that only doses at 40 mg and higher reduced total cholesterol and lipoprotein levels as compared to placebo. *Id.* Therefore, a POSA reading

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"Stein proposes using dose escalation to simply determine what the maximum tolerated dose ("MTD") is – patients are started at lower doses and slowly titrated upward until 'safety' problems occur.

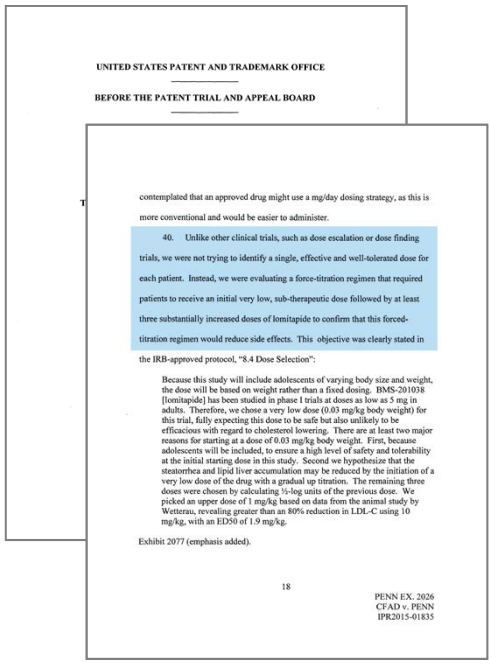
This approach to identifying a MTD is typically used in many drugs entering early human testing."

* * *

"In contrast to Stein's proposed study, the dose escalation regimens claimed in the patents-at-issue are significantly different. The forced dose titration in the claimed invention is used to build resistance, or adaptation, to the liver toxicity and gastrointestinal side effects over time, . . . "

Source: Ex. 2024, Baillie Decl., ¶ ¶ 116, 117; POR at 35

Dr. Rader's Dosing Regimen Is Fundamentally Different Than That Used by Stein and Pink Sheet 2004



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contemplated that an approved drug might use a mg/day dosing strategy, as this is more conventional and would be easier to administer.

40. Unlike other clinical trials, such as dose escalation or dose finding trials, we were not trying to identify a single, effective and well-tolerated dose for each patient. Instead, we were evaluating a force-titration regimen that required patients to receive an initial very low, sub-therapeutic dose followed by at least three substantially increased doses of lomitapide to confirm that this forced-titration regimen would reduce side effects. This objective was clearly stated in the IRB-approved protocol, "8.4 Dose Selection":

> Because this study will include adolescents of varying body size and weight, the dose will be based on weight rather than a fixed dosing. BMS-201038 [lomitapide] has been studied in phase I trials at doses as low as 5 mg in adults. Therefore, we chose a very low dose (0.03 mg/kg body weight) for this trial, fully expecting this dose to be safe but also unlikely to be efficacious with regard to cholesterol lowering. There are at least two major reasons for starting at a dose of 0.03 mg/kg body weight. First, because adolescents will be included, to ensure a high level of safety and tolerability at the initial starting dose in this study. Second we hypothesize that the steatorrhea and lipid liver accumulation may be reduced by the initiation of a very low dose of the drug with a gradual up titration. The remaining three doses were chosen by calculating ½-log units of the previous dose. We picked an upper dose of 1 mg/kg based on data from the animal study by Wetterau, revealing greater than an 80% reduction in LDL-C using 10 mg/kg, with an ED50 of 1.9 mg/kg.

Exhibit 2077 (emphasis added).

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"Unlike other clinical trials, such as dose escalation or dose finding trials, we were not trying to identify a single, effective and well-tolerated dose for each patient. Instead, we were evaluating a force-titration regimen that required patients to receive an initial very low, sub-therapeutic dose followed by at least three substantially increased doses of lomitapide to confirm that this forced-titration regimen would reduce side effects."

Source: Ex. 2026, Rader Decl., ¶ 40; POR at 36

Dr. Kimball: A POSA Would Be Reluctant to Develop a Compound Which Had Been Removed from the Clinic for Safety Reasons

Q. Would a POSA be influenced by the stigma of a drug being publicly withdrawn?

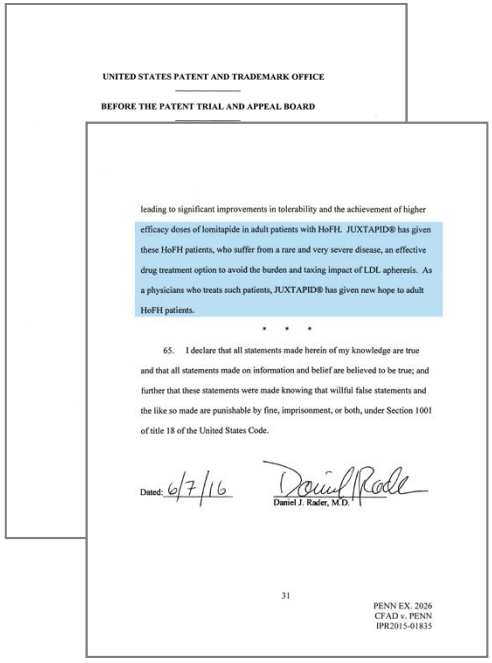
A. The POSA, being a drug development team, would be very concerned going back into human trials with a molecule that had already demonstrated and had published toxicity in humans. It's a huge risk.

Q. Does stigma in this context mean anything more than they would consider it a risk?

A. The stigma is not only the risk, it's the stain on the brand as it were. If it were to go back and fail, that would be bad for the company, probably worse for the POSA.

Source: Ex. 1056 [1052], Kimball Tr., 170:22-171:10; POR at 26-28

JUXTAPID® Has Given Hope to HoFH Patients



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leading to significant improvements in tolerability and the achievement of higher efficacy doses of lomitapide in adult patients with HoFH. JUXTAPID® has given these HoFH patients, who suffer from a rare and very severe disease, an effective drug treatment option to avoid the burden and taxing impact of LDL apheresis. As a physicians who treats such patients, JUXTAPID® has given new hope to adult HoFH patients.

* * *

65. I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made knowing that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of title 18 of the United States Code.

Dated: 6/7/16 Daniel J. Rader, M.D.

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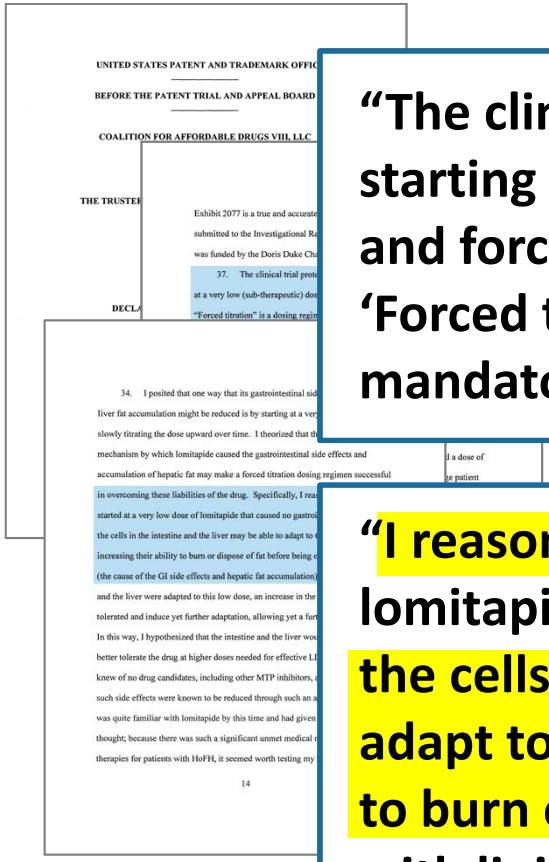
"JUXTAPID® has given these HoFH patients, who suffer from a rare and very severe disease, an effective drug treatment option to avoid the burden and taxing impact of LDL apheresis. As a physician who treats such patients, JUXTAPID® has given new hope to adult HoFH patients."

Source: Ex. 2026, Rader Decl., ¶ 64; MTA at 23

Dr. Rader Hypothesized that a Forced Titration Dosing Mechanism Might Reduce Side Effects via Adaptation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COALITION FOR AFFORDABLE DRUGS VIII, LLC

THE TRUSTEE

Exhibit 2077 is a true and accurate

submitted to the Investigational Re

was funded by the Doris Duke Cha

37. The clinical trial proto

at a very low (sub-therapeutic) dos

"Forced titration" is a dosing regim

DECL

34. I posited that one way that its gastrointestinal sid

liver fat accumulation might be reduced is by starting at a ver

slowly titrating the dose upward over time. I theorized that th

mechanism by which lomitapide caused the gastrointestinal side effects and

accumulation of hepatic fat may make a forced titration dosing regimen successful

in overcoming these liabilities of the drug. Specifically, I rea

started at a very low dose of lomitapide that caused no gastroi

the cells in the intestine and the liver may be able to adapt to t

increasing their ability to burn or dispose of fat before being e

(the cause of the GI side effects and hepatic fat accumulation)

and the liver were adapted to this low dose, an increase in the

tolerated and induce yet further adaptation, allowing yet a furt

In this way, I hypothesized that the intestine and the liver wou

better tolerate the drug at higher doses needed for effective LI

knew of no drug candidates, including other MTP inhibitors,

such side effects were known to be reduced through such an a

was quite familiar with lomitapide by this time and had given

thought; because there was such a significant unmet medical n

therapies for patients with HoFH, it seemed worth testing my

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d a dose of

e patient

"The clinical trial protocol that I developed called for starting patients at a very low (sub-therapeutic) dose and force-titrating them to a therapeutic dose. 'Forced titration' is a dosing regimen that includes a mandatory dose increase up to a final target dose."

"I reasoned that if we started at a very low dose of lomitapide that caused no gastrointestinal side effects, the cells in the intestine and the liver may be able to adapt to the MTP inhibition by increasing their ability to burn or dispose of fat before being overloaded with lipid (the cause of the GI side effects and hepatic fat accumulation)."

Source: Ex. 2026, Rader Decl., ¶¶ 34, 37; POR at 23-26

Dr. Rader's Idea is Described in the Patent Specification

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

Source: Ex. 1001, '135 Patent, 6:20-25

Dr. Rader's Idea is Described in the Patent Specification

"The methods comprise administering to the subject an amount of an MTP inhibitor effective to inhibit MTP, wherein said administration comprises at lease three step-wise, increasing dosages of the MTP inhibitor . . . a treatment regimen that reduces and/or eliminates side-effects associated with the use of the inhibitors."

Source: Ex. 1001, '135 Patent, 6:66-7:24

Dr. Rader's Idea is Described in the Patent Specification

"Starting at a low dose and titrating up slowly may improve GI-related tolerability as well as provide time for the liver to adjust to the inhibition of MTP, perhaps decreasing hepatic fat build up. This theory was applied in designing a study investigating the safety, tolerability and efficacy of BMS-201038 in patients with homozygous familial hypercholesterolemia (hoFH)."

Source: Ex. 1001, '135 Patent, 18:64-19:3

Claim 1 of the ’135 Patent

A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor wherein a first dose level is from about 2 to about 13 mg/day, a second dose level is from about 5 to about 30 mg/day, and a third dose level is from about 10 to about 50 mg/day; and wherein the MTP inhibitor is [lomitapide] or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof, and wherein each dose level is administered to the subject for about 1 to about 5 weeks

Source: Ex. 1001 (’135 Patent) at 19:41-67

Claim 1 of the ’268 Patent

A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor wherein a first dose level is from about 2 to about 13 mg/day, a second dose level is from about 5 to about 30 mg/day, and a third dose level is from about 10 to about 50 mg/day; and wherein the MTP inhibitor is [lomitapide] or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof, and wherein each dose level is administered to the subject for about 1 to about 4 weeks

Source: [Ex. 1001 (’268 Patent) at 19:40-20:23]

Claims 3, 4, and 8 of the ’135 Patent

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.

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.

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.

Source: Ex. 1001 (’135 Patent) at 20:3-22

Claims 3, 4, and 8 of the ’268 Patent

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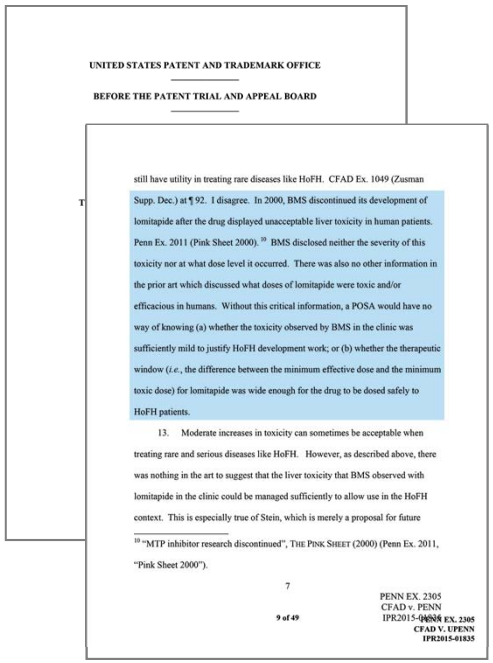
Claim 8:

The method of claim 1 wherein said fourth dose level from about 20 to about 60 mg/day, and said fifth dose level from about 30 to about 75 mg/day.

Source: [Ex. 1001 (’268 Patent) at 20:26-43]

It Would Not Have Been Obvious to Develop Lomitapide for HoFH



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BEFORE THE PATENT TRIAL AND APPEAL BOARD

still have utility in treating rare diseases like HoFH. CFAD Ex. 1049 (Zusman Supp. Dec.) at ¶ 92. I disagree. In 2000, BMS discontinued its development of lomitapide after the drug displayed unacceptable liver toxicity in human patients. Penn Ex. 2011 (Pink Sheet 2000).[9] BMS disclosed neither the severity of this toxicity nor at what dose level it occurred. There was also no other information in the prior art which discussed what doses of lomitapide were toxic and/or efficacious in humans. Without this critical information, a POSA would have no way of knowing (a) whether the toxicity observed by BMS in the clinic was sufficiently mild to justify HoFH development work; or (b) whether the therapeutic window (*i.e.*, the difference between the minimum effective dose and the minimum toxic dose) for lomitapide was wide enough for the drug to be dosed safely to HoFH patients.

13. Moderate increases in toxicity can sometimes be acceptable when treating rare and serious diseases like HoFH. However, as described above, there was nothing in the art to suggest that the liver toxicity that BMS observed with lomitapide in the clinic could be managed sufficiently to allow use in the HoFH context. This is especially true of Stein, which is merely a proposal for future

[9] "MTP inhibitor research discontinued", THE PINK SHEET (2000) (Penn Ex. 2011, "Pink Sheet 2000").

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PENN EX. 2305
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PENN EX. 2305
CFAD V. UPENN
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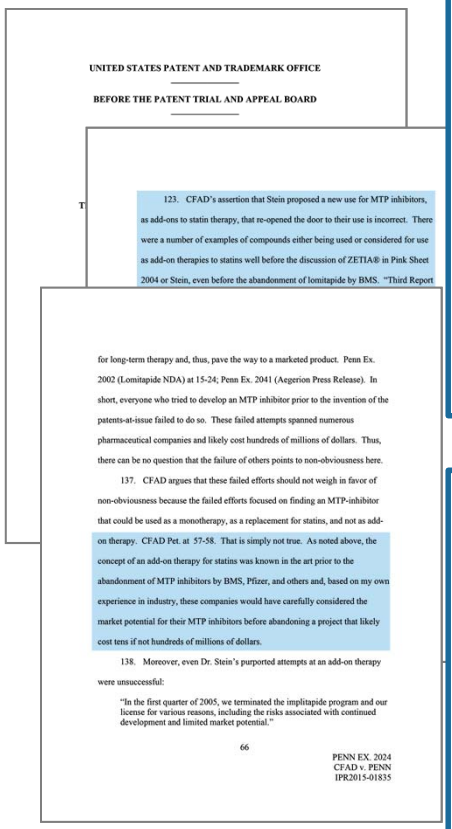
"In 2000, BMS discontinued its development of lomitapide after the drug displayed unacceptable liver toxicity in human patients. Penn Ex. 2011 (Pink Sheet 2000). BMS disclosed neither the severity of this toxicity nor at what dose level it occurred. There was also no other information in the prior art which discussed what doses of lomitapide were toxic and/or efficacious in humans. Without this critical information, a POSA would have no way of knowing (a) whether the toxicity observed by BMS in the clinic was sufficiently mild to justify HoFH development work; or (b) whether the therapeutic window (*i.e.*, the difference between the minimum effective dose and the minimum toxic dose) for lomitapide was wide enough for the drug to be dosed safely to HoFH patients."

