

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 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. 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

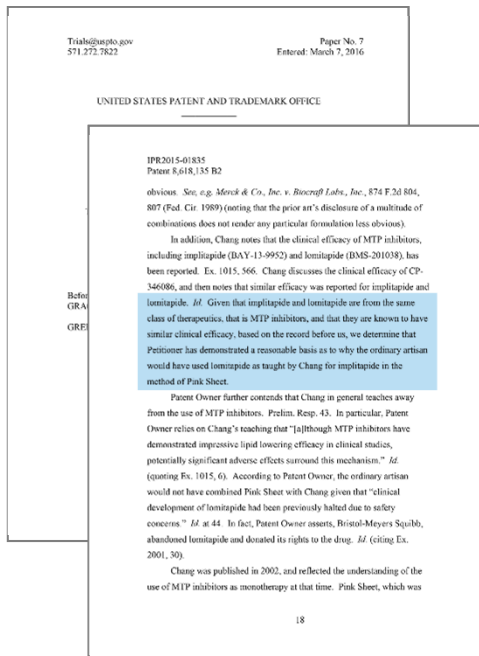
Chang Provides No Information Regarding the Human Dosing of Lomitapide

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



“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



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

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.

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. ♦ ♦

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



“WILMINGTON, NC, January 15, 2004 -- PPD, Inc. (Nasdaq: PPD) 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.ppd.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

Agenda

PPD

0800 - 0815	Welcome & PPD Overview	Fred Eshelman
0815 - 0830	Compound Partnering	Fred Eshelman
0830 - 0850	Dapoxetine	Gail McIntyre
0850 - 0910	Implitapide	Evan Stein
0910 - 0930	Chemokine/CT-0214	Hassan Salari
0930 - 0950	Syrrx/DP IV	Steve Kaldor
0950 - 1010	BDSI/Accentia	Frank O'Donnell
1010 - 1020	Break	
1020 - 1040	Business Units/initiatives	Fred Davenport
1040 - 1100	Business Development	Frank Casieri
1100 - 1200	Wrap-up and Q&A	Fred Eshelman

CFAD Ex. 1014 (1 of 45)

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 Implisitapide

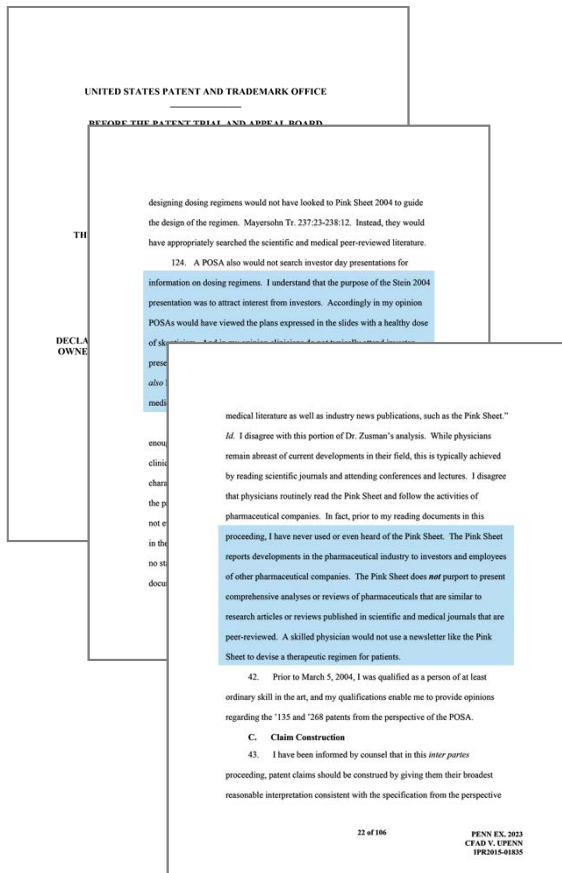
Proposed MTP Development plan *PPD*

- Monitor for hepatic fat accumulation by hepatic transaminases and CT scan - main 'safety' concern
- Start at low doses, 10mg and dose titrate by 5mg based on 'safety' every 5 weeks, placebo control group (3:1 active:placebo)
- In hyperTG subjects (>1000 mg/dL) follow similar titration schedule, but no placebo group
- Once long term 'safety' assessed (at least 6 months) at effective dose move to lower risk groups

CFAD Ex. 1014 (37 of 45)

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



“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

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

52

PENN EX. 2024
CFAD v. PENN
IPR2015-01835

“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.”

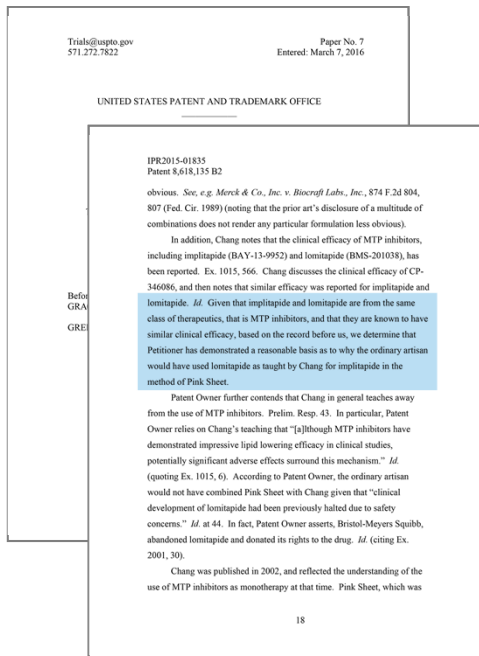
Source: Ex. 2024, Baillie Decl., ¶ 115; POR at 38-44

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



“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

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 microosomal 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 microosomal 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

47

CFAD Ex. 1002 (55 of 150)

“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, . . .

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 hepatotoxic 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)**

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.

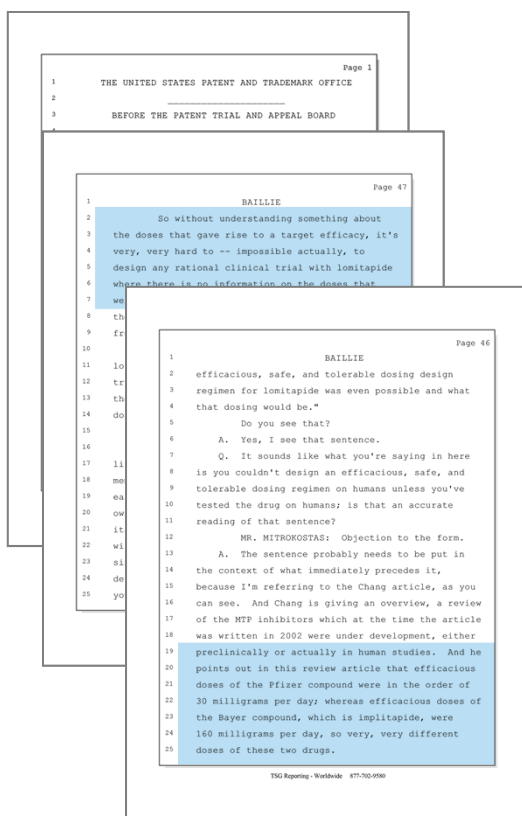
A. Based on only reading Chang, that's correct.

* * *

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.

Chang Provides No Guidance on Dosing Lomitapide to Humans



“. . . 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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BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION

THE TRUSTEES

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)	?	?	?	

caused a POSA to conclude that Chang's statement that lomitapide 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

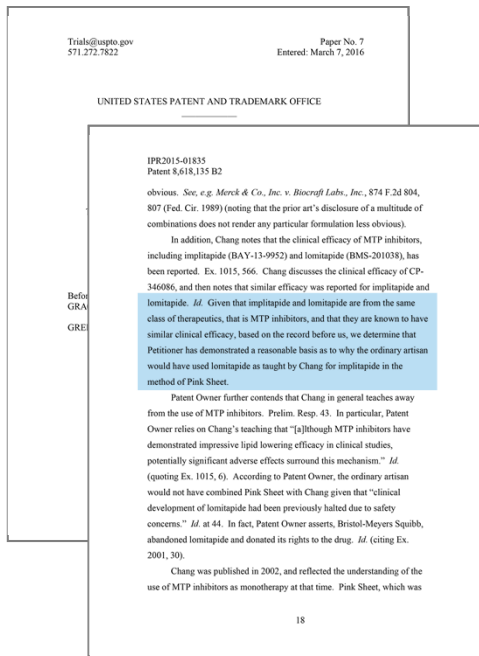
54 of 106

PENN EX. 2023
CPAD V. UPENN
IPR2015-01435

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%, 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



“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

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

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.