Source: Ex. 2305, Baillie Suppl. Decl., ¶ 12; RMTA at 3

Statin Add-On Therapy Was Known in the Art



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123. CFAD's assertion that Stein proposed a new use for MTP inhibitors, as add-ons to statin therapy, that re-opened the door to their use is incorrect. There were a number of examples of compounds either being used or considered for use as add-on therapies to statins well before the discussion of ZETIA® in Pink Sheet 2004 or Stein, even before the abandonment of lomitapide by BMS. "Third Report

for long-term therapy and, thus, pave the way to a marketed product. Penn Ex. 2002 (Lomitapide NDA) at 15-24; Penn Ex. 2041 (Aegerion Press Release). In short, everyone who tried to develop an MTP inhibitor prior to the invention of the patents-at-issue failed to do so. These failed attempts spanned numerous pharmaceutical companies and likely cost hundreds of millions of dollars. Thus, there can be no question that the failure of others points to non-obviousness here.

137. CFAD argues that these failed efforts should not weigh in favor of non-obviousness because the failed efforts focused on finding an MTP-inhibitor that could be used as a monotherapy, as a replacement for statins, and not as add-on therapy. CFAD Pet. at 57-58. That is simply not true. As noted above, the concept of an add-on therapy for statins was known in the art prior to the abandonment of MTP inhibitors by BMS, Pfizer, and others and, based on my own experience in industry, these companies would have carefully considered the market potential for their MTP inhibitors before abandoning a project that likely cost tens if not hundreds of millions of dollars.

138. Moreover, even Dr. Stein's purported attempts at an add-on therapy were unsuccessful:

"In the first quarter of 2005, we terminated the implitapide program and our license for various reasons, including the risks associated with continued development and limited market potential."

66

PENN EX. 2024
CFAD v. PENN
IPR2015-01835

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". . . the concept of an add-on therapy for statins was known in the art prior to the abandonment of MTP inhibitors by BMS, Pfizer, and others and, based on my own experience in industry, these companies would have carefully considered the market potential for their MTP inhibitors before abandoning a project that likely cost tens if not hundreds of millions of dollars."

Source: Ex. 2024, Baillie Decl., ¶¶ 123, 137; POR at 29, 49

Dr. Zusman: The FDA Was "Extraordinarily Sensitized" To Liver Toxicity

Q. . . . And so a person of ordinary skill in the art reading Exhibit 2020 as of March 2004 would have understood that there was a superior compound to lomitapide, BMS-212122, and would have evaluated that compound for potential human use, correct?

A. Well, would have considered it, but at the time that this was being done, the Food & Drug Administration was extraordinarily sensitized to issues of hepatotoxicity and remains sensitized. And drugs that demonstrated significant hepatotoxic effects were considered themselves to be toxic in terms of future presentation to the FDA.

Source: Ex. 2022, Zusman Tr., 171:17-172:6 (Objection Omitted); MTA at 18

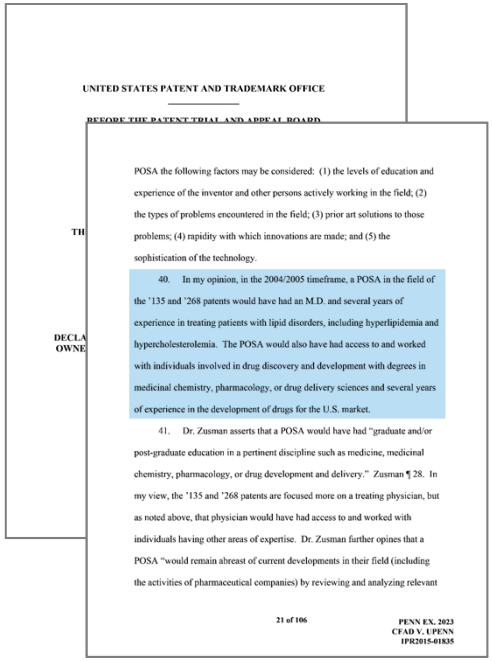
Dr. Zusman: A Compound Which Caused a Twofold Increase in Liver Enzymes Is "Too Hot to Handle"

Q. -- it says, "Tolerability was good in this study and an approximate twofold increase in plasma ALT, AST, and CPK levels was observed."

A. Right. So a twofold increase in seven days might have made this compound too hot to handle, if you will, but at such a marked increase in such a short period of time, might have discouraged their subsequent development of the compound.

Source: Ex. 2022, Zusman Tr., 172:16-24; POR at 2, 27-28; MTA at 18

Dr. Sacks: POSA Definition



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POSA the following factors may be considered: (1) the levels of education and experience of the inventor and other persons actively working in the field; (2) the types of problems encountered in the field; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology.

40. In my opinion, in the 2004/2005 timeframe, a POSA in the field of the '135 and '268 patents would have had an M.D. and several years of experience in treating patients with lipid disorders, including hyperlipidemia and hypercholesterolemia. The POSA would also have had access to and worked with individuals involved in drug discovery and development with degrees in medicinal chemistry, pharmacology, or drug delivery sciences and several years of experience in the development of drugs for the U.S. market.

41. Dr. Zusman asserts that a POSA would have had "graduate and/or post-graduate education in a pertinent discipline such as medicine, medicinal chemistry, pharmacology, or drug development and delivery." Zusman ¶ 28. In my view, the '135 and '268 patents are focused more on a treating physician, but as noted above, that physician would have had access to and worked with individuals having other areas of expertise. Dr. Zusman further opines that a POSA "would remain abreast of current developments in their field (including the activities of pharmaceutical companies) by reviewing and analyzing relevant

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Source: Ex. 2023, Sacks Decl., ¶ 40; POR at 9; MTA at 10

Patent Owner's Expert: Frank Sacks, M.D.

- M.D. from Columbia University
- Professor of Cardiovascular Disease Prevention at the Harvard School of Public Health and a Professor of Medicine at Harvard Medical School
- Leader in the field of lipid disorders; has treated hundreds of patients with hypercholesterolemia and hyperlipidemia
- Began treating patients with lomitapide (compassionate use) in 1999

Source: Ex. 2023 (Sacks Dec.) at ¶1-21

Patent Owner's Expert: Thomas A. Baillie, Ph.D., D.Sc.

- **Ph.D. in organic chemistry, Glasgow University in Scotland**
- **Professor of Medicinal Chemistry and Dean Emeritus of the School of Pharmacy at the University of Washington; thirty years of teaching experience**
- **Served as global head of the Drug Metabolism and Pharmacokinetics (DMPK) function at Merck Research Laboratories for nearly fifteen years**
- **Participated in the design of numerous Merck clinical trials; specialized in the analysis of animal PK/PD data to determine a first-in-human dose**

Source: Ex. 2024 (Baillie Decl.) at ¶¶7-13

Patent Owner's Expert: S. David Kimball, Ph.D.

- **Ph.D. in organic chemistry and chemical biology from SUNY Stony Brook**
- **Medicinal chemist at Bristol-Myers Squibb for nineteen years; led drug discovery efforts in cardiovascular disease, oncology, and infectious disease**
- **Associate Vice President for Research Commercialization in the Office of Research and Economic Development at Rutgers University**
- **Over ten years of executive leadership experience at biotechnology companies**

Source: Ex. 2025 (Kimball Decl.) at ¶¶7-16

Patent Owner's Declarant: Daniel J. Rader, M.D.

- **Sole Inventor of the '268 and '135 Patents**
- **M.D. from the Medical College of Pennsylvania**
- **Seymour Gray Professor of Molecular Medicine at the University of Pennsylvania Perelman School of Medicine**
- **Conducted clinical trials with lomitapide on behalf of both BMS and Patent Owner**
- **Forty years of experience treating patients with lipid disorders**

Source: Ex. 2026 (Rader Decl.) at ¶¶1-9

Patent Owner's Declarant: Richard E. Gregg, M.D.

- **M.D. from Stanford University**
- **Chief Scientific Officer at Vitae Pharmaceuticals, Inc.**
- **Worked at Bristol-Myers Squibb from 1988–2007; initiated and led MTP Inhibitor program; facilitated donation of lomitapide from BMS to Patent Owner**

Source: Ex. 2083 (Gregg Decl.) at ¶¶1-3

Motion to Amend

Patent Owner's Contingent Motion To Amend Should Be Granted

(1) The substitute claims remove the basis for instituting these IPRs

- Antedate Pink Sheet and Stein
- General "industry guidance" documents at most support a mere invitation to experiment and do not render the claims obvious

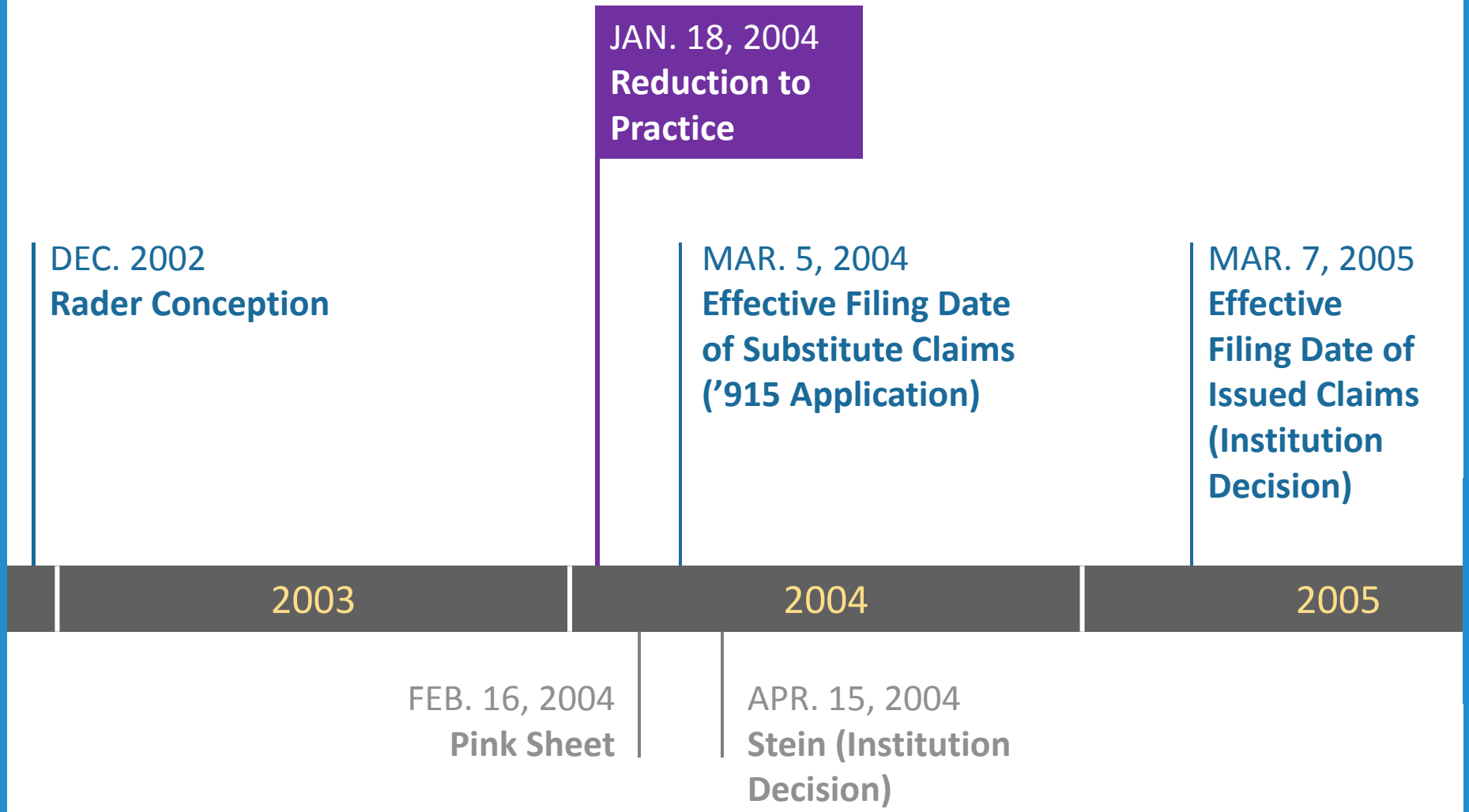
(2) The substitute claims present additional bases for patentability over the issued claims

- Stepwise dose-doubling method that is indisputably not in the prior art with respect to any MTP inhibitor

(3) The remaining requirements for the motion to amend are not disputed

- The substitute claims are narrower than the issued claims and supported by the written descriptions

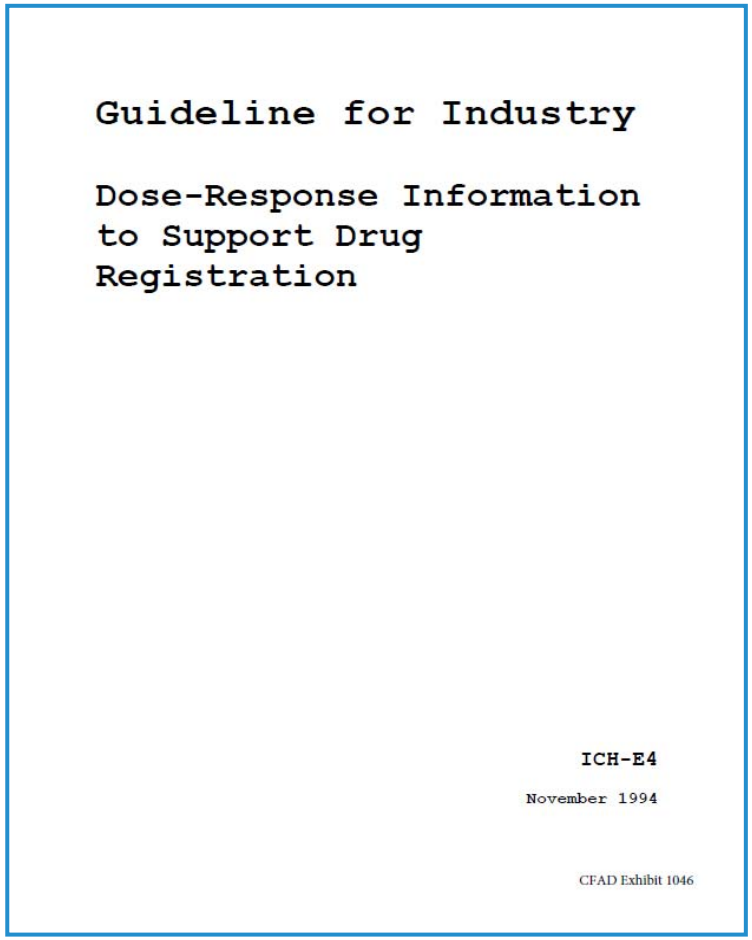
The Substitute Claims Pre-Date Pink Sheet And Stein



Ex. 2026, Rader Dec., ¶¶34-52, 54-55, 59-61, 62; Ex. 2077, 2002 Clinical Trial Protocol, at 4, 8, 14; MTA at 11-14; Ex. 2079 at 1; Ex. 2082 at 1, 3; Ex. 2081 at 1; Ex. 2005 at 9; Institution Decision at 17

ICH-E4 And FDA Draft Guidance Are Mere Invitations To Experiment

Without Pink Sheet and Stein, Petitioner can only point to generic "industry guidance" documents



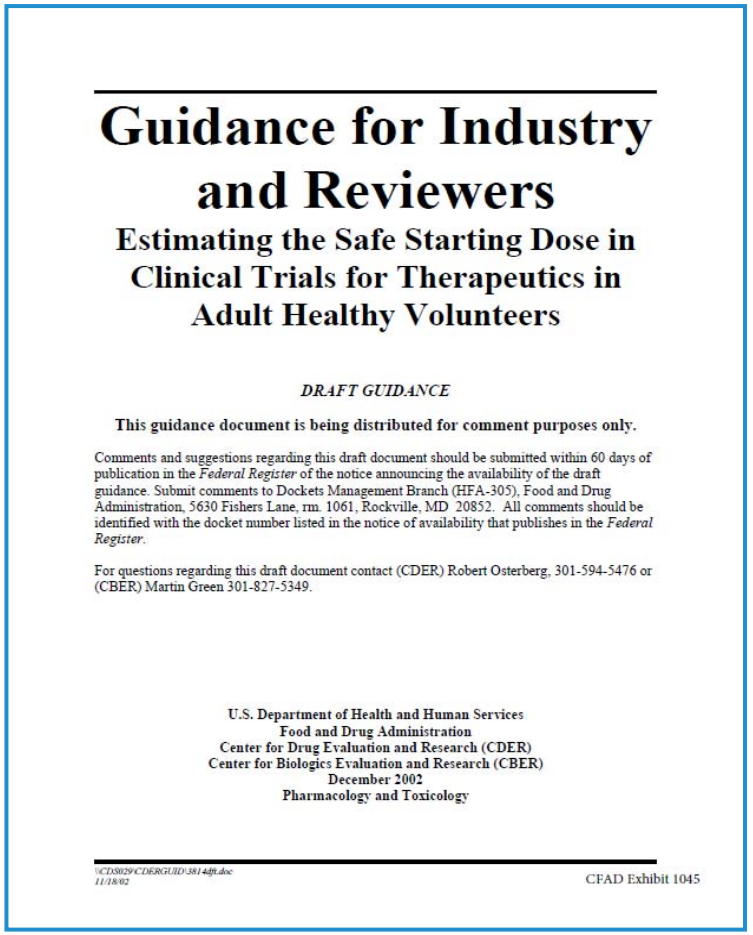
Guideline for Industry

Dose-Response Information to Support Drug Registration

ICH-E4

November 1994

CFAD Exhibit 1046



Guidance for Industry and Reviewers

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Osterberg, 301-594-5476 or (CBER) Martin Green 301-827-5349.

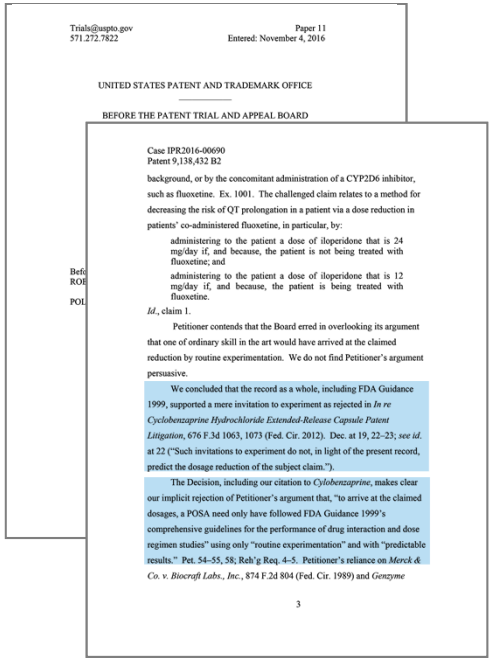
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
December 2002
Pharmacology and Toxicology

\\CDS029\CDERGUID\3814dft.doc 11/18/02

CFAD Exhibit 1045

Source: Ex. 1046 [1043] at 1; Ex. 1045 [1042] at 1

Mere Invitations To Experiment From General Guidance Documents Is Not Enough



Trials@uspto.gov
571.272.7822

Paper 11
Entered: November 4, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR2016-00690
Patent 9,138,432 B2

background, or by the concomitant administration of a CYP2D6 inhibitor, such as fluoxetine. Ex. 1001. The challenged claim relates to a method for decreasing the risk of QT prolongation in a patient via a dose reduction in patients' co-administered fluoxetine, in particular, by:

> administering to the patient a dose of iloperidone that is 24 mg/day if, and because, the patient is not being treated with fluoxetine; and
>
> administering to the patient a dose of iloperidone that is 12 mg/day if, and because, the patient is being treated with fluoxetine.

Id., claim 1.

Petitioner contends that the Board erred in overlooking its argument that one of ordinary skill in the art would have arrived at the claimed reduction by routine experimentation. We do not find Petitioner's argument persuasive.

We concluded that the record as a whole, including FDA Guidance 1999, supported a mere invitation to experiment as rejected in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012). Dec. at 19, 22–23; *see id.* at 22 ("Such invitations to experiment do not, in light of the present record, predict the dosage reduction of the subject claim.").

The Decision, including our citation to *Cyclobenzaprine*, makes clear our implicit rejection of Petitioner's argument that, "to arrive at the claimed dosages, a POSA need only have followed FDA Guidance 1999's comprehensive guidelines for the performance of drug interaction and dose regimen studies" using only "routine experimentation" and with "predictable results." Pet. 54–55, 58; Reh'g Req. 4–5. Petitioner's reliance on *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804 (Fed. Cir. 1989) and *Genzyme*

3

The Board has previously rejected obviousness arguments premised on generic industry guidance documents

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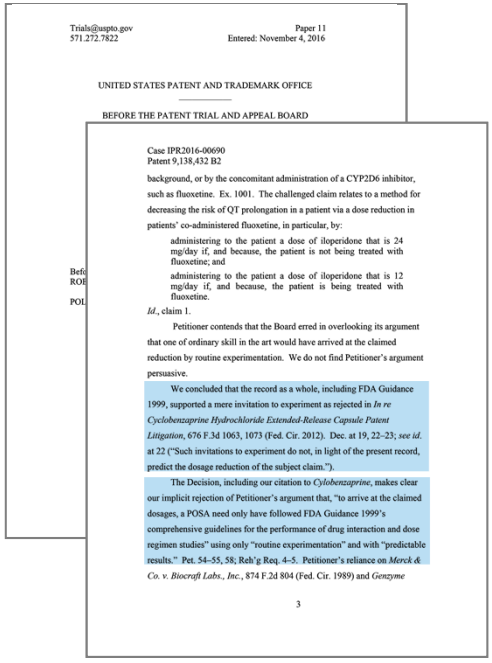
Source: *Roxane Laboratories v. Vanda Pharmaceuticals Inc.*, Case IPR2016-00690, slip op. at 3 (Paper 11, PTAB, Nov. 6, 2016)

Mere Invitations To Experiment From General Guidance Documents Is Not Enough



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Source: *Roxane Laboratories v. Vanda Pharmaceuticals Inc.*, Case IPR2016-00690, slip op. at 3 (Paper 11, PTAB, Nov. 6, 2016)

The Substitute Claims Are Directed To A More Aggressive Dosing Method with Lomitapide

Substitute Claim

11. (Proposed substitute for original claim 1) A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises **at least three step-wise, increasing dose levels** of the MTP inhibitor, wherein a first and second dose level is **50% of the immediately following dose level**, and wherein a third dose level is **from about 0.2 to about 0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg**; and wherein the MTP inhibitor is N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl) [1,1'-biphenyl]-2-yl] carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, **methanesulfonate**, and wherein each dose level is administered to the subject for **about 1 to about 5 weeks**.

Source: Ex. 1001, '135 Patent; MTA Appendix A at 7

The Aggressive Dosing Method Of The Substitute Claims Was Not In The Prior Art

Claim Element of Substitute Claim 11	Wetterau	Chang
A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises **at least three step-wise, increasing dose levels of the MTP inhibitor**,	Not disclosed	Not disclosed
wherein a first and a second dose level is **50% of the immediately following dose level**, and	Not disclosed	Not disclosed
wherein a **third dose level is from about 0.2 to about 0.59 mg/kg/day**	10 mg/kg in 5 rabbits	10 mg/kg in 5 rabbits
based on a **weight between 62.5 and 74.9 kg**; and	Not disclosed	Not disclosed
wherein the MTP inhibitor is N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl] amino]-1 piperidinyl]butyl]-9H-fluorene-9-carboxamide, **methanesulfonate**, and	Not disclosed	Not disclosed
wherein each dose level is administered to the subject for **about 1 to about 5 weeks**.	Not disclosed	Not disclosed

Source: MTA at 2, 14-15; RMTA at 7-8; Ex. 2305, Baillie Suppl. Decl., ¶¶ 10, 21-23, 34-40, 42-43; Ex. 1018 at 3; Ex. 1015

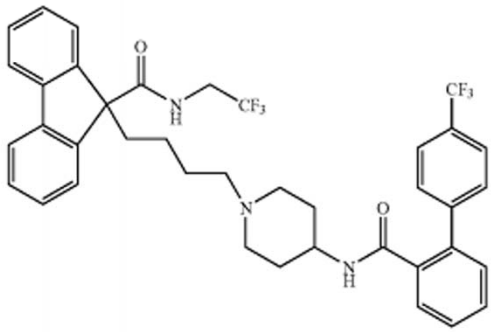
Patent Owner's Contingent Motion To Amend Should Be Granted

- **There is no dispute that the substitute claims are narrower than the issued claims**
- **There is no dispute that the substitute claims are supported by the written description**
- **The substitute claims are patentable**
  - Stein and Pink Sheet are not prior art to the substitute claims
  - The substitute claims are patentable over the six prior art references raised by Petitioner

Source: MTA at 2-25; RMTA at 1-12; Paper 31 [Paper 33]; Ex. 2305, Baillie Suppl. Decl., ¶¶ 19-40

The Substitute Claims Are Narrower

11. (Proposed substitute for original claim 1) A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor, wherein a first ~~dose level is from about 2 to about 13 mg/day,~~ and a second dose level is ~~from about 5 to about 30 mg/day~~ 50% of the immediately following dose level, and wherein a third dose level is from about ~~10~~ 0.2 to about ~~50~~ 0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg; and wherein the MTP inhibitor is ~~represented by:~~



~~or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof~~ N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate, and wherein each dose level is administered to the subject for about 1 to about 5 weeks.

- **Restricts the dose range**
- **Limits to one specific salt form of lomitapide**

Source: MTA at 3-5

The Substitute Claims Are Narrower

(1) By requiring the 1st and 2nd dose levels to be 50% of the doses they precede (i.e., dose-doubling)

(2) By restricting the dose range to an amount that is a subset of that originally claimed

	Dose 1	Dose 2	Dose 3
Original Claim 1	About **2** to about **13** mg/day	About **5** to about **30** mg/day	About **10** to about **50** mg/day
Limiting Amendments	**50%** of Dose 2	**50%** of Dose 3	About **0.2** to about **0.59 mg/kg/day** based on a weight between **62.5 kg** and **74.9 kg**
Substitute Claim 11 (converted to mg/day)	About **3.13** to about **11.05** mg/day	About **6.25** to about **22.1** mg/day	About **12.5** to about **44.19** mg/day

Source: MTA (01835) at 4-5

Patent Owner's Contingent Motion To Amend Should Be Granted

- **There is no dispute that the substitute claims are narrower than the issued claims**
- **There is no dispute that the substitute claims are supported by the written description**
- **The substitute claims are patentable**
  - Stein and Pink Sheet are not prior art to the substitute claims
  - The substitute claims are patentable over the six prior art references raised by Petitioner

Source: MTA at 2-25; RMTA at 1-12; Paper 31 [Paper 33]; Ex. 2305, Baillie Suppl. Decl., ¶¶ 19-40

The Substitute Claims Are Supported

- **There is no dispute that each and every limitation of the substitute claims appear in the written description**
  - "[T]he hallmark of written description is disclosure." *Ariad Pharms, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)
- **Unrebutted testimony from Dr. Sacks establishes that a POSA would understand that Dr. Rader was in possession of the claimed upward dose titration regimen at the time of filing**

Source: MTA at 5-10; Ex. 2023, Sacks Decl., at ¶¶26, 47, 154, 164-73

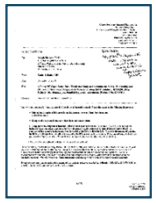
Patent Owner's Contingent Motion To Amend Should Be Granted

- **There is no dispute that the substitute claims are narrower than the issued claims**
- **There is no dispute that the substitute claims are supported by the written description**
- **The substitute claims are patentable**
  - Stein and Pink Sheet are not prior art to the substitute claims
  - The substitute claims are patentable over the six prior art references raised by Petitioner

Source: MTA at 2-25; RMTA at 1-12; Paper 31 [Paper 33]; Ex. 2305, Baillie Suppl. Decl., at ¶¶ 19-40

The Substitute Claims Pre-Date Pink Sheet And Stein

DEC. 2002
Rader Conception



Ex. 2077, p. 1

JUN. 2003
Dr. Rader's Clinical Trial Begins

Ex. 2079, p. 2

JAN. 18, 2004
Dr. Rader's Trial Ends – Reduction to Practice

Ex. 2082, p. 1

2002 | 2003 | 2004

FEB. 16, 2004
Pink Sheet 2004

Ex. 1013, p. 1

APR. 15, 2004
Stein (Institution Decision)

Ex. 1014, p. 1

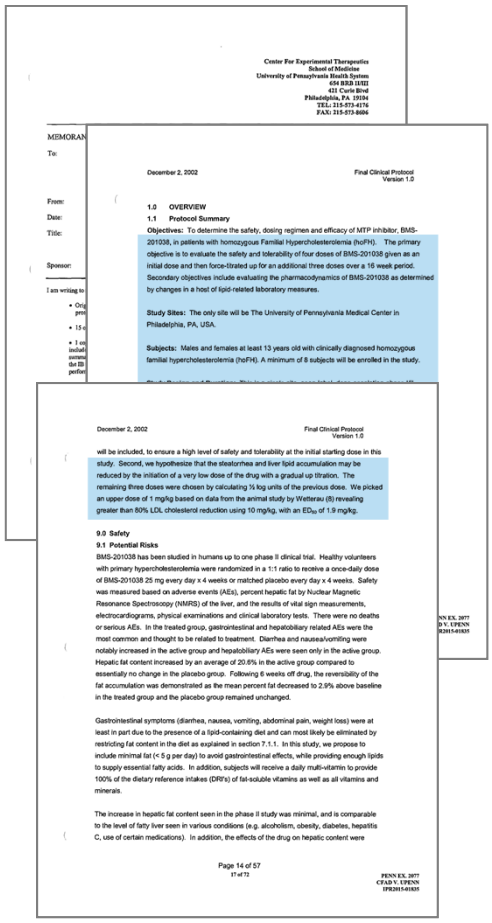
Ex. 2026, Rader Dec., at ¶¶34-52, 54-55, 59-61, 62; Ex. 2077, 2002 Clinical Trial Protocol, at 4, 8, 14; MTA at 11-14; Ex. 2079 at 1; Ex. 2082 at 1, 3; Ex. 2081 at 1; Ex. 2005 at 9; Institution Decision at 17

The Substitute Claims Were Reduced to Practice by January 18, 2004

Date	Event	Corroborating Evidence
Mid 2002	**Dr. Rader conceived upward dose titration with lomitapide to address side effects**	Ex. 2026
Dec. 2002	**Dr. Rader drafted clinical trial protocol testing an exemplary embodiment of his invention: upward dose titration (3x)**	Ex. 2026, 2077
March 2003	**Dr. Rader's clinical trial protocol approved by the IRB**	Ex. 2026, 2079
June 2003	**Clinical trial began**	Ex. 2026, 2082
October 2003	**Interim data reported good tolerability and efficacy with upward dose titration**	Ex. 2026, 2081
Jan. 18, 2004	**Clinical trial ended; Dr. Rader knows that upward dose titration works for intended purpose**	Ex. 2026, 2005

Source: Ex., 2026, Rader Dec., at ¶¶34-52, 54, 59-61, 62; Ex. 2077, 2002 Clinical Trial Protocol, at 4, 8, 14, 16; MTA at 11-13; Ex. 2079; Ex. 2082 at 1, 3-4; Ex. 2081 at 1-2; Ex. 2005 at 9

The Substitute Claims Were Conceived By December 2002



December 2, 2002 — Final Clinical Protocol Version 1.0

1.0 OVERVIEW

1.1 Protocol Summary

Objectives: To determine the safety, dosing regimen and efficacy of MTP inhibitor, BMS-201038, in patients with homozygous Familial Hypercholesterolemia (hoFH). The primary objective is to evaluate the safety and tolerability of four doses of BMS-201038 given as an initial dose and then force-titrated up for an additional three doses over a 16 week period. Secondary objectives include evaluating the pharmacodynamics of BMS-201038 as determined by changes in a host of lipid-related laboratory measures.

Study Sites: The only site will be The University of Pennsylvania Medical Center in Philadelphia, PA, USA.

Subjects: Males and females at least 13 years old with clinically diagnosed homozygous familial hypercholesterolemia (hoFH). A minimum of 8 subjects will be enrolled in the study.

December 2, 2002 — Final Clinical Protocol Version 1.0

will be included, to ensure a high level of safety and tolerability at the initial starting dose in this study. Second, we hypothesize that the steatorrhea and liver lipid accumulation may be reduced by the initiation of a very low dose of the drug with a gradual up titration. The remaining three doses were chosen by calculating ½ log units of the previous dose. We picked an upper dose of 1 mg/kg based on data from the animal study by Wetterau (8) revealing greater than 80% LDL cholesterol reduction using 10 mg/kg, with an ED_{50} of 1.9 mg/kg.

9.0 Safety

9.1 Potential Risks

BMS-201038 has been studied in humans up to one phase II clinical trial. Healthy volunteers with primary hypercholesterolemia were randomized in a 1:1 ratio to receive a once-daily dose of BMS-201038 25 mg every day x 4 weeks or matched placebo every day x 4 weeks. Safety was measured based on adverse events (AEs), percent hepatic fat by Nuclear Magnetic Resonance Spectroscopy (NMRS) of the liver, and the results of vital sign measurements, electrocardiograms, physical examinations and clinical laboratory tests. There were no deaths or serious AEs. In the treated group, gastrointestinal and hepatobiliary related AEs were the most common and thought to be related to treatment. Diarrhea and nausea/vomiting were notably increased in the active group and hepatobiliary AEs were seen only in the active group. Hepatic fat content increased by an average of 20.6% in the active group compared to essentially no change in the placebo group. Following 6 weeks off drug, the reversibility of the fat accumulation was demonstrated as the mean percent fat decreased to 2.9% above baseline in the treated group and the placebo group remained unchanged.

Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain, weight loss) were at least in part due to the presence of a lipid-containing diet and can most likely be eliminated by restricting fat content in the diet as explained in section 7.1.1. In this study, we propose to include minimal fat (< 5 g per day) to avoid gastrointestinal effects, while providing enough lipids to supply essential fatty acids. In addition, subjects will receive a daily multi-vitamin to provide 100% of the dietary reference intakes (DRI's) of fat-soluble vitamins as well as all vitamins and minerals.

The increase in hepatic fat content seen in the phase II study was minimal, and is comparable to the level of fatty liver seen in various conditions (e.g. alcoholism, obesity, diabetes, hepatitis C, use of certain medications). In addition, the effects of the drug on hepatic content were

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PENN EX. 2077 CFAD V. UPENN IPR2015-01035

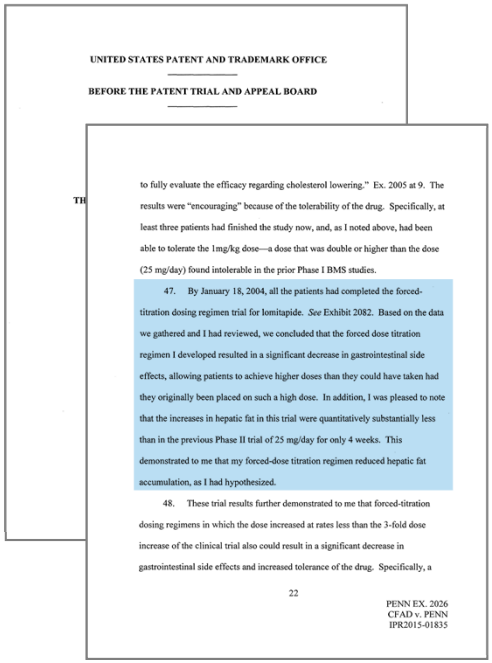
Dr. Rader conceived of general idea that an upward dose titration would ameliorate the side effects associated with lomitapide

"The primary objective is to evaluate the safety and tolerability of four doses of BMS-201038 given as an initial dose and then force-titrated up for an additional three doses over a 16 week period."

"…we hypothesize that the steatorrhea and liver lipid accumulation may be reduced by the initiation of a very low dose of the drug with a gradual up titration."

Source: Ex. 2077, December 2002 Clinical Trial Protocol, at 7, 17

The Substitute Claims Were Reduced To Practice By January 18, 2004



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BEFORE THE PATENT TRIAL AND APPEAL BOARD

to fully evaluate the efficacy regarding cholesterol lowering." Ex. 2005 at 9. The results were "encouraging" because of the tolerability of the drug. Specifically, at least three patients had finished the study now, and, as I noted above, had been able to tolerate the 1mg/kg dose—a dose that was double or higher than the dose (25 mg/day) found intolerable in the prior Phase I BMS studies.

47. By January 18, 2004, all the patients had completed the forced-titration dosing regimen trial for lomitapide. *See* Exhibit 2082. Based on the data we gathered and I had reviewed, we concluded that the forced dose titration regimen I developed resulted in a significant decrease in gastrointestinal side effects, allowing patients to achieve higher doses than they could have taken had they originally been placed on such a high dose. In addition, I was pleased to note that the increases in hepatic fat in this trial were quantitatively substantially less than in the previous Phase II trial of 25 mg/day for only 4 weeks. This demonstrated to me that my forced-dose titration regimen reduced hepatic fat accumulation, as I had hypothesized.

48. These trial results further demonstrated to me that forced-titration dosing regimens in which the dose increased at rates less than the 3-fold dose increase of the clinical trial also could result in a significant decrease in gastrointestinal side effects and increased tolerance of the drug. Specifically, a

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PENN EX. 2026
CFAD v. PENN
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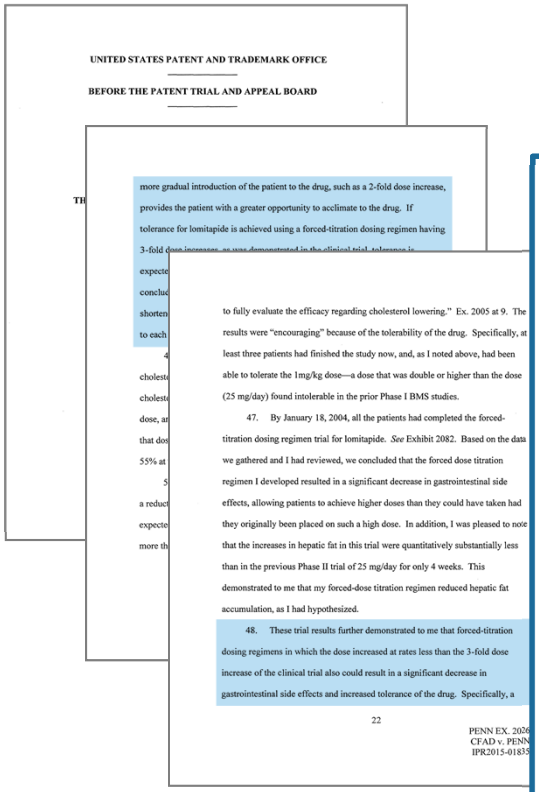
Results from the clinical trial proved Dr. Rader's general hypothesis

47. By January 18, 2004, all the patients had completed the forced-titration dosing regimen trial for lomitapide. *See* Exhibit 2082. Based on the data we gathered and I had reviewed, we concluded that the forced dose titration regimen I developed resulted in a significant decrease in gastrointestinal side effects, allowing patients to achieve higher doses than they could have taken had they originally been placed on such a high dose. In addition, I was pleased to note that the increases in hepatic fat in this trial were quantitatively substantially less than in the previous Phase II trial of 25 mg/day for only 4 weeks. This demonstrated to me that my forced-dose titration regimen reduced hepatic fat accumulation, as I had hypothesized.

Source: Ex. 2026, Rader Decl., ¶ 47

The Substitute Claims Were Reduced To Practice By January 18, 2004


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

more gradual introduction of the patient to the drug, such as a 2-fold dose increase, provides the patient with a greater opportunity to acclimate to the drug. If tolerance for lomitapide is achieved using a forced-titration dosing regimen having

to fully evaluate the efficacy regarding cholesterol lowering." Ex. 2005 at 9. The results were "encouraging" because of the tolerability of the drug. Specifically, at least three patients had finished the study now, and, as I noted above, had been able to tolerate the 1mg/kg dose—a dose that was double or higher than the dose (25 mg/day) found intolerable in the prior Phase I BMS studies.

47. By January 18, 2004, all the patients had completed the forced-titration dosing regimen trial for lomitapide. *See* Exhibit 2082. Based on the data we gathered and I had reviewed, we concluded that the forced dose titration regimen I developed resulted in a significant decrease in gastrointestinal side effects, allowing patients to achieve higher doses than they could have taken had they originally been placed on such a high dose. In addition, I was pleased to note that the increases in hepatic fat in this trial were quantitatively substantially less than in the previous Phase II trial of 25 mg/day for only 4 weeks. This demonstrated to me that my forced-dose titration regimen reduced hepatic fat accumulation, as I had hypothesized.

48. These trial results further demonstrated to me that forced-titration dosing regimens in which the dose increased at rates less than the 3-fold dose increase of the clinical trial also could result in a significant decrease in gastrointestinal side effects and increased tolerance of the drug. Specifically, a

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PENN EX. 2026
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Results from the 3x dosing trial demonstrated that a less-aggressive 2x administration would also work

48. These trial results further demonstrated to me that forced-titration dosing regimens in which the dose increased at rates less than the 3-fold dose increase of the clinical trial also could result in a significant decrease in gastrointestinal side effects and increased tolerance of the drug. Specifically, a more gradual introduction of the patient to the drug, such as a 2-fold dose increase, provides the patient with a greater opportunity to acclimate to the drug. If tolerance for lomitapide is achieved using a forced-titration dosing regimen having 3-fold dose increases, as was demonstrated in the clinical trial, tolerance is expected for a forced-titration dosing regimen having 2-fold dose increases. I also concluded that the dosing intervals of 4 weeks used in the clinical trial could be shortened or lengthened, to adjust to the individual patients' abilities to acclimate to each dose.

Source: Ex. 2026, Rader Decl., ¶ 48 ; RMTA at 12

The Substitute Claims Were Reduced To Practice By January 18, 2004

Petitioner's expert agrees that it would be reasonable to expect success with 2x dosing based on success with 3x dosing

Q. And given what was known about the drug, would a person of skill in the art have had a reasonable expectation that **if a patient could tolerate a titration regimen where the dosage was tripled**, that they could also tolerate a titration regimen where the dosage was **doubled**?

A. Yes. I believe there was a reasonable expectation of success for what you've just described.

Source: Ex. 2306, Zusman Dep., 6:19 –7:3

The Substitute Claims Are Patentable Over The Prior Art

- **Stein and Pink Sheet are not prior art to the substitute claims**
  - Dr. Rader invented the subject matter of the substitute claims no later than January 18, 2014
  - Pink Sheet published Feb. 16, 2004; Stein allegedly published April 15, 2004 (Institution Decision)
- **The substitute claims are patentable over Petitioner's new six-way combination based on Wetterau**
- **The substitute claims are also patentable even if Stein or Pink Sheet is prior art**

Source: MTA at 11-14; RMTA at 1-3, 12; Baillie Suppl. Decl. (Ex. 2305) at ¶¶ 10-40; Institution Decision at 17

The Substitute Claims Are Patentable Over Petitioner's New Six-Way Obviousness Combination

- **No motivation to combine:**
  - No reason to select lomitapide over other MTP inhibitors
  - Counter-intuitive to use a 2x escalating dosing regimen to address lomitapide's side effects
- **No reasonable expectation of success:**
  - Wetterau's single rabbit study provides insufficient data
  - No PK/PD (or any other data) available
  - Could not predict that a 2x escalating dosing regimen would address lomitapide's side effects
- **Objective indicia of non-obviousness**
  - For the same reasons they favor patentability of the original claims

Source: RMTA at 3-12; Ex. 2305, Baillie Supp. Decl. at ¶¶ 20-40

No Motivation To Resurrect Development With Lomitapide

- **The 1998 Wetterau rabbit study pre-dates lomitapide's withdrawal from the clinic**
  - Wetterau data was published by BMS, i.e., the same company that withdrew lomitapide
  - POSA would not start down the same failed path
- **No other data regarding lomitapide was available in the prior art (human, animal, in vitro, PK/PD)**
- **BMS was actively looking for a replacement MTP Inhibitor (Robl)**

Source: Ex. 2305, Baillie Supp. Decl. at ¶¶ 17, 34, 40; MTA at 17-18, 20-22; RMTA at 1-3, 7-8; Ex. 2020, Robl 2001, at 1

No Motivation To Use A 2x Escalating Dosing Method

- **Lomitapide was known to cause side effects that increased with the dose (Chang)**
- **Counter-intuitive to use a 2x escalating dosing method with a compound that caused dose-dependent side effects**

Source: Ex. 2305, Baillie Supp. Decl. at ¶¶ 24-25, 28; MTA at 16, 19-20; RMTA at 2, 4-8

No Reasonable Expectation That A 2x Escalating Dosing Method Would Address Side Effects

- **A POSA would not extrapolate a human dose based solely on Wetterau's rabbit study**
  - The data was generated prior to lomitapide's withdrawal from the clinic
  - The WHHL rabbit model has limited predictive power
  - No other data was available in the art (e.g., PK/PD)
- **Not predictable that a 2x escalating dosing method would work with a compound that caused dose-dependent side effects**

Source: Ex. 2305, Baillie Supp. Decl. at ¶¶ 17, 24-25, 28, 34, 40; MTA at 16-22; RMTA at 1-8

The Substitute Claims are Patentable Over Petitioner's New Six-Way Obviousness Combination

	Petitioner Alleges	Petitioner Fails to Mention:
Wetterau (Ex. 1018)	**Results in WHHL rabbit model would motivate a POSA to develop lomitapide for HoFH**	**Published prior to lomitapide's withdrawal from the clinic. WHHL rabbit study consisted of five rabbits at a single dose for two weeks; no PK Data and scant toxicity data**
ICH-E4 (Ex. 1046/1043)	**Discusses forced titration**	**Teaches numerous titration strategies; teaches that forced titration has "critical disadvantage" in terms of studying adverse events; emphasizes the importance of PK/PD data**
Reigner (Ex. 1047/1044)	**Discusses two-fold dose escalation**	**Teaches numerous dose escalation strategies, and that the escalation factor should be adjusted based on toxicity; emphasizes the importance of PK/PD data**
FDA Guidance (Ex. 1045/1042)	**Discusses possible conversion of animal data into a starting human dose**	**Requires detailed analysis to determine safety factor and "most appropriate" animal species; emphasizes the importance of PK/PD data**
Chang (Ex. 1015)	**Identifies Wetterau compound 9 (lomitapide) as BMS-201038**	**Provides no data for lomitapide beyond citations to Wetterau; teaches that MTP inhibitors exhibit dose-dependent toxicity**
'653 Patent (Ex. 2095)	**Disclosed oral formulations containing lomitapide mesylate salt**	**No evidence that the human oral formulation disclosed is the same or similar to the formulation used in Wetterau's rabbit study**

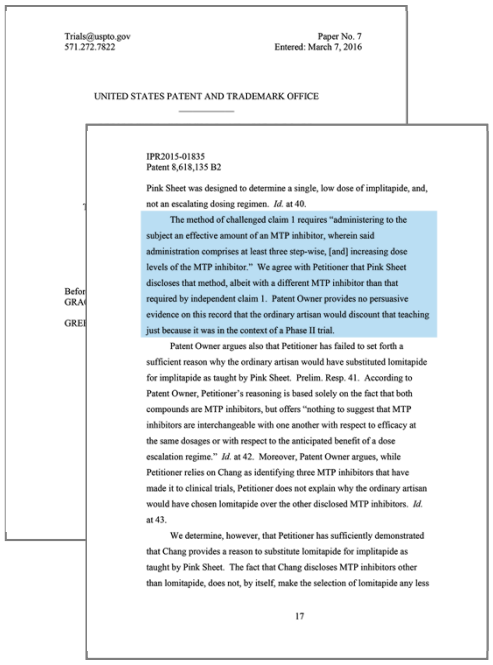
Source: Petitioner's Opposition to Motion to Amend at 11-16; RMTA at 3-8; Ex. 2305, Baillie Suppl. Decl. at ¶¶ 19-43

The Substitute Claims Are Patentable Over Petitioner's Original Obviousness Combination

- **Pink Sheet and Stein do not teach the two-fold increasing dose regimen in the substitute claims**
  - Stein / Pink Sheet:
    - Conservative titration
    - Gradual dose increase of 5 mg per level over five week intervals
    - No specified target dose
  - Substitute claims:
    - Aggressive titration
    - Dose is doubled at each level at intervals as short as one week
    - Specified target dose
- **No teaching of specific salt form required by substitute claims**

Source: Ex. 2305, Baillie Suppl. Decl. at ¶¶ 15-17, 34; RMTA at 9-10

The Motion To Amend Overcomes The Instituted Grounds



Trials@uspto.gov
571.272.7822

Paper No. 7
Entered: March 7, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

IPR2015-01835
Patent 8,618,135 B2

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

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

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

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

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The Institution Decision was premised on the availability of Pink Sheet and Stein as prior art

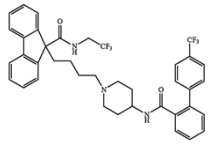
"The method of challenged claim 1 requires 'administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, [and] increasing dose levels of the MTP inhibitor.' We agree with Petitioner that Pink Sheet discloses that method, albeit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

Source: Institution Decision at 17

The Substitute Claims Are Narrower

Changes to Issued Claim

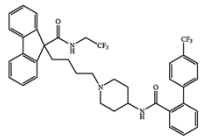
11. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia,
the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor**,** wherein a first ~~dose level is from about 2 to about 13 mg/day~~, **and** a second dose level is ~~from about 5 to about 30 mg/day~~ **50% of the immediately following dose level**, and **wherein** a third dose level is from about ~~10~~ **0.2** to about ~~50 mg/day~~ **0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg**; and wherein the MTP inhibitor is ~~represented by~~:



~~or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof~~ **N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl] amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate**, and wherein each dose level is administered to the subject for about 1 to about 5 weeks.

Final Substitute Claim

11. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor, wherein a first and a second dose level is 50% of the immediately following dose level, and wherein a third dose level is from about 0.2 to about 0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg; and wherein the MTP inhibitor is:



N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl] amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate, and wherein each dose level is administered to the subject for about 1 to about 5 weeks.