Id. For efficacy, fluvastatin, UPenn group, atorvastatin, simvastatin, 40 mg, (80 mg)

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

Statins	LDL-C Lowering (%)	HDL-C Lowering (%)	LDL-C Lowering (mg/dL)	HDL-C Lowering (mg/dL)
Atorvastatin	60	20	100	20
Fluvastatin	50	15	75	15
Pravastatin	40	10	50	10
Rosuvastatin	60	20	100	20
Simvastatin	50	15	75	15
Lovastatin	40	10	50	10

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

38 of 106 PENN EX. 2023
CFAD V. UPENN
IPR2019-01835

“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

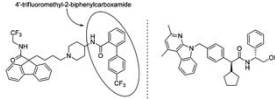
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... true of two drugs from different *structural classes*, which would generally be expected to have distinct PK/PD profiles.

b. Example: Phosphodiesterase Type 5 (PDE₅) Inhibitors

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

Figure 2: Lomitapide vs. Imipitapide
4-(4-fluoromethyl-2-phenyl)carbamamide



Lomitapide Imipitapide

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 imipitapide, 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

31

PENN EX. 2024
CFAD v. PENN
IPR2015-01835

“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.”

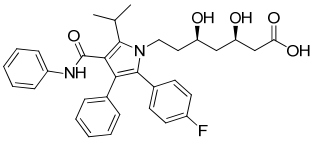
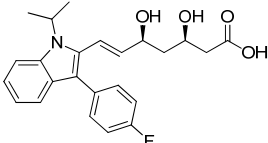
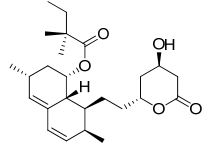
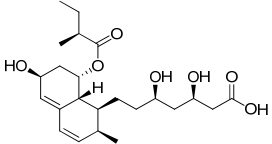
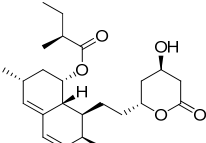
Source: Ex. 2024, Baillie Decl., ¶ 84; POR at 17, 42

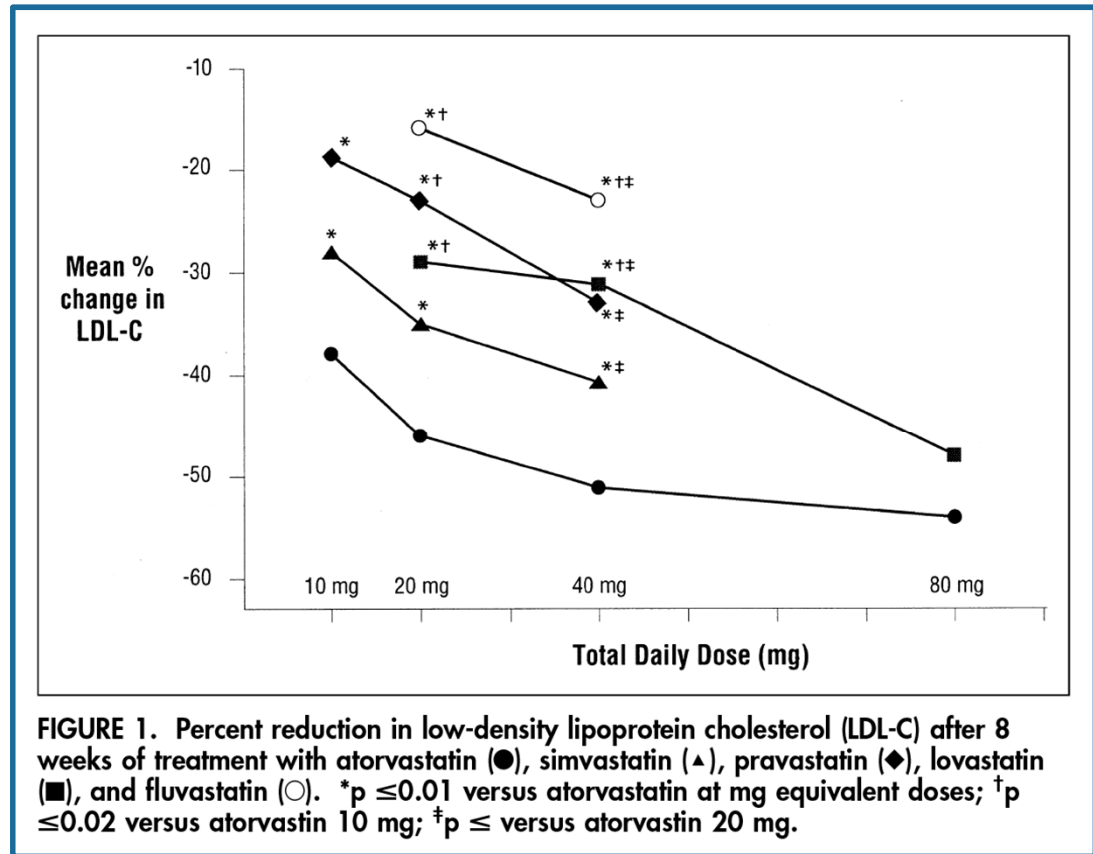
Dr. Baillie: Each Drug In a Therapeutic Class Has To Be Evaluated on Its Own Merits

- 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

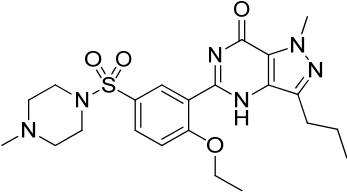
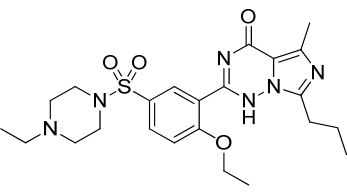
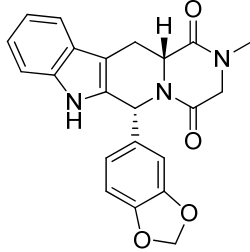
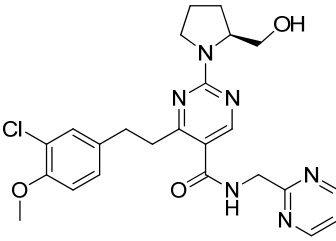
Drug	LDL Reduction		
	10 mg	20 mg	40 mg
 Atorvastatin	38%	46%	51%
 Fluvastatin	n/d	17%	23%
 Simvastatin	28%	35%	41%
 Pravastatin	19%	24%	34%
 Lovastatin	n/d	29%	31%



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

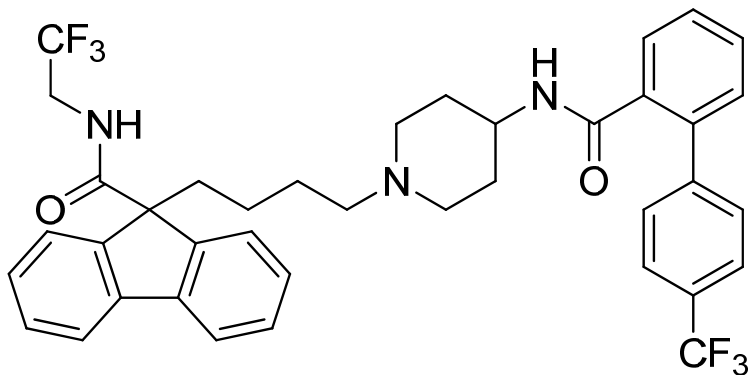
Drugs in the Same Therapeutic Class Often Do Not Have Interchangeable Dosing Regimens – PDE₅ Inhibitors

Figure 4: PK/PD Properties of PDE₅ Inhibitors

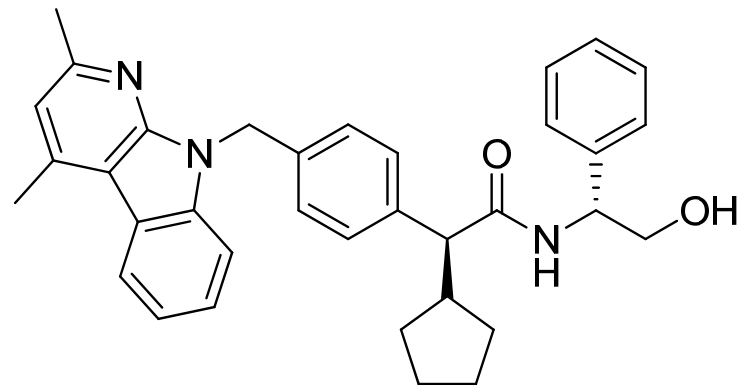
Drug	Viagra® (Sildenafil)	Levitra® (Vardenafil)	Cialis® (Tadalafil)	Stendra® (Avanafil)
Structure				
Biological half-life (T _{1/2})	4 hrs	4–5 hrs	17.5 hrs	5 hrs
Absorption Time (T _{max})	0.5–2.0 hrs	0.5–2.0 hrs	0.5–6.0 hrs	0.50–0.75 hrs
Off-Target PDE Inhibition	PDE ₁ , PDE ₆	PDE ₁ , PDE ₆	PDE ₁₁	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.
TRUSTEES OF
Patent Owner
U.S.
TITLE: METHODS FOR
WITH HYPERLIPIDEMIA
Implitapide
Declaration of Michael Mayersohn, Ph.D.
Inter Partes

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

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

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.