Source: Ex. 1001, '135 Patent; MTA at 3-5; MTA Appendix A at 2-3, 7

The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
11. A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, increasing dose levels of the MTP inhibitor,	[0020]: "The present invention relates to methods of treating a subject suffering from a disorder associated with hyperlipidemia. The methods comprise administering to the subject an effective amount of an MTP inhibitor to ameliorate hyperlipidemia in the subject. The administration comprises at least three step-wise, increasing dosages of the MTP inhibitor." *See also* [0033] (hypercholesterolemia); ¶ [0001] (Abstract); Claim 2. Source: Ex. 1006, '915 Appl., at [0020], [0033], [0001], Claim 2	[0024]: "In some embodiments the invention relates to methods of treating a subject suffering from a disorder associated with hyperlipidemia and/or hypercholesterolemia. The methods comprise administering to the subject an amount of an MTP inhibitor effective to ameliorate the disorder, wherein said administration comprises at least three step-wise, increasing dosages of the MTP inhibitor." *See also* [0042]; [0027] Source: Ex. 1008, '118 Appl., at [0024], [0042], [0027]

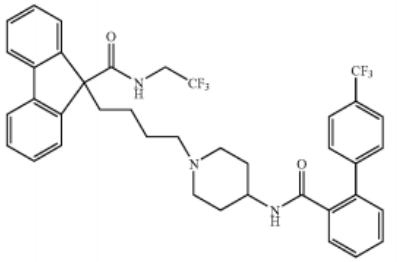
The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
wherein a first ~~dose level is from about 2 to about 13 mg/day~~, and a second dose level is ~~from about 5 to about 30 mg/day~~ 50% of the immediately following dose level, and	[0046] "In some embodiments, **each dose level is no more than 50% of the immediately following dose level."** [0093] (Example 5) showing a 50% escalation between doses 1-4: "For BMS-201038-treated patients, study drug will be initiated at 6.25 mg/d for 1 week and then will be titrated up to 12.5 mg/day for 2 weeks followed by 25 mg/day for 4 weeks and then to 50 mg/day for 4 weeks." *See also* Claim 18: "A method of claim 17 wherein each said dose level is no more than 50% of the immediately following dose level." Source: Ex. 1006, '915 Appl., at [0046], [0093], Claim 18	[0053] "In some embodiments, **each dose level is no more than 50% of the immediately following dose level."** [00112] (Example 7) showing a 50% escalation between doses 1-4: "For BMS-201038-treated patients, study drug will be initiated at 6.25 mg/d for 1 week and then will be titrated up to 12.5 mg/day for 2 weeks followed by 25 mg/day for 4 weeks and then to 50 mg/day for 4 weeks." [0074] (50% escalation between doses 1-3) Source: Ex. 1008, '118 Appl., at [0053], [00112], [0074]

The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
wherein a third dose level is from about ~~10~~ 0.2 to about ~~50 mg/day~~ 0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg; and	[0047] "In some embodiments, **the third dose level is from about 0.2 to about 0.59 mg/kg/day."** [0093] (Example 5): "For BMS-201038-treated patients, study drug will be initiated at 6.25 mg/d for 1 week and then will be titrated up to 12.5 mg/day for 2 weeks followed by 25 mg/day for 4 weeks and then to 50 mg/day for 4 weeks. BMS-201038 treated **subjects whose weight is between 62.5 and 74.9 kg** will titrate up to 62.5 mg/day for an additional 4 weeks." [0097] (Example 6): "70 kg man" Source: Ex. 1006, '915 Appl., at [0047], [0093], [0097]]	[0054] "In some embodiments, **the third dose level is from about 0.2 to about 0.59 mg/kg/day."** [00112] (Example 7): "For BMS-201 038- treated patients, study drug will be initiated at 6.25 mg/d for **1** week and then will be titrated up to 12.5 mg/day for 2 weeks followed by 25 mg/day for 4 weeks and then to 50 mg/day for 4 weeks. BMS-20 I 038 treated **subjects whose weight is between 62.5 and 74.9 kg** will titrate up to 62.5 mg/day for an additional 4 weeks." [00116] (Example 8): "70 kg man" Source: Ex. 1008, '118 Appl.,, at [0054], [00112], [00116]

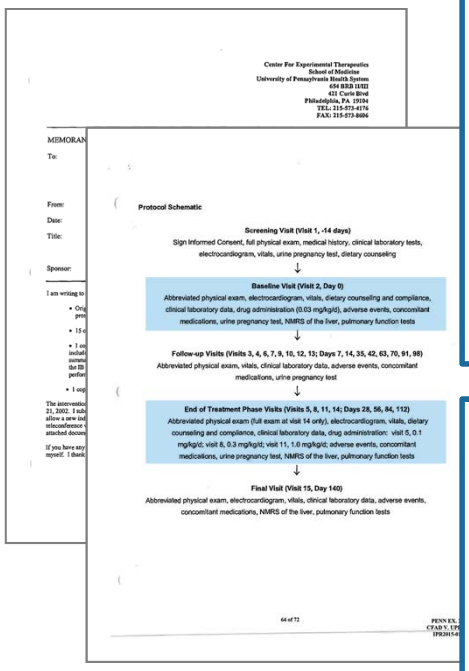
The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
wherein the MTP inhibitor is ~~represented by~~:  ~~or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof~~ N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl] carbonyl] amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate, and	[0043] "In some embodiments, the inhibitor is BMS-201038. As used herein, the phrase **'BMS-201038' refers to a compound known as N-(2,2,2-Trifluorethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[l,1'biphenyl]-2-Yl]carbonyl]amino]-1-piperidinyl]butyl]9H-fluorene-9-carboxamide, methanesulfonate."** Source: Ex. 1006, '915 Appl., at [0043]	[0034] "In some embodiments, the MTP inhibitor is BMS-20 1038. As used herein, the phrase **'BMS-201038' refers to a compound known as N-(2,2,2-Trifluorethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1, l 'biphenyl]-2Yl]carbonyl]amino]-l-piperidinyl]butyl]9H-fluorene-9-carboxamide, methanesulfonate"** Source: Ex. 1008, '118 Appl., at [0034]

The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
wherein each dose level is administered to the subject for about 1 to about 5 weeks.	[0048] "In some embodiments, each dose level is administered to the subject for 1-5 weeks." *See also* [0049]; [0050]; Claims 24, 33, 61 Source: Ex. 1006, '915 Appl., at [0048], [0049], [0050], Claims 24, 33, 61	[0063] "In some embodiments, each dose level is administered to the subject for 1 week to 5 weeks." *See also* [0056] Source: Ex. 1008, '118 Appl., at [0063], [0056]

The Substitute Claims Were Conceived By December 2002



Baseline Visit (Visit 2, Day 0)

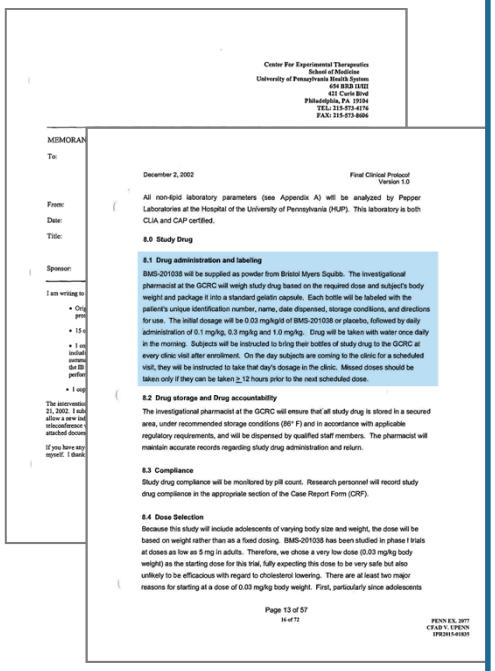
"Abbreviated physical exam, electrocardiogram, vitals, dietary counseling and compliance, clinical laboratory data, drug administration (0.03 mg/kg/d), adverse events, concomitant medications, urine pregnancy test, NMRS of the liver, pulmonary function tests"

End of Treatment Phase Visits (Visits 5, 8, 11, 14; Days 28, 56, 84, 112)

"Abbreviated physical exam (full exam at visit 14 only), electrocardiogram, vitals, dietary counseling and compliance, clinical laboratory data, drug administration: visit 5, 0.1 mg/kg/d; visit 8, 0.3 mg/kg/d; visit 11, 1.0 mg/kg/d; adverse events, concomitant medications, urine pregnancy test, NMRS of the liver, pulmonary function tests"

Source: December 2002 Clinical Trial Protocol (Ex. 2077) at 64, 72

The Substitute Claims Were Conceived By December 2002



December 2, 2002 Final Clinical Protocol Version 1.0

All non-lipid laboratory parameters (see Appendix A) will be analyzed by Pepper Laboratories at the Hospital of the University of Pennsylvania (HUP). This laboratory is both CLIA and CAP certified.

8.0 Study Drug

8.1 Drug administration and labeling

BMS-201038 will be supplied as powder from Bristol Myers Squibb. The investigational pharmacist at the GCRC will weigh study drug based on the required dose and subject's body weight and package it into a standard gelatin capsule. Each bottle will be labeled with the patient's unique identification number, name, date dispensed, storage conditions, and directions for use. The initial dosage will be 0.03 mg/kg/d of BMS-201038 or placebo, followed by daily administration of 0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg. Drug will be taken with water once daily in the morning. Subjects will be instructed to bring their bottles of study drug to the GCRC at every clinic visit after enrollment. On the day subjects are coming to the clinic for a scheduled visit, they will be instructed to take that day's dosage in the clinic. Missed doses should be taken only if they can be taken ≥ 12 hours prior to the next scheduled dose.

8.2 Drug storage and Drug accountability

The investigational pharmacist at the GCRC will ensure that all study drug is stored in a secured area, under recommended storage conditions (86° F) and in accordance with applicable regulatory requirements, and will be dispensed by qualified staff members. The pharmacist will maintain accurate records regarding study drug administration and return.

8.3 Compliance

Study drug compliance will be monitored by pill count. Research personnel will record study drug compliance in the appropriate section of the Case Report Form (CRF).

8.4 Dose Selection

Because this study will include adolescents of varying body size and weight, the dose will be based on weight rather than as a fixed dosing. BMS-201038 has been studied in phase I trials at doses as low as 5 mg in adults. Therefore, we chose a very low dose (0.03 mg/kg body weight) as the starting dose for this trial, fully expecting this dose to be very safe but also unlikely to be efficacious with regard to cholesterol lowering. There are at least two major reasons for starting at a dose of 0.03 mg/kg body weight. First, particularly since adolescents

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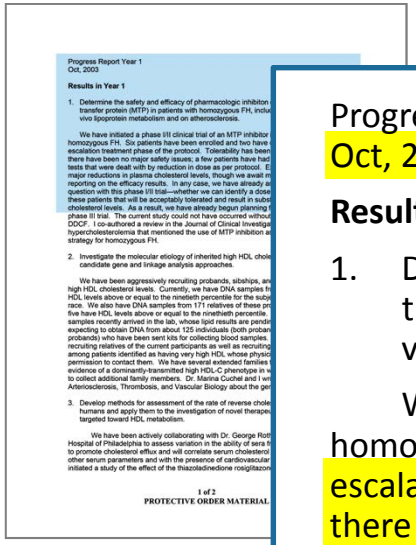
PENN EX. 2077
CFAD V. UPENN
IPR2015-01035

8.1 Drug administration and labeling

"BMS-201038 will be supplied as powder from Bristol Myers Squibb. The investigational pharmacist at the GCRC will weigh study drug based on the required dose and subject's body weight and package it into a standard gelatin capsule. Each bottle will be labeled with the patient's unique identification number, name, date dispensed, storage conditions. and directions for use. The initial dosage will be 0.03 mg/kg/d of BMS-201038 or placebo, followed by daily administration of 0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg. Drug will be taken with water once daily in the morning. Subjects will be instructed to bring their bottles of study drug to the GCRC at every clinic visit after enrollment. On the day subjects are coming to the clinic for a scheduled visit, they will be instructed to take that day's dosage in the clinic. Missed doses should be taken only if they can be taken ≥ 12 hours prior to the next scheduled dose."

Source: December 2002 Clinical Trial Protocol (Ex. 2077) at 16, 64

Interim Data From Dr. Rader's Study Shows Tolerability And Efficacy



Progress Report Year 1
Oct, 2003

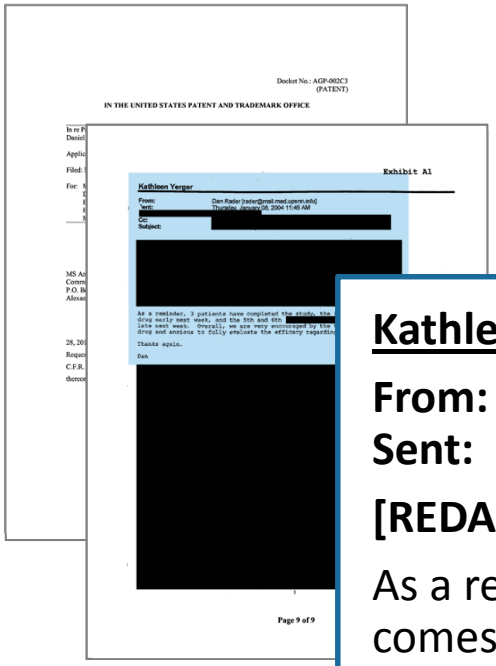
Results in Year 1

1. Determine the safety and efficacy of pharmacologic inhibition of the microsomal transfer protein (MTP) in patients with homozygous FH, including the effects on in vivo lipoprotein metabolism and on atherosclerosis.

We have initiated a phase I/II clinical trial of an MTP inhibitor in patients with homozygous FH. Six patients have been enrolled and two have completed the dose escalation treatment phase of the protocol. Tolerability has been surprisingly good, and there have been no major safety issues; a few patients have had increased liver function tests that were dealt with by reduction in dose as per protocol. Excitingly, we have seen major reductions in plasma cholesterol levels, though we await more data before reporting on the efficacy results. In any case, we have already answered our major question with this phase I/II trial—whether we can identify a dose of the MTP inhibitor in these patients that will be acceptably tolerated and result in substantial reduction in cholesterol levels.

Source: Ex. 2081 at 1

Interim Data From Dr. Rader's Study Shows Tolerability And Efficacy



Kathleen Yerger

From: **Dan Rader [rader@mail.med.upenn.edu]**
Sent: **Thursday, January 08, 2004 11:46 AM**

[REDACTED]

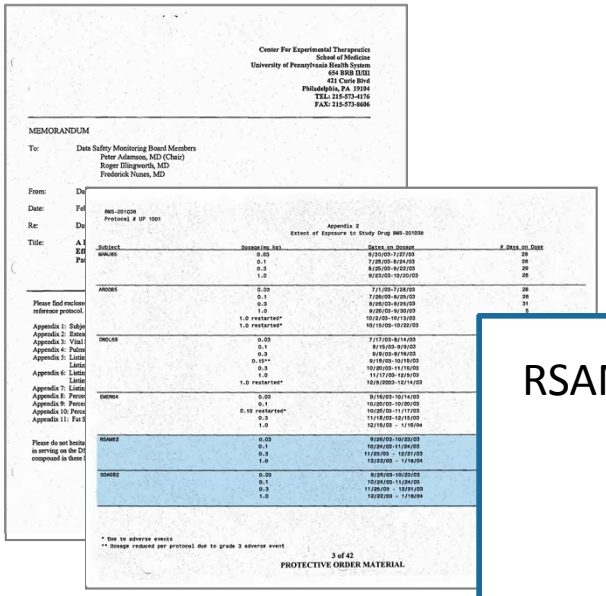
As a reminder, 3 patients have completed the study, the fourth comes off drug early next week, and the 5th and 6th [REDACTED] came off late next week. Overall, we are very encouraged by the tolerability of the drug and anxious to fully evaluate the efficacy regarding cholesterol lowering.

Thanks again.

Dan

Source: Ex. 2005 at 9

The Substitute Claims Were Reduced To Practice By January 18, 2004 (filed under seal)



MEMORANDUM

To: Data Safety Monitoring Board Members
Peter Adamson, MD (Chair)
Roger Illingworth, MD
Frederick Nunes, MD

Appendix 2
Extent of Exposure in Study Drug BMS-201038

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PROTECTIVE ORDER MATERIAL

Last patient received final dose on 01/18/04

RSAM82	0.03	9/26/03-10/23/03	28
	0.1	10/24/03-11/24/03	32
	0.3	11/25/03-12/21/03	27
	1.0	12/22/03-1/18/04	28
S0AG82	0.03	9/28/03-10/23/03	28
	0.1	10/24/03-11/24/03	32
	0.3	11/25/03-12/21/03	27
	1.0	12/22/03-1/18/04	28

Source: Ex. 2082 at 3

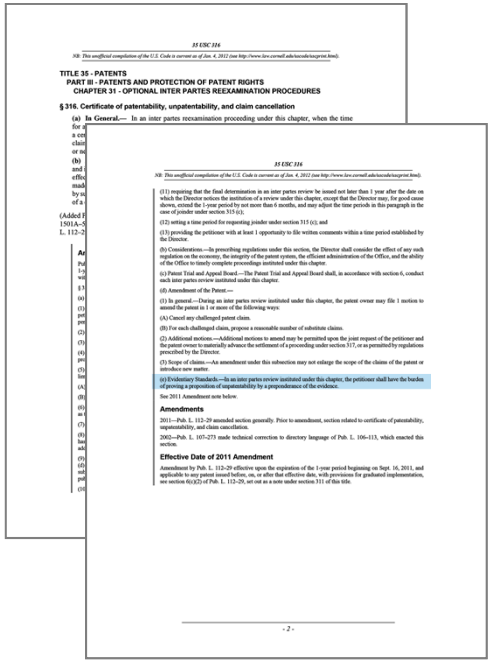
The Substitute Claims Were Reduced To Practice By January 18, 2004

"The adequacy of a reduction to practice is to be tested by what one of ordinary skill in the art would conclude from the results of the tests."

- *Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304 F.3d 1256, 1265 (Fed. Cir. 2002).

Source: RMTA at 12

Petitioner Has The Burden On All Propositions Of Unpatentability



35 USC 316

NB: This unofficial compilation of the U.S. Code is current as of Jan. 4, 2012 (see http://www.law.cornell.edu/uscode/uscprint.html).

TITLE 35 - PATENTS
PART III - PATENTS AND PROTECTION OF PATENT RIGHTS
CHAPTER 31 - OPTIONAL INTER PARTES REEXAMINATION PROCEDURES

§ 316. Certificate of patentability, unpatentability, and claim cancellation

(a) In General.— In an inter partes reexamination proceeding under this chapter, when the time

35 USC 316

NB: This unofficial compilation of the U.S. Code is current as of Jan. 4, 2012 (see http://www.law.cornell.edu/uscode/uscprint.html).

(11) requiring that the final determination in an inter partes review be issued not later than 1 year after the date on which the Director notices the institution of a review under this chapter, except that the Director may, for good cause shown, extend the 1-year period by not more than 6 months, and may adjust the time periods in this paragraph in the case of joinder under section 315 (c);

(12) setting a time period for requesting joinder under section 315 (c); and

(13) providing the petitioner with at least 1 opportunity to file written comments within a time period established by the Director.

(b) Considerations.—In prescribing regulations under this section, the Director shall consider the effect of any such regulation on the economy, the integrity of the patent system, the efficient administration of the Office, and the ability of the Office to timely complete proceedings instituted under this chapter.

(c) Patent Trial and Appeal Board.—The Patent Trial and Appeal Board shall, in accordance with section 6, conduct each inter partes review instituted under this chapter.

(d) Amendment of the Patent.—

(1) In general.—During an inter partes review instituted under this chapter, the patent owner may file 1 motion to amend the patent in 1 or more of the following ways:

(A) Cancel any challenged patent claim.

(B) For each challenged claim, propose a reasonable number of substitute claims.

(2) Additional motions.—Additional motions to amend may be permitted upon the joint request of the petitioner and the patent owner to materially advance the settlement of a proceeding under section 317, or as permitted by regulations prescribed by the Director.

(3) Scope of claims.—An amendment under this subsection may not enlarge the scope of the claims of the patent or introduce new matter.

(e) Evidentiary Standards.—In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.

See 2011 Amendment note below.

Amendments

2011—Pub. L. 112–29 amended section generally. Prior to amendment, section related to certificate of patentability, unpatentability, and claim cancellation.

2002—Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113, which enacted this section.

Effective Date of 2011 Amendment

Amendment by Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to any patent issued before, on, or after that effective date, with provisions for graduated implementation, see section 6(c)(2) of Pub. L. 112–29, set out as a note under section 311 of this title.

- 2 -

35 U.S.C. 316(e)

"Evidentiary Standards.—In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence."

Source: 35 U.S.C. 316(e)

Substitute Independent Claim For The ’135 Patent

Substitute Claim

11. (Proposed substitute for original claim 1) A method of treating a subject suffering from hyperlipidemia or hypercholesterolemia, the method comprising administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises **at least three step-wise, increasing dose levels** of the MTP inhibitor, wherein a first and second dose level is **50% of the immediately following dose level**, and wherein a third dose level is **from about 0.2 to about 0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg**; and wherein the MTP inhibitor is N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4’-(trifluoromethyl) [1,1’-biphenyl]-2-yl] carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, **methanesulfonate**, and wherein each dose level is administered to the subject for **about 1 to about 5 weeks**.

Source: Ex. 1001, ’135 Patent; MTA Appendix A at 7

No Motivation To Use A 2x Escalating Dosing Method

Petitioner's expert conceded that it is "inherent" that side effects will increase with the dose

Q. Right. But with respect to the dose-dependent side effects, you typically would expect to see the patient experience more of that particular side effect as you increase the dose, correct?

A. That's inherent to the dose-dependent definition.

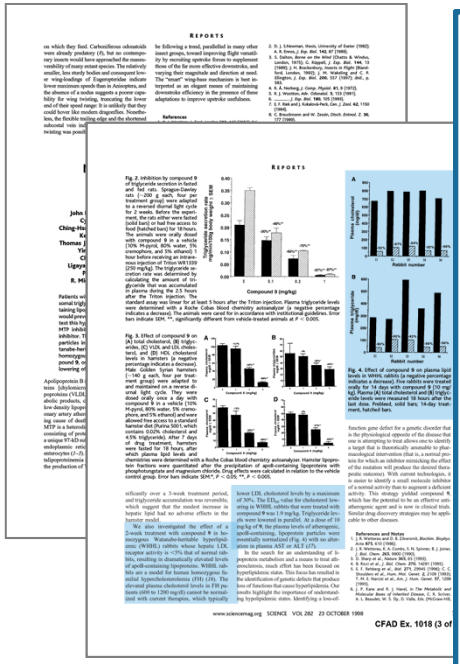
Source: Ex. 2022, Zusman Tr., 55:4-12 (objection omitted); MTA at 19-20

Wetterau Does Not Provide Motivation To Resurrect Development With Lomitapide

- **Wetterau involves pre-clinical testing of various different MTP inhibitors to rodents and WHHL rabbits to determine which compound has potential for further study**
- **Petitioner relies on single two-week WHHL rabbit study that pre-dates lomitapide withdrawal**
  - No alterations in ALT or AST levels reported in the study
  - No toxicity concerns reported in this study
  - No PK data, no PD data
- **No guidance how to dose in humans without causing side effects**

Source: Ex. 1018 at 1, 3; RMTA at 2, 4, 8; Ex. 2305, Baillie Suppl. Decl., at ¶¶ 34-39, 47, 68

Wetterau Reports A Single Dose, Two-Week Study In Rabbits And Provides No PK Data



We also investigated the effect of a 2-week treatment with compound **9** in homozygous Watanabe-heritable hyperlipidemic (WHHL) rabbits whose hepatic LDL receptor activity is <5% that of normal rabbits, resulting in dramatically elevated levels of apoB-containing lipoproteins. WHHL rabbits are a model for human homozygous familial hypercholesterolemia (FH) (*16*). The elevated plasma cholesterol levels in FH patients (600 to 1200 mg/dl) cannot be normalized with current therapies, which typically lower LDL cholesterol levels by a maximum of 30%. The ED_{50} value for cholesterol lowering in WHHL rabbits that were treated with compound **9** was 1.9 mg/kg. Triglyceride levels were lowered in parallel. At a dose of 10 mg/kg of **9**, the plasma levels of atherogenic, apoB-containing, lipoprotein particles were essentially normalized (Fig. 4) with no alteration in plasma AST or ALT (*17*).

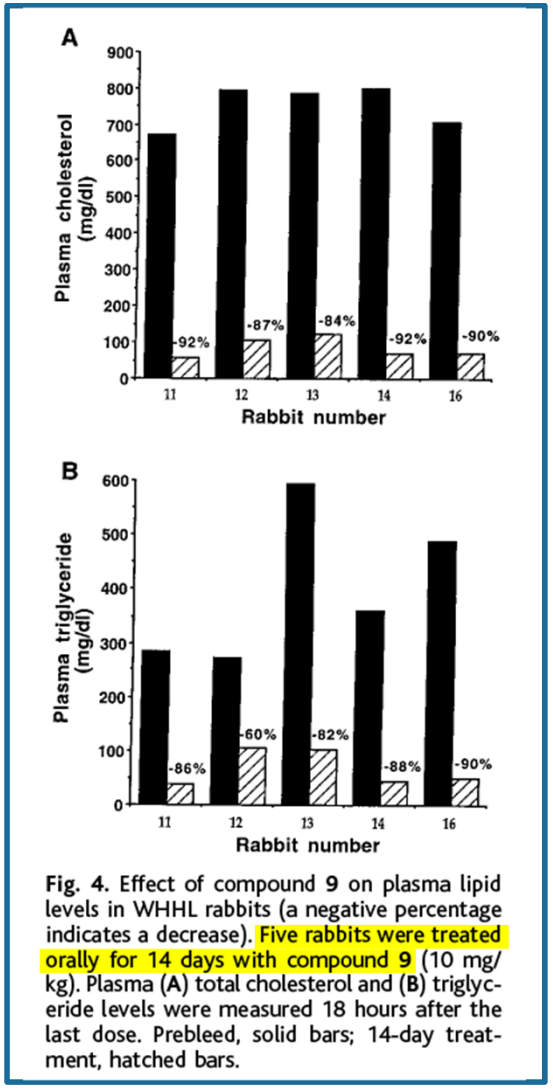


Fig. 4. Effect of compound **9** on plasma lipid levels in WHHL rabbits (a negative percentage indicates a decrease). Five rabbits were treated orally for 14 days with compound **9** (10 mg/kg). Plasma (**A**) total cholesterol and (**B**) triglyceride levels were measured 18 hours after the last dose. Prebleed, solid bars; 14-day treatment, hatched bars.

Source: Ex. 1018, Wetterau, at 3; RMTA at 8

Wetterau Does Not Provide A Reasonable Expectation Of Success

Petitioner's expert concedes that Wetterau's WHHL rabbit model has limited predictive power

Q. You don't contend that the efficacy on a dosage basis seen in the WHHL rabbit model would be identical to what you would expect a human patient, right?

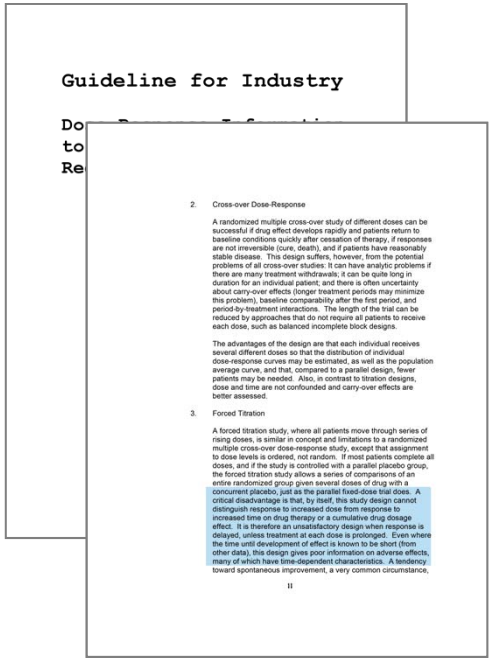
A. No, I don't believe that would be the case.

Q. Right. And WHHL rabbits don't necessarily have the same rate of absorption, metabolism, distribution and excretion
as human patients, correct?

A. That's correct.

Source: Ex. 2022, Zusman Tr., 92:22-93:9 (objection omitted)

ICH-E4 Discourages From Using Forced Titration


Guideline for Industry

2. Cross-over Dose-Response

A randomized multiple cross-over study of different doses can be successful if drug effect develops rapidly and patients return to baseline conditions quickly after cessation of therapy, if responses are not irreversible (cure, death), and if patients have reasonably stable disease. This design suffers, however, from the potential problems of all cross-over studies: It can have analytic problems if there are many treatment withdrawals; it can be quite long in duration for an individual patient; and there is often uncertainty about carry-over effects (longer treatment periods may minimize this problem), baseline comparability after the first period, and period-by-treatment interactions. The length of the trial can be reduced by approaches that do not require all patients to receive each dose, such as balanced incomplete block designs.

The advantages of the design are that each individual receives several different doses so that the distribution of individual dose-response curves may be estimated, as well as the population average curve, and that, compared to a parallel design, fewer patients may be needed. Also, in contrast to titration designs, dose and time are not confounded and carry-over effects are better assessed.

3. Forced Titration

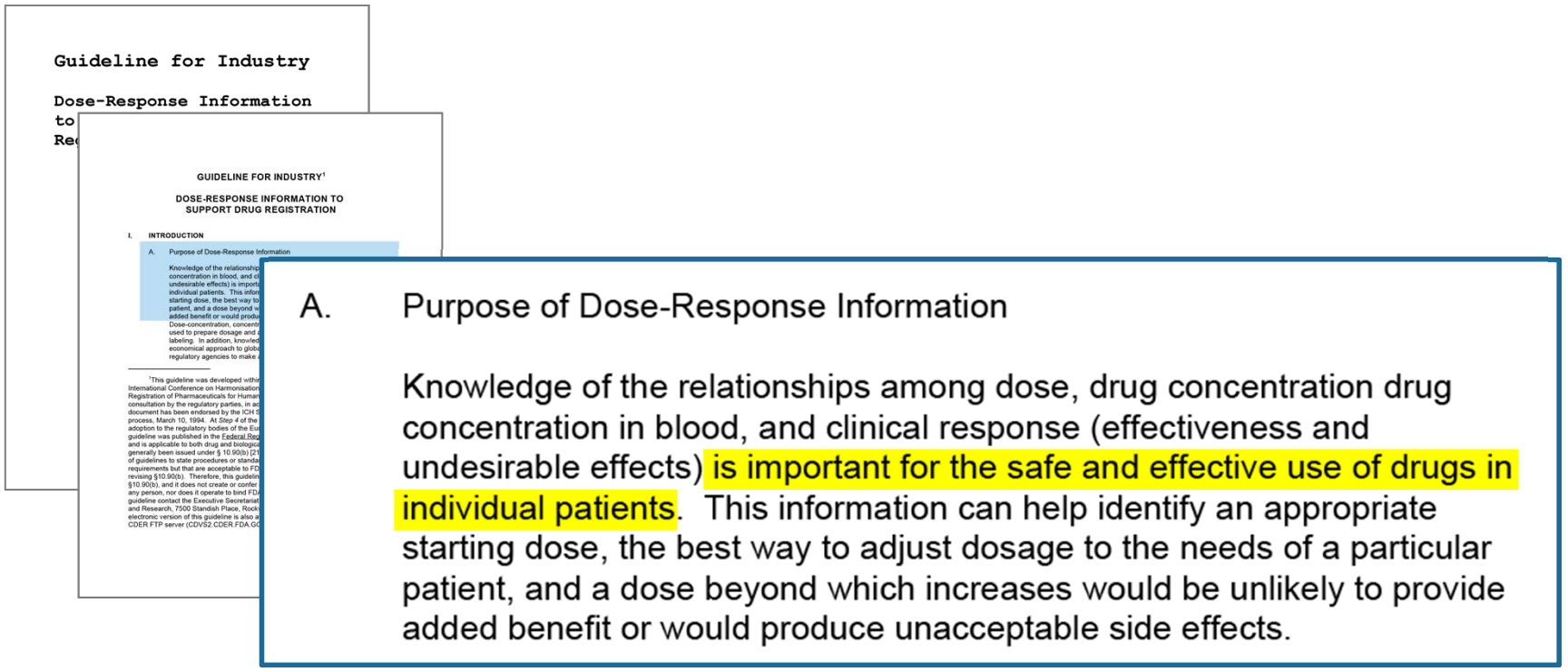
A forced titration study, where all patients move through series of rising doses, is similar in concept and limitations to a randomized multiple cross-over dose-response study, except that assignment to dose levels is ordered, not random. If most patients complete all doses, and if the study is controlled with a parallel placebo group, the forced titration study allows a series of comparisons of an entire randomized group given several doses of drug with a concurrent placebo, just as the parallel fixed-dose trial does. A critical disadvantage is that, by itself, this study design cannot distinguish response to increased dose from response to increased time on drug therapy or a cumulative drug dosage effect. It is therefore an unsatisfactory design when response is delayed, unless treatment at each dose is prolonged. Even where the time until development of effect is known to be short (from other data), this design gives poor information on adverse effects, many of which have time-dependent characteristics. A tendency toward spontaneous improvement, a very common circumstance,

11

"A critical disadvantage is that, by itself, this study design cannot distinguish response to increased dose from response to increased time on drug therapy or a cumulative drug dosage effect. It is therefore an unsatisfactory design when response is delayed, unless treatment at each dose is prolonged. Even where the time until development of effect is known to be short (from other data), this design gives poor information on adverse effects, many of which have time-dependent characteristics."