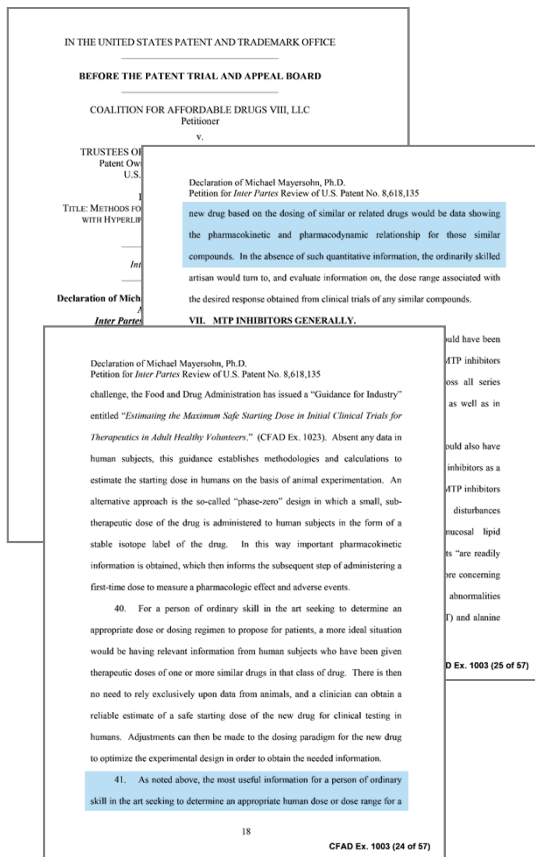
* * *

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

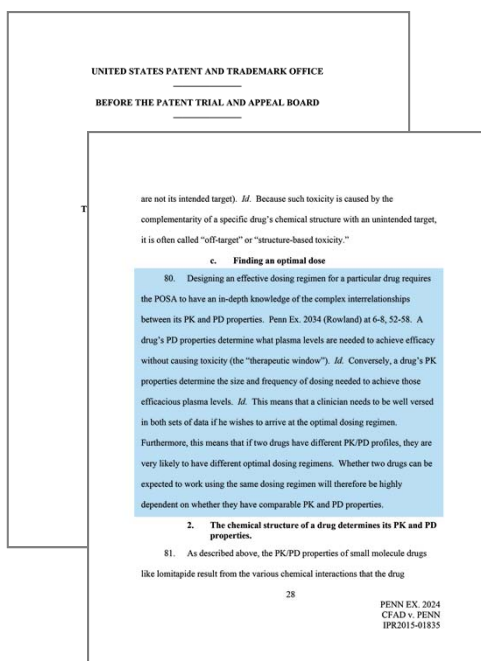
Dr. Mayersohn: PK/PD Data Is the Most Useful Information to a POSA in Designing a Dosing Regimen



“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



“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

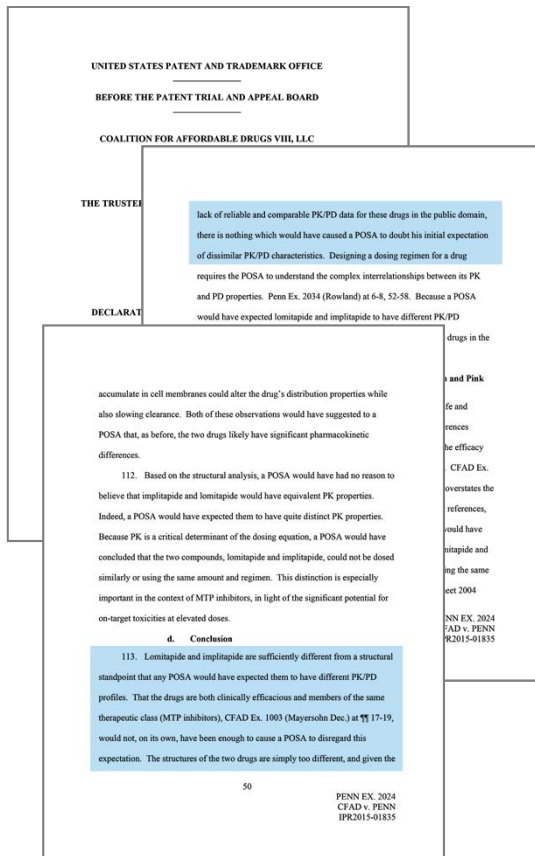
Dr. Zusman: The Prior Art Provides No PK/PD Data for Lomitapide

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

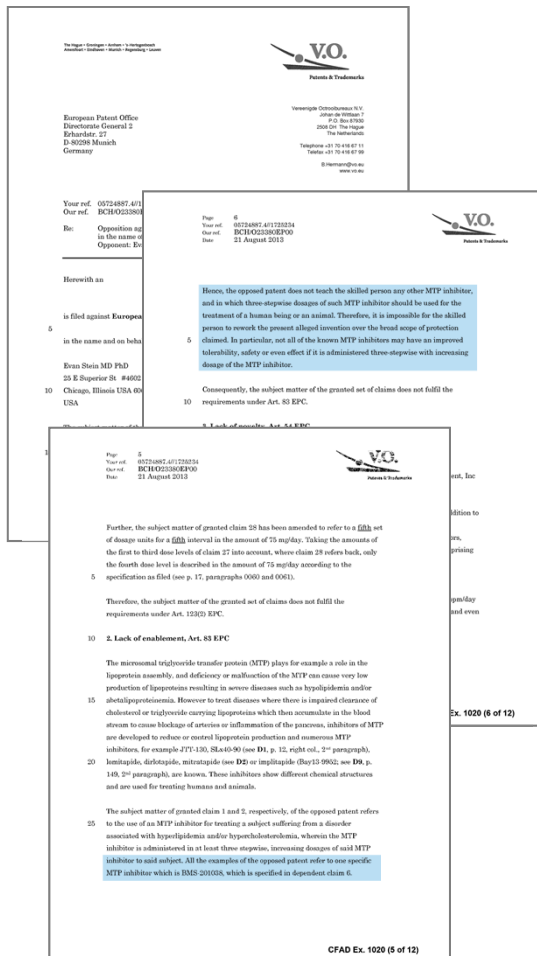
Dr. Baillie: The Structural Differences Between Lomitapide and Implitapide Suggest Different PK/PD Properties



“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



“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?

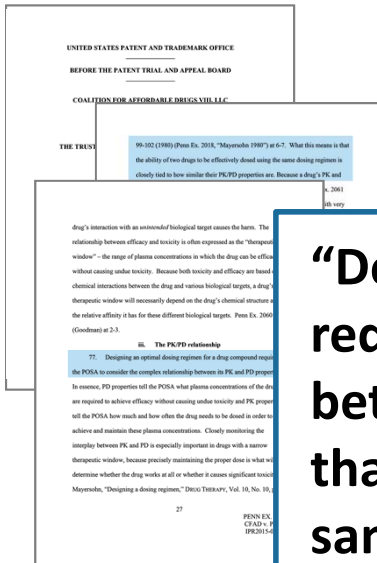
A. I do.

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



“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.”

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

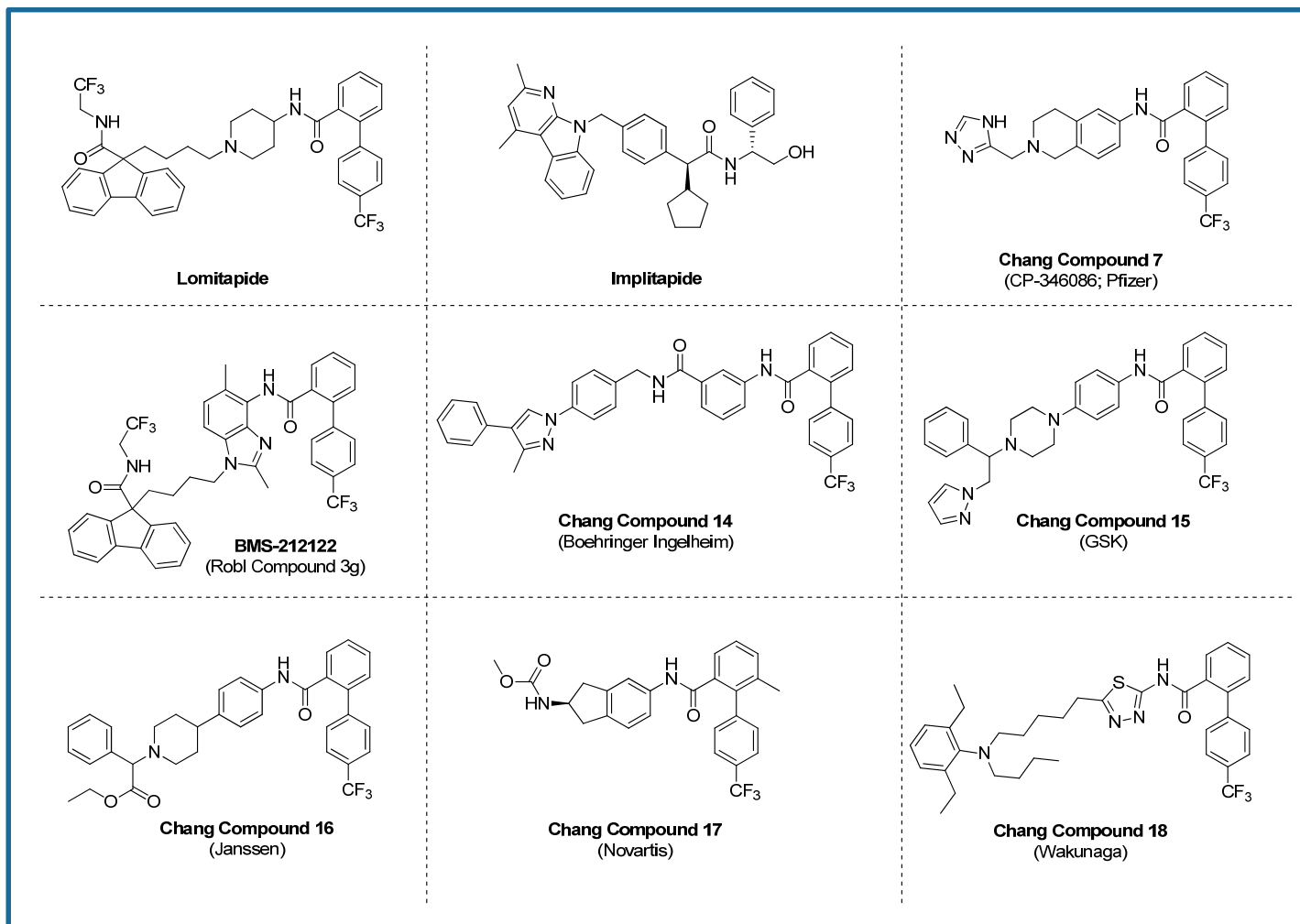
Dr. Baillie: A POSA Would Not Expect Lomitapide And Implitapide to Be Interchangeable

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

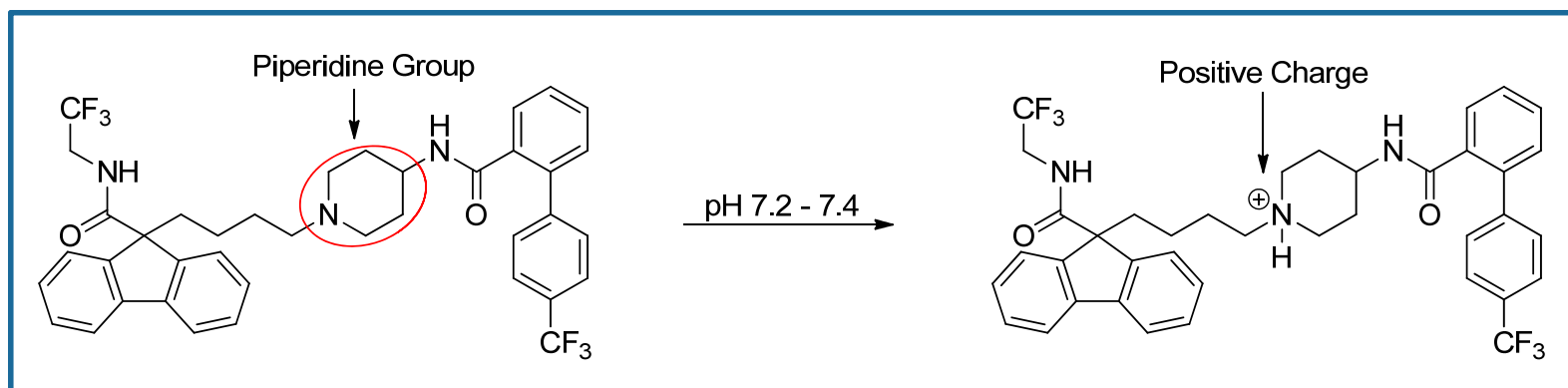
The Prior Art Disclosed a Large Number of MTP Inhibitors



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**



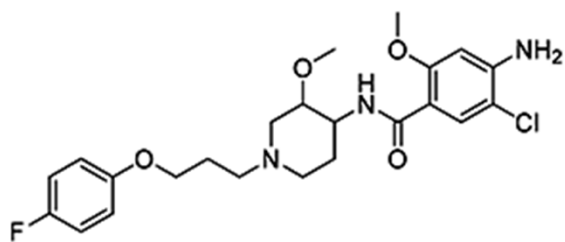
- **CADs are associated with several membrane-related toxicities such as phospholipidosis and hERG blockade**

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

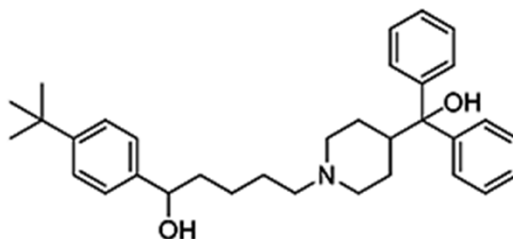
hERG Blockade Causes Potentially Fatal Arrhythmias

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

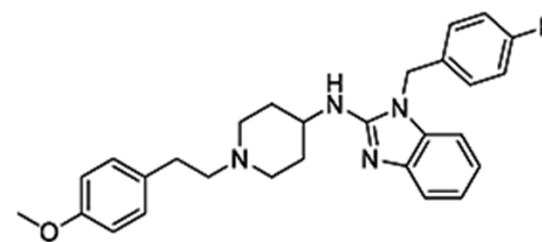
Drugs Withdrawn from Market Due to hERG Toxicity:



Cisapride
(PROPULSID, withdrawn 2000)



Terfenadine
(SELDANE, withdrawn 1997)

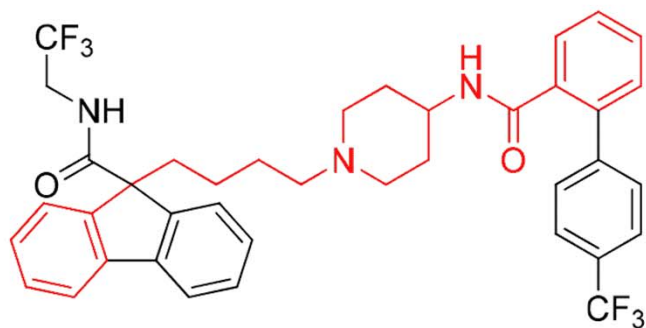


Astemizole
(HISMANAL, withdrawn 1999)

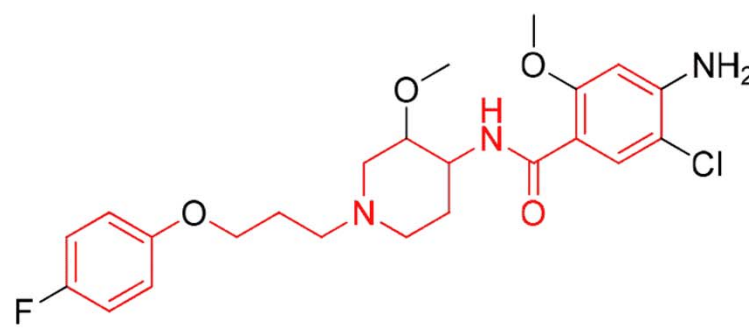
Source: Ex. 2025, Kimball Decl., ¶¶ 87-89; POR at 18

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.