Source: Ex. 1046 [1043], ICH-E4, at 13/17

ICH-E4 Emphasizes Importance Of PK Data



Guideline for Industry

Dose-Response Information
to
Re

GUIDELINE FOR INDUSTRY[1]

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

I. INTRODUCTION

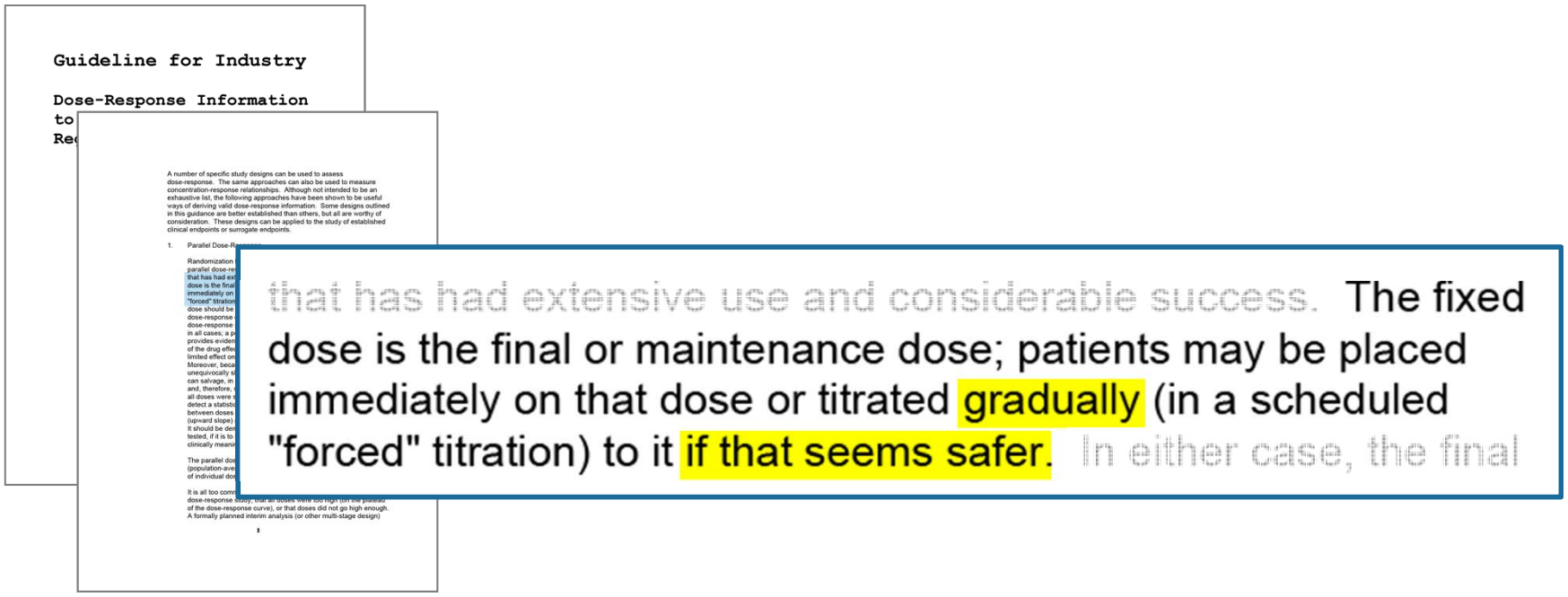
A. Purpose of Dose-Response Information

A. Purpose of Dose-Response Information

Knowledge of the relationships among dose, drug concentration drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects.

Source: Ex. 1046 [1043], ICH-E4, at 3; RMTA at 5

ICH-E4: Any Titration Should Occur Gradually



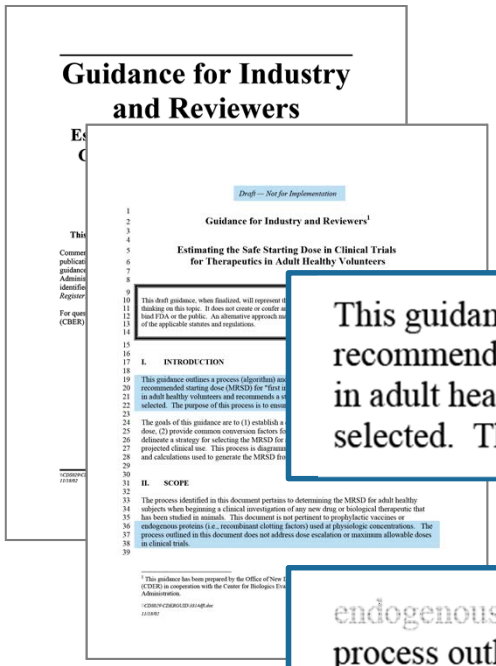
Source: Ex. 1046 [1043], ICH-E4, at 11; RMTA at 7

FDA Draft Guidance Document

- **"Draft" document "not for implementation"**
- **Limited to determining "the maximum recommended starting dose for "first in human" studies**
  - First in human trial of lomitapide had already occurred
- **Expressly states that it is not directed to "dose escalation"**
- **Emphasizes the importance of PK/PD data**
- **Stresses the need to account for known safety issues**

Source: Ex. 1045 [1042], FDA Guidance, at 4-5/29, 8/29; RMTA at 8; Ex. 2305, Baillie Supp. Decl. at ¶¶ 30-32

FDA Draft Guidance Is Directed Specifically To First-In-Man Studies, And Not "Dose Escalation"


Guidance for Industry and Reviewers

Draft — Not for Implementation

Guidance for Industry and Reviewers[1]

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

I. INTRODUCTION

II. SCOPE

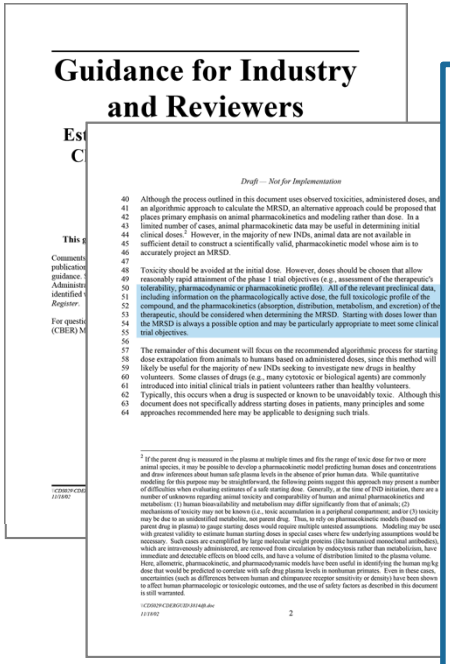
Draft — Not for Implementation

This guidance outlines a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MRSD) for "first in human" clinical trials of new molecular entities in adult healthy volunteers and recommends a standardized process by which the MRSD can be selected. The purpose of this process is to ensure the safety of the human volunteers.

endogenous proteins (i.e., recombinant clotting factors) used at physiologic concentrations. The process outlined in this document does not address dose escalation or maximum allowable doses in clinical trials.

Source: Ex. 1045 [1042], FDA Guidance, at 4; RMTA at 8

FDA Draft Guidance Emphasizes Importance Of PK Data



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Although the process outlined in this document uses observed toxicities, administered doses, and an algorithmic approach to calculate the MRSD, an alternative approach could be proposed that places primary emphasis on animal pharmacokinetics and modeling rather than dose. In a limited number of cases, animal pharmacokinetic data may be useful in determining initial clinical doses.[2] However, in the majority of new INDs, animal data are not available in sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to accurately project an MRSD.

Toxicity should be avoided at the initial dose. However, doses should be chosen that allow reasonably rapid attainment of the phase 1 trial objectives (e.g., assessment of the therapeutic's tolerability, pharmacodynamic or pharmacokinetic profile). All of the relevant preclinical data, including information on the pharmacologically active dose, the full toxicologic profile of the compound, and the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the therapeutic, should be considered when determining the MRSD. Starting with doses lower than the MRSD is always a possible option and may be particularly appropriate to meet some clinical trial objectives.

The remainder of this document will focus on the recommended algorithmic process for starting dose extrapolation from animals to humans based on administered doses, since this method will likely be useful for the majority of new INDs seeking to investigate new drugs in healthy volunteers. Some classes of drugs (e.g., many cytotoxic or biological agents) are commonly introduced into initial clinical trials in patient volunteers rather than healthy volunteers. Typically, this occurs when a drug is suspected or known to be unavoidably toxic. Although this document does not specifically address starting doses in patients, many principles and some approaches recommended here may be applicable to designing such trials.

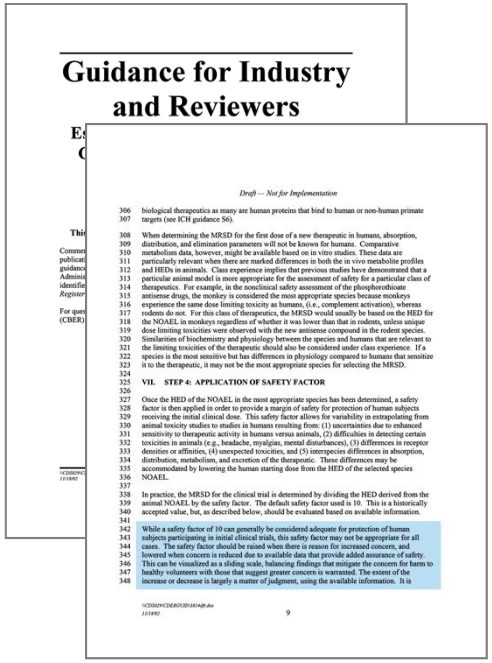
[2] If the parent drug is measured in the plasma at multiple times and fits the range of toxic dose for two or more animal species, it may be possible to develop a pharmacokinetic model predicting human doses and concentrations and draw inferences about human safe plasma levels in the absence of prior human data. While quantitative modeling for this purpose may be straightforward, the following points suggest this approach may present a number of difficulties when evaluating estimates of a safe starting dose. Generally, at the time of IND initiation, there are a number of unknowns regarding animal toxicity and comparability of human and animal pharmacokinetics and metabolism: (1) human bioavailability and metabolism may differ significantly from that of animals; (2) mechanisms of toxicity may not be known (i.e., toxic accumulation in a peripheral compartment; and/or (3) toxicity may be due to an unidentified metabolite, not parent drug. Thus, to rely on pharmacokinetic models (based on parent drug in plasma) to gauge starting doses would require multiple untested assumptions. Modeling may be used with greatest validity to estimate human starting doses in special cases where few underlying assumptions would be necessary. Such cases are exemplified by large molecular weight proteins (like humanized monoclonal antibodies), which are intravenously administered, are removed from circulation by endocytosis rather than metabolism, have immediate and detectable effects on blood cells, and have a volume of distribution limited to the plasma volume. Here, allometric, pharmacokinetic, and pharmacodynamic models have been useful in identifying the human mg/kg dose that would be predicted to correlate with safe drug plasma levels in nonhuman primates. Even in these cases, uncertainties (such as differences between human and chimpanzee receptor sensitivity or density) have been shown to affect human pharmacologic or toxicologic outcomes, and the use of safety factors as described in this document is still warranted.

2

"All of the relevant preclinical data, including information on the pharmacologically active dose, the full toxicologic profile of the compound, and the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the therapeutic, should be considered when determining the MSRD. Starting with doses lower than the MSRD is always a possible option and may be particularly appropriate to meet some clinical trial objectives."

Source: Ex. 1045 [1042], FDA Guidance, at 5

FDA Draft Guidance: Safety Factor Should Be Adjusted Based On Safety Concerns



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biological therapeutics as many are human proteins that bind to human or non-human primate targets (see ICH guidance S6).

When determining the MRSD for the first dose of a new therapeutic in humans, absorption, distribution, and elimination parameters will not be known for humans. Comparative metabolism data, however, might be available based on in vitro studies. These data are particularly relevant when there are marked differences in both the in vivo metabolite profiles and HEDs in animals. Class experience implies that previous studies have demonstrated that a particular animal model is more appropriate for the assessment of safety for a particular class of therapeutics. For example, in the nonclinical safety assessment of the phosphorothioate antisense drugs, the monkey is considered the most appropriate species because monkeys experience the same dose limiting toxicity as humans, (i.e., complement activation), whereas rodents do not. For this class of therapeutics, the MRSD would usually be based on the HED for the NOAEL in monkeys regardless of whether it was lower than that in rodents, unless unique dose limiting toxicities were observed with the new antisense compound in the rodent species. Similarities of biochemistry and physiology between the species and humans that are relevant to the limiting toxicities of the therapeutic should also be considered under class experience. If a species is the most sensitive but has differences in physiology compared to humans that sensitize it to the therapeutic, it may not be the most appropriate species for selecting the MRSD.

VII. STEP 4: APPLICATION OF SAFETY FACTOR

Once the HED of the NOAEL in the most appropriate species has been determined, a safety factor is then applied in order to provide a margin of safety for protection of human subjects receiving the initial clinical dose. This safety factor allows for variability in extrapolating from animal toxicity studies to studies in humans resulting from: (1) uncertainties due to enhanced sensitivity to therapeutic activity in humans versus animals, (2) difficulties in detecting certain toxicities in animals (e.g., headache, myalgias, mental disturbances), (3) differences in receptor densities or affinities, (4) unexpected toxicities, and (5) interspecies differences in absorption, distribution, metabolism, and excretion of the therapeutic. These differences may be accommodated by lowering the human starting dose from the HED of the selected species NOAEL.

In practice, the MRSD for the clinical trial is determined by dividing the HED derived from the animal NOAEL by the safety factor. The default safety factor used is 10. This is a historically accepted value, but, as described below, should be evaluated based on available information.

While a safety factor of 10 can generally be considered adequate for protection of human subjects participating in initial clinical trials, this safety factor may not be appropriate for all cases. The safety factor should be raised when there is reason for increased concern, and lowered when concern is reduced due to available data that provide added assurance of safety. This can be visualized as a sliding scale, balancing findings that mitigate the concern for harm to healthy volunteers with those that suggest greater concern is warranted. The extent of the increase or decrease is largely a matter of judgment, using the available information. It is

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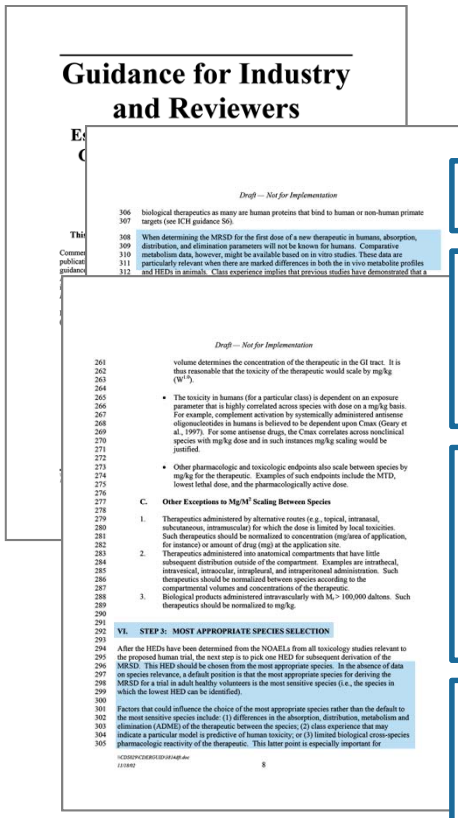
"While a safety factor of 10 can generally be considered adequate for protection of human subjects participating in initial clinical trials, this safety factor may not be appropriate for all cases. The safety factor should be raised when there is reason for increased concern, and lowered when concern is reduced due to available data that provide added assurance of safety. This can be visualized as a sliding scale, balancing findings that mitigate the concern for harm to healthy volunteers with those that suggest greater concern is warranted. The extent of the increase or decrease is largely a matter of judgment, using the available information."

Source: Ex. 1045 [1042], FDA Guidance, at 12

FDA Draft Guidance: A POSA Must Carefully Determine The "Most Appropriate Species"



Guidance for Industry and Reviewers

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biological therapeutics as many are human proteins that bind to human or non-human primate targets (see ICH guidance S6).

When determining the MRSD for the first dose of a new therapeutic in humans, absorption, distribution, and elimination parameters will not be known for humans. Comparative metabolism data, however, might be available based on in vitro studies. These data are particularly relevant when there are marked differences in both the in vivo metabolite profiles and HEDs in animals. Class experience implies that previous studies have demonstrated that a

Draft — Not for Implementation

volume determines the concentration of the therapeutic in the GI tract. It is thus reasonable that the toxicity of the therapeutic would scale by mg/kg ($W^{1.0}$).

- The toxicity in humans (for a particular class) is dependent on an exposure parameter that is highly correlated across species with dose on a mg/kg basis. For example, complement activation by systemically administered antisense oligonucleotides in humans is believed to be dependent upon Cmax (Geary et al., 1997). For some antisense drugs, the Cmax correlates across nonclinical species with mg/kg dose and in such instances mg/kg scaling would be justified.

- Other pharmacologic and toxicologic endpoints also scale between species by mg/kg for the therapeutic. Examples of such endpoints include the MTD, lowest lethal dose, and the pharmacologically active dose.