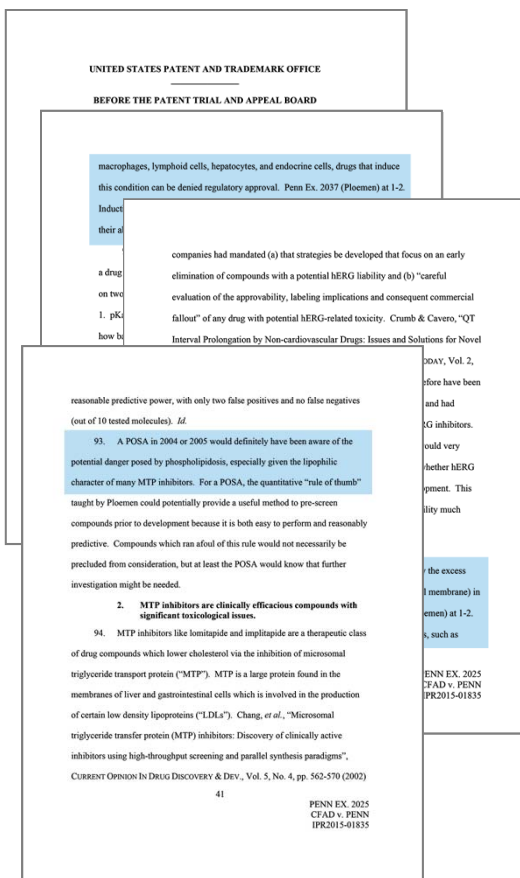
* * *

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

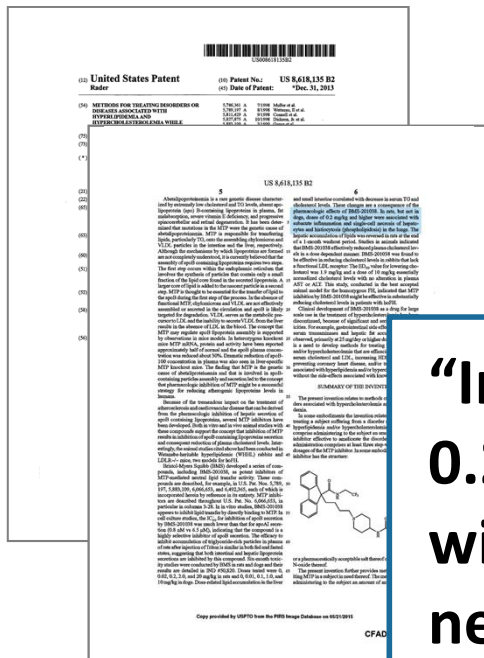


“Phospholipidosis is a type of cellular toxicity caused by the excess accumulation of phospholipids (which are normally found in the cell membrane) in a cell’s lysosomes. . . . Induction of phospholipidosis is classically associated with CAD molecules due to their ability to accumulate within and thus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

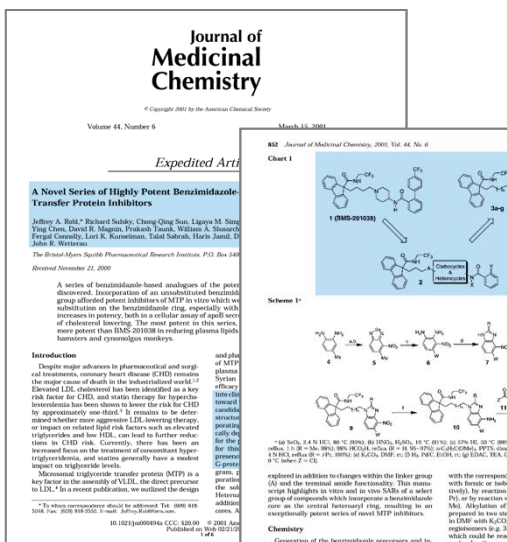
Lomitapide Caused Phospholipidosis in Rats



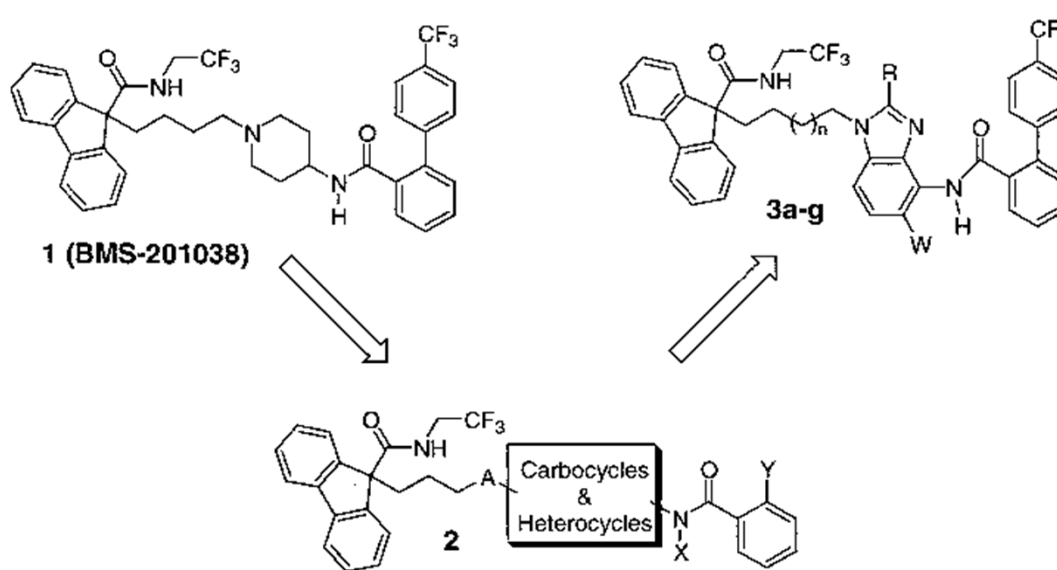
“In rats, but not in dogs, doses of 0.2 mg/kg and higher were associated with subacute inflammation and single-cell necrosis of hepatocytes and histiocytosis (phospholipidosis) in the lungs.”

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

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

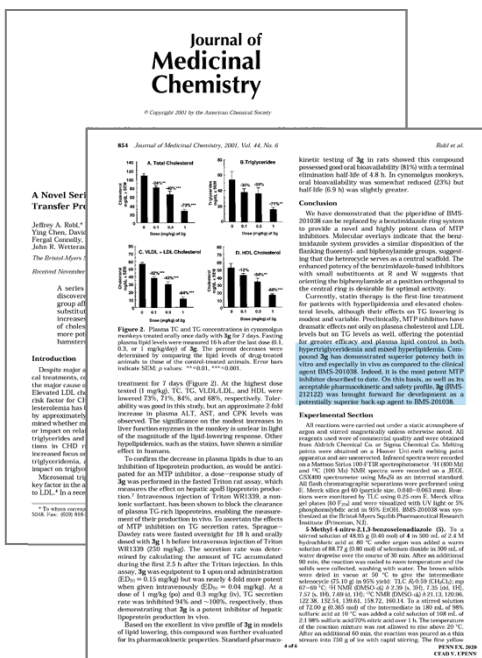


“Our focus was subsequently directed toward the identification of a suitable back-up clinical candidate to BMS-201038. A substantial amount of structure-activity studies (SAR) were performed incorporating various carbocycles and heterocycles, generically depicted by structure 2 (Chart 1), as replacements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



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

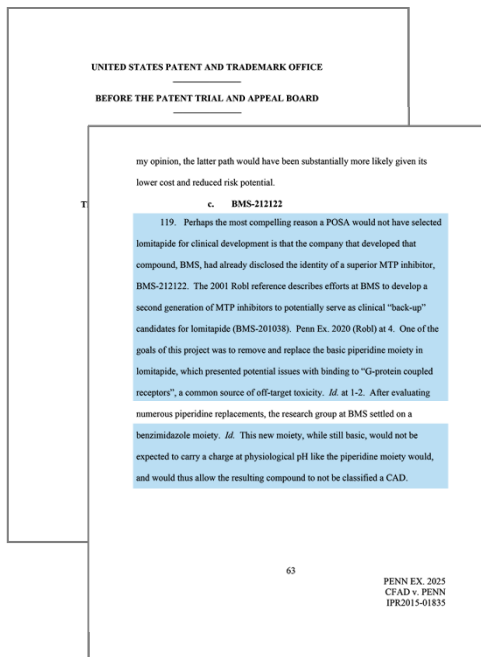
BMS' Modification of Lomitapide Produced A Potentially Superior MTP Inhibitor



“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



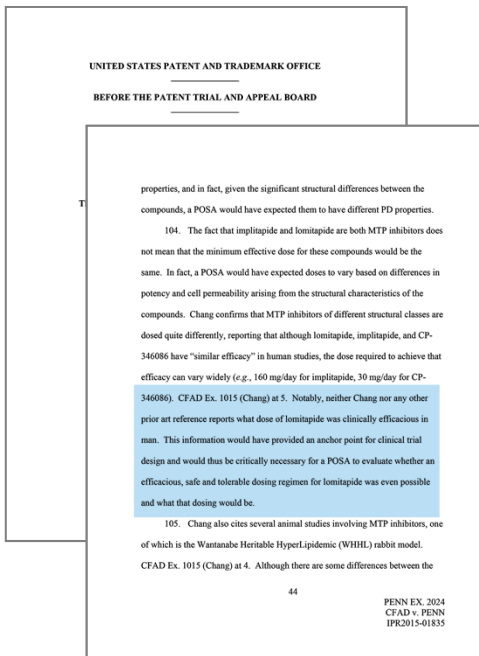
“Perhaps the most compelling reason a POSA would not have selected lomitapide for clinical development is that the company that developed that compound, BMS, had already disclosed the identity of a superior MTP inhibitor, BMS-212122.”

“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

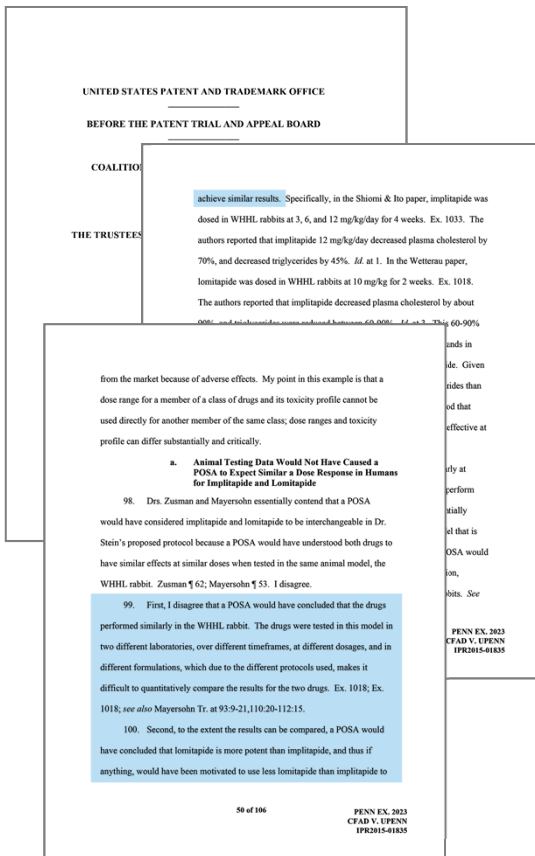
The Prior Art Does Not Identify a Clinically Effective Dose for Lomitapide



“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 Implipitapide Similarly



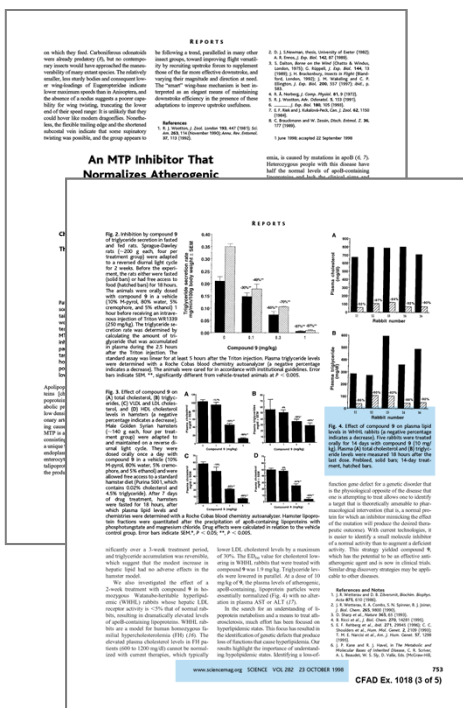
“First, I disagree that a POSA would have concluded that the drugs performed similarly in the WHHL rabbit. The drugs were tested in this model in two different laboratories, over different timeframes, at different dosages, and in different formulations, which due to the different protocols used, makes 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 implipitapide, and thus if anything, would have been motivated to use less lomitapide than implipitapide 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.**



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.

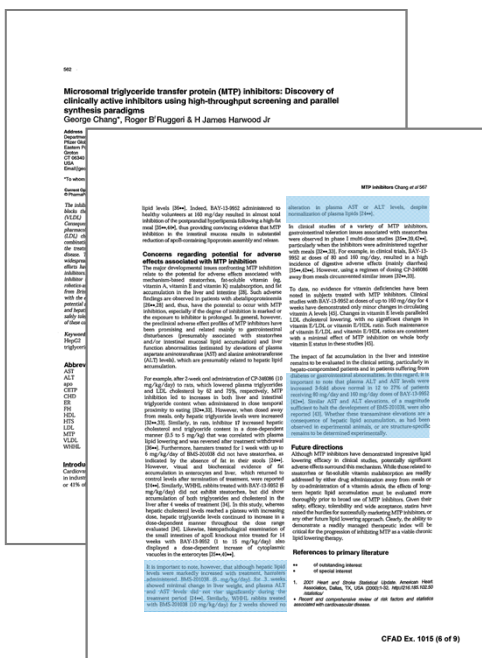
A. My prediction would be they would both be effective in reducing the lipids we're concerned about but perhaps not to the same extent.

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



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.**

A POSA Would Have No Reasonable Expectation of Success

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

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.

59

PENN EX. 2024
CFAD v. PENN
IPR2015-01835

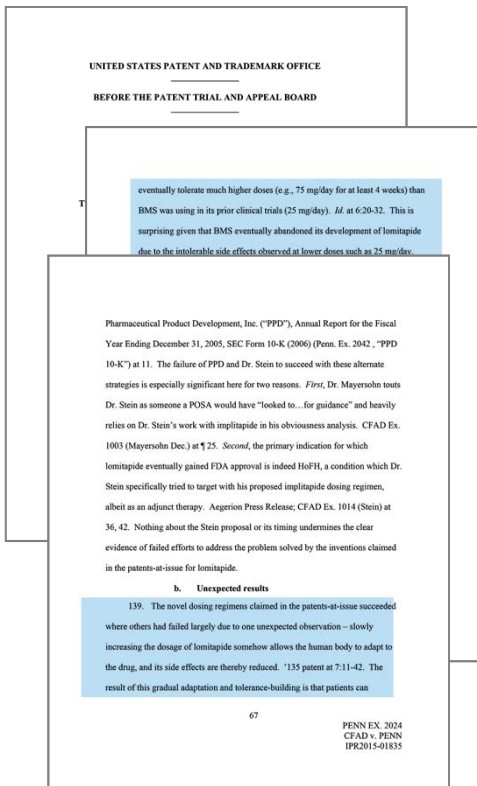
“... there is nothing in the art which would have given him or her a reasonable expectation of successfully using Stein's dosing regimen with this compound.”