C. **Other Exceptions to Mg/M² Scaling Between Species**

1. Therapeutics administered by alternative routes (e.g., topical, intranasal, subcutaneous, intramuscular) for which the dose is limited by local toxicities. Such therapeutics should be normalized to concentration (mg/area of application, for instance) or amount of drug (mg) at the application site.
2. Therapeutics administered into anatomical compartments that have little subsequent distribution outside of the compartment. Examples are intrathecal, intravesical, intraocular, intrapleural, and intraperitoneal administration. Such therapeutics should be normalized between species according to the compartmental volumes and concentrations of the therapeutic.
3. Biological products administered intravascularly with $M_r > 100{,}000$ daltons. Such therapeutics should be normalized to mg/kg.

VI. STEP 3: MOST APPROPRIATE SPECIES SELECTION

After the HEDs have been determined from the NOAELs from all toxicology studies relevant to the proposed human trial, the next step is to pick one HED for subsequent derivation of the MRSD. This HED should be chosen from the most appropriate species. In the absence of data on species relevance, a default position is that the most appropriate species for deriving the MRSD for a trial in adult healthy volunteers is the most sensitive species (i.e., the species in which the lowest HED can be identified).

Factors that could influence the choice of the most appropriate species rather than the default to the most sensitive species include: (1) differences in the absorption, distribution, metabolism and elimination (ADME) of the therapeutic between the species; (2) class experience that may indicate a particular model is predictive of human toxicity; or (3) limited biological cross-species pharmacologic reactivity of the therapeutic. This latter point is especially important for

8

VI. STEP 3: MOST APPROPRIATE SPECIES SELECTION

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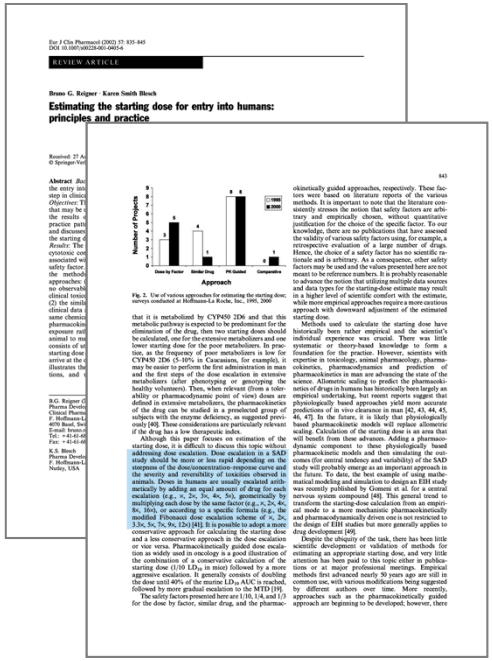
Source: Ex. 1045 [1042], FDA Guidance, at 11-12; RMTA at 8

Reigner: Toxicity Should Be Considered When Selecting A Dose Escalation Strategy



Eur J Clin Pharmacol (2002) 57: 835–845
DOI 10.1007/s00228-001-0402-8

REVIEW ARTICLE

Bruno G. Reigner · Karen Smith Blesch

Estimating the starting dose for entry into humans: principles and practice

Received: 27 A
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Abstract *Bac*
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Objectives: Th
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Fig. 2. Use of various approaches for estimating the starting dose; surveys conducted at Hoffmann-La Roche, Inc., 1995, 2000

that it is metabolized by CYP450 2D6 and that this metabolic pathway is expected to be predominant for the elimination of the drug, then two starting doses should be calculated, one for the extensive metabolizers and one lower starting dose for the poor metabolizers. In practice, as the frequency of poor metabolizers is low for CYP450 2D6 (5–10% in Caucasians, for example), it may be easier to perform the first administration in man and the first steps of the dose escalation in extensive metabolizers (after phenotyping or genotyping the healthy volunteers). Then, when relevant (from a tolerability or pharmacodynamic point of view) doses are defined in extensive metabolizers, the pharmacokinetics of the drug can be studied in a preselected group of subjects with the enzyme deficiency, as suggested previously [40]. These considerations are particularly relevant if the drug has a low therapeutic index.

Although this paper focuses on estimation of the starting dose, it is difficult to discuss this topic without addressing dose escalation. Dose escalation in a SAD study should be more or less rapid depending on the steepness of the dose/concentration–response curve and the severity and reversibility of toxicities observed in animals. Doses in humans are usually escalated arithmetically by adding an equal amount of drug for each escalation (e.g., ×, 2×, 3×, 4×, 5×), geometrically by multiplying each dose by the same factor (e.g., ×, 2×, 4×, 8×, 16×), or according to a specific formula (e.g., the modified Fibonacci dose escalation scheme of ×, 2×, 3.3×, 5×, 7×, 9×, 12×) [41]. It is possible to adopt a more conservative approach for calculating the starting dose and a less conservative approach in the dose escalation or vice versa. Pharmacokinetically guided dose escalation as widely used in oncology is a good illustration of the combination of a conservative calculation of the starting dose ($1/10$ LD_{10} in mice) followed by a more aggressive escalation. It generally consists of doubling the dose until 40% of the murine LD_{10} AUC is reached, followed by more gradual escalation to the MTD [19].

The safety factors presented here are 1/10, 1/4, and 1/3 for the dose by factor, similar drug, and the pharmacokinetically guided approaches, respectively. These factors were based on literature reports of the various methods. It is important to note that the literature consistently stresses the notion that safety factors are arbitrary and empirically chosen, without quantitative justification for the choice of the specific factor. To our knowledge, there are no publications that have assessed the validity of various safety factors using, for example, a retrospective evaluation of a large number of drugs. Hence, the choice of a safety factor has no scientific rationale and is arbitrary. As a consequence, either safety factors may be used and the values presented here are not meant to be reference numbers. It is probably reasonable to advance the notion that utilizing multiple data sources and data types for the starting-dose estimate may result in a higher level of scientific comfort with the estimate, while more empirical approaches require a more cautious approach with downward adjustment of the estimated starting dose.

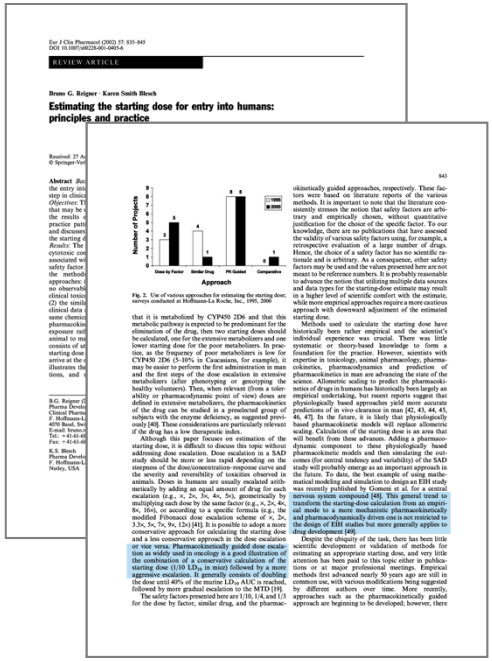
Methods used to calculate the starting dose have historically been rather empirical and the scientist's individual experience was crucial. There was little systematic or theory-based knowledge to form a foundation for the practice. However, scientists with expertise in toxicology, animal pharmacology, pharmacokinetics, pharmacodynamics and prediction of pharmacokinetics in man are advancing the state of the science. Allometric scaling to predict the pharmacokinetics of drugs in humans has historically been largely an empirical undertaking, but recent reports suggest that physiologically based approaches yield more accurate predictions of in vivo clearance in man [42, 43, 44, 45, 46, 47]. In the future, it is likely that physiologically based pharmacokinetic models will replace allometric scaling. Calculation of the starting dose is an area that will benefit from these advances. Adding a pharmacodynamic component to these physiologically based pharmacokinetic models and then simulating the outcomes (for central tendency and variability) of the SAD study will probably emerge as an important approach in the future. To date, the best example of using mathematical modeling and simulation to design an EH study was recently published by Gomeni et al. for a central nervous system compound [48]. This general trend to transform the starting-dose calculation from an empirical mode to a more mechanistic pharmacokinetically and pharmacodynamically driven one is not restricted to the design of EH studies but more generally applies to drug development [49].

Despite the ubiquity of the task, there has been little scientific development or validation of methods for estimating an appropriate starting dose, and very little attention has been paid to this topic either in publications or at major professional meetings. Empirical methods first advanced nearly 50 years ago are still in common use, with various modifications being suggested by different authors over time. More recently, approaches such as the pharmacokinetically guided approach are beginning to be developed; however, there

"Dose escalation in a SAD study should be more or less rapid depending on the steepness of the dose/concentration-response curve and the severity and reversability of toxicities observed in animals. Doses in humans are usually escalated arithmetically by adding an equal amount of drug for each escalation (e.g., ×, 2×, 3×, 4×, 5×), geometrically by multiplying each dose by the same factor (e.g., ×, 2×, 4×, 8×, 16×), or according to a specific formula (e.g., the modified Fibonacci dose escalation scheme of ×, 2×, 3.3×, 5×, 7×, 9×, 12×) [41]."

Source: Ex. 1047 [1044], Reigner, at 843; RMTA at 6-7

Reigner Emphasizes Importance Of PK/PD Data



REVIEW ARTICLE

Bruno G. Reigner · Karen Smith Blesch

Estimating the starting dose for entry into humans: principles and practice

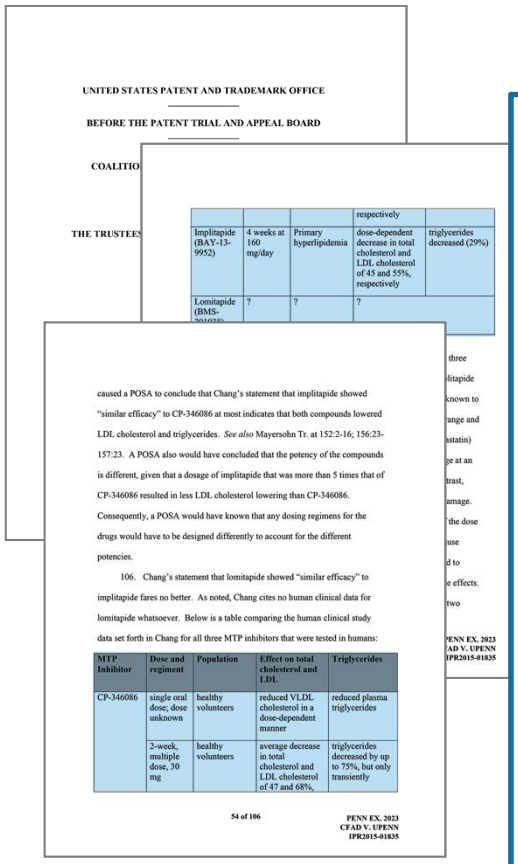
Fig. 2. Use of various approaches for estimating the starting dose; survey conducted at Hoffmann-La Roche, Inc., 1995, 2000

> **"Pharmacokinetically guided dose escalation as widely used in oncology is a good illustration of the combination of a conservative calculation of the starting dose (1/10 LD10 in mice) followed by a more aggressive escalation."**

> **"This general trend to transform the starting-dose calculation from an empirical mode to a more mechanistic pharmacokinetically and pharmacodynamically driven one is not restricted to the design of EIH studies but more generally applies to drug development [49]."**

Source: Ex. 1047 [1044], Reigner, at 843; RMTA at 6-7

Dr. Sacks: Chang's Disclosures Regarding Lomitapide Are Limited



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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			respectively	
Implitapide (BAY-13-9952)	4 weeks at 160 mg/day	Primary hyperlipidemia	dose-dependent decrease in total cholesterol and LDL cholesterol of 45 and 55%, respectively	triglycerides decreased (29%)
Lomitapide (BMS-	?	?	?	

caused a POSA to conclude that Chang's statement that implitapide showed "similar efficacy" to CP-346086 at most indicates that both compounds lowered LDL cholesterol and triglycerides. *See also* Mayersohn Tr. at 152:2-16; 156:23-157:23. A POSA also would have concluded that the potency of the compounds is different, given that a dosage of implitapide that was more than 5 times that of CP-346086 resulted in less LDL cholesterol lowering than CP-346086. Consequently, a POSA would have known that any dosing regimens for the drugs would have to be designed differently to account for the different potencies.

106. Chang's statement that lomitapide showed "similar efficacy" to implitapide fares no better. As noted, Chang cites no human clinical data for lomitapide whatsoever. Below is a table comparing the human clinical study data set forth in Chang for all three MTP inhibitors that were tested in humans:

MTP Inhibitor	Dose and regimen	Population	Effect on total cholesterol and LDL	Triglycerides
CP-346086	single oral dose; dose unknown	healthy volunteers	reduced VLDL cholesterol in a dose-dependent manner	reduced plasma triglycerides
	2-week, multiple dose, 30 mg	healthy volunteers	average decrease in total cholesterol and LDL cholesterol of 47 and 68%,	triglycerides decreased by up to 75%, but only transiently

54 of 106

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MTP Inhibitor	Dose and Regimen	Population	Effect on total cholesterol and LDL	Triglycerides
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Implitapide (BAY-13-9952)	4 weeks at 160 mg/day	Primary hyperlipidemia	dose-dependent decrease in total cholesterol and LDL cholesterol of 45 and 55%, respectively	triglycerides decreased (29%)
Lomitapide (BMS-201038)	?	?	?	

Source: Ex. 2023, Sack Decl., ¶ 106; POR at 12-13, 31

Petitioner's Expert Concedes That Just A Twofold Increase In Plasma ALT, AST, And CPK Levels Would Have Discouraged Subsequent Development

Q. "Tolerability was good in this study and an approximate twofold increase in plasma ALT, AST, and CPK levels was observed."

A. Right. So a twofold increase in seven days might have made this compound too hot to handle, if you will, but at such a marked increase in such a short period of time, might have discouraged their subsequent development of the compound . . . ."

Source: Ex. 2022, Zusman Tr., 172:16-24

Petitioner's Expert Concedes That Just A Twofold Increase In Plasma ALT, AST, And CPK Levels Would Have Discouraged Subsequent Development

Q. . . . Because in your opinion, if the company had performed clinical data and determined that it was unsafe or could not be administered, they abandoned the project, correct?

A. They, more likely than not, would have done so, yes, that's correct.

Q. Right. And the abandonment of this compound, in your opinion, would have dissuaded a person of ordinary skill in the art from pursuing it?

A. From pursuing this compound?

Q. Yeah.

A. It might have. It depends on how that data was acquired and what types of settings and what dosages with what intent. Again, I think a person of ordinary skill in the art in thinking about drug development thinks about all of these factors, and one of them, of course, is likelihood of success in getting a drug approved at the Food & Drug Administration. So whether this drug was developed to any further degree, I don't know, but those – that phraseology would have told me as a person of ordinary skill in the art that this drug was potentially too hot to handle because of the position of the Food & Drug Administration.

Source: Ex. 2022, Zusman Tr., 174:4-175:15 (objection omitted)

Key Authority In Support Of Motion To Amend

Narrowing

- Because each independent substitute claim only adds features to the corresponding original claim, and does not remove any, the proposed amendments do not enlarge the scope of the patent.
  - *REG Synthetic Fuels LLC v. Neste Oil OYJ*, IPR2014-00192 (Final Decision June 5, 2015 (granting motion to amend where Patent Owner replaced broad ranges with narrowing ranges)

Support

- "[T]he hallmark of written description is disclosure."
  - *Ariad Pharms, Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*)

Reduction to Practice

- "The adequacy of a reduction to practice is to be tested by what one of ordinary skill in the art would conclude from the results of the tests."
  - *Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304 F.3d 1256, 1265 (Fed. Cir. 2002) ("Testing is not itself a requisite for reduction to practice . . . .")

Source: MTA at 5, 9; RMTA at 12

Key Authority In Support Of Motion To Amend

Prior art directed to "different problems" do not raise an inference of obviousness

- The analysis of whether a POSA would have been motivated to combine elements of different references does not depend on the recitation in the claims, but looks to whether the references proposed to be combined were compatible with each other and likely to succeed.
  - *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334-35 (Fed. Cir. 2013) (no obviousness where the references proposed to be combined addressed "different problems" from that described in the patent)

Unexpected results are not limited to claimed features

- "We are aware of no law requiring that unexpected results relied upon for patentability be recited in the claims."
  - *In re Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978)

Source: RMTA at 4, 7-9

CERTIFICATE OF SERVICE

The undersigned hereby certifies that pursuant to 37 C.F.R. 42.70(b) I caused the foregoing **PATENT OWNER'S DEMONSTRATIVE EXHIBITS** to be served electronically via e-mail on November 21, 2016 on the counsel below, and pursuant to the Board's November 23, 2016 Order on Trial Hearing, I re-served the foregoing **PATENT OWNER'S DEMONSTRATIVE EXHIBITS** on November 23, 2016, on the counsel below:

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Counsel for Petitioner Coalition for Affordable Drugs VIII, LLC

Dated: November 23, 2016

/Eric T. Romeo/
Eric T. Romeo