“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

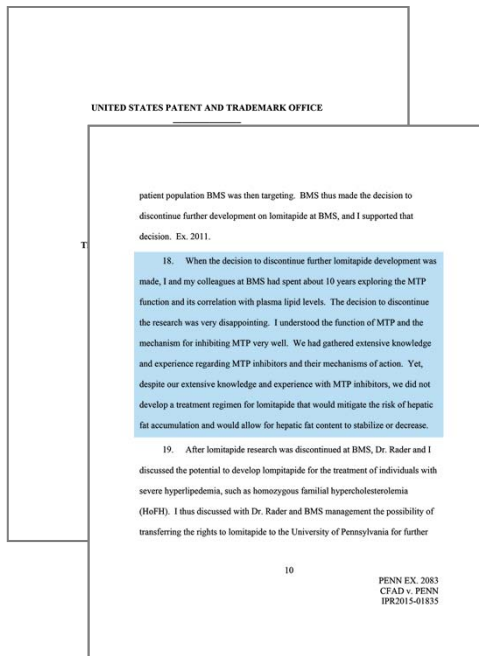
The Claimed Dosing Regimen Produced Unexpected Results



“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



“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

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

b. 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

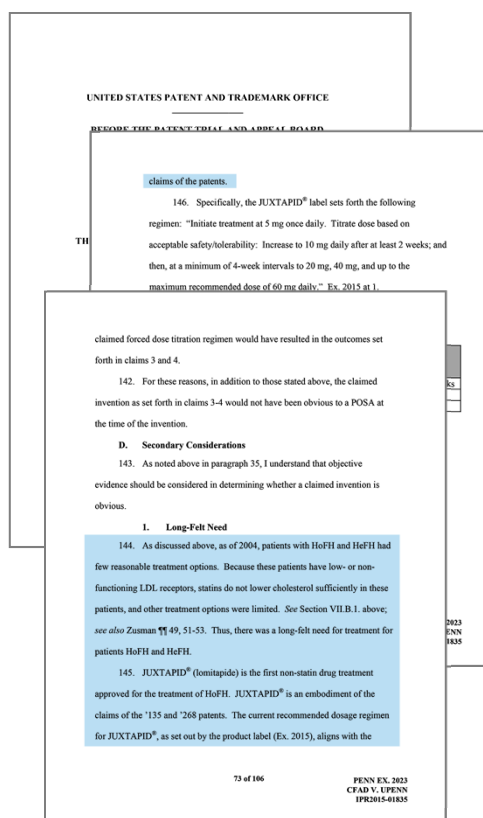
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PENN EX. 2024
CFAD v. PENN
IPR2015-01835

“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

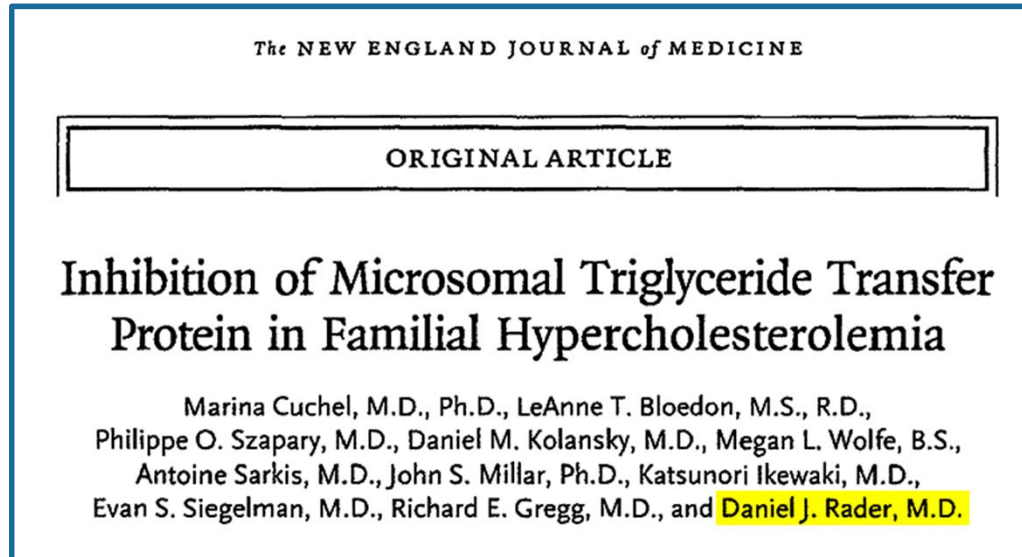


“ . . . patients with HoFH and HeFH had few reasonable treatment options. Because these patients have low- or nonfunctioning LDL receptors, statins do not lower cholesterol sufficiently in these patients, and other treatment options were limited. . . . Thus, there was a long-felt need for treatment for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



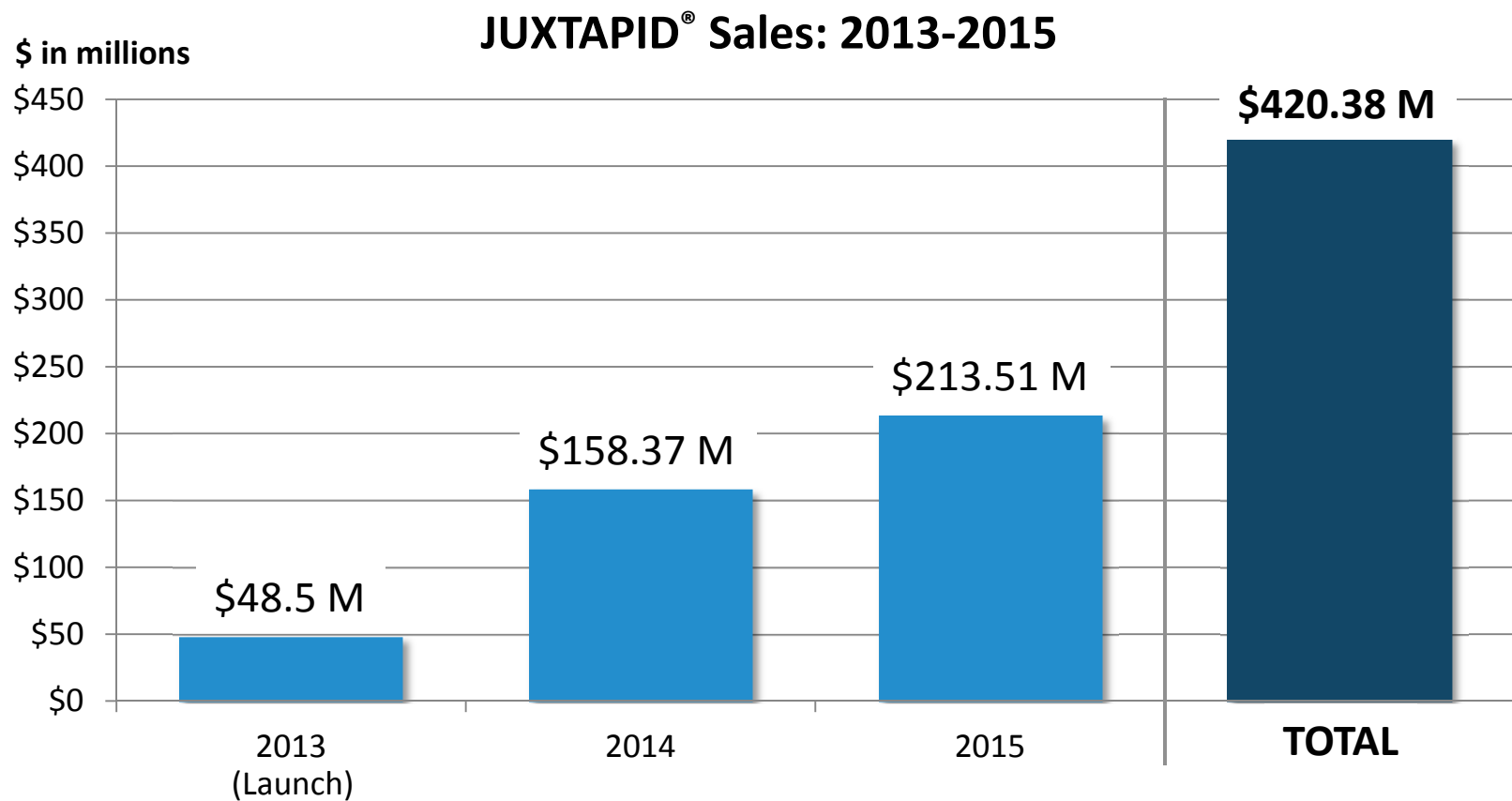
Dr. Mayersohn:

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

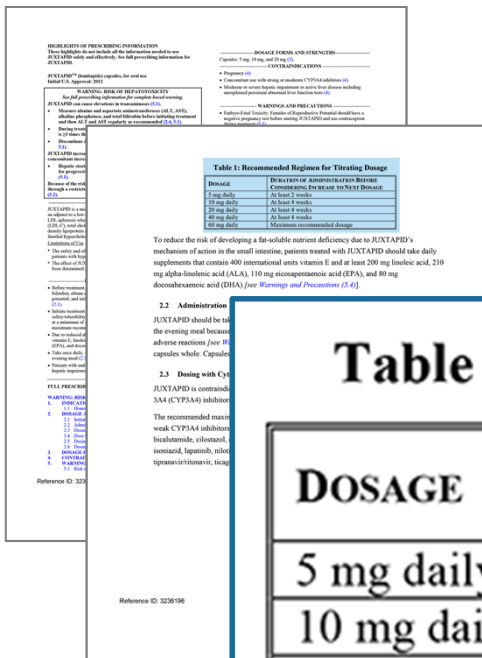


Table 1: Recommended Regimen for Titrating Dosage

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

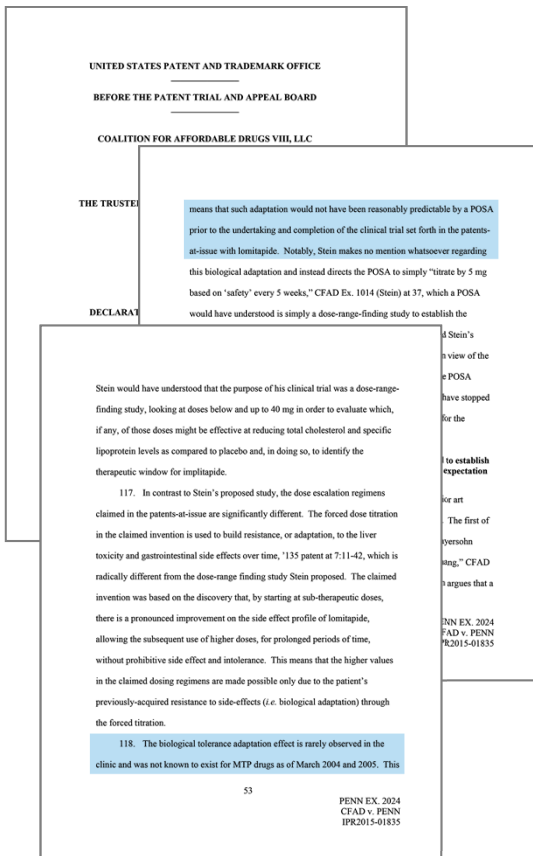
Source: Ex. 2015, Juxtapid Label, p. 5; POPR at 54-55 [52-53]

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.

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



“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.”

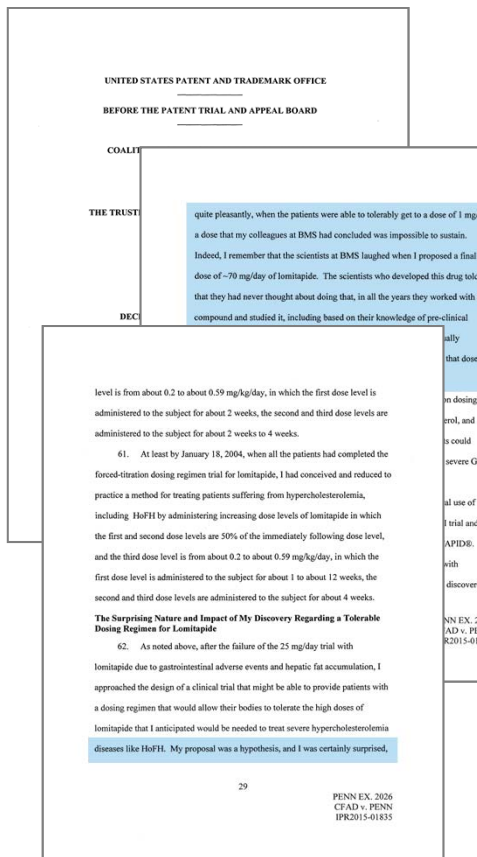
Source: Ex. 2024, Baillie Decl., ¶¶ 117-118; POR at 58

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

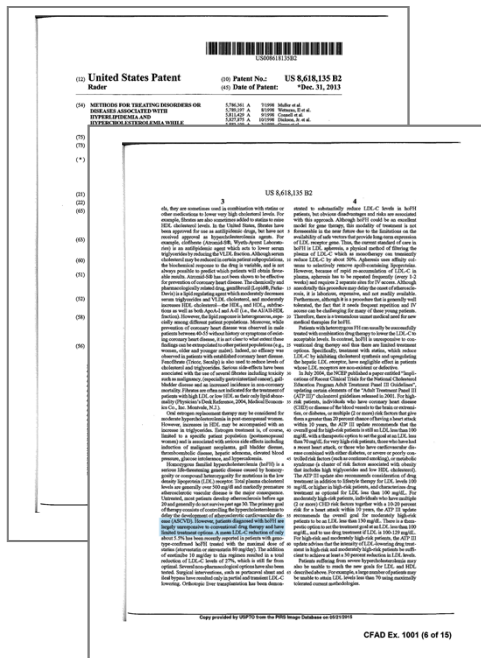
BMS Scientists Doubted That Dr. Rader's Dosing Regimen Would Succeed



“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

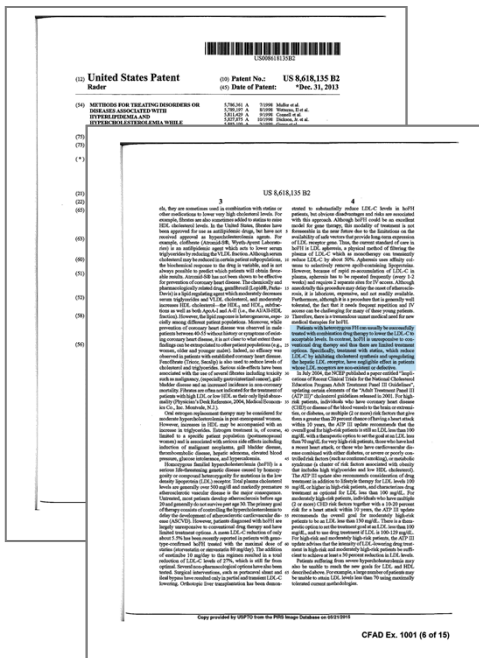
Standard Therapies Are Ineffective Against HoFH



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



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:

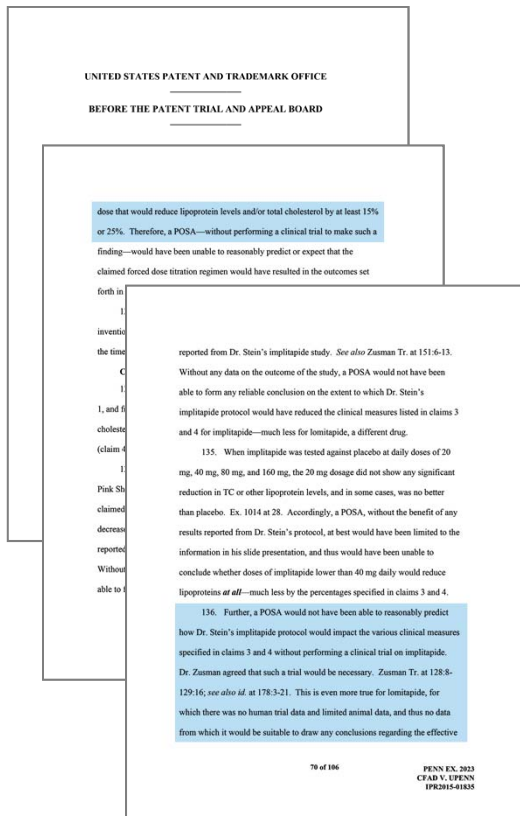
The method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-I, A-II, B, and E are reduced by at least 15%, compared to control levels.

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



“... 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%.”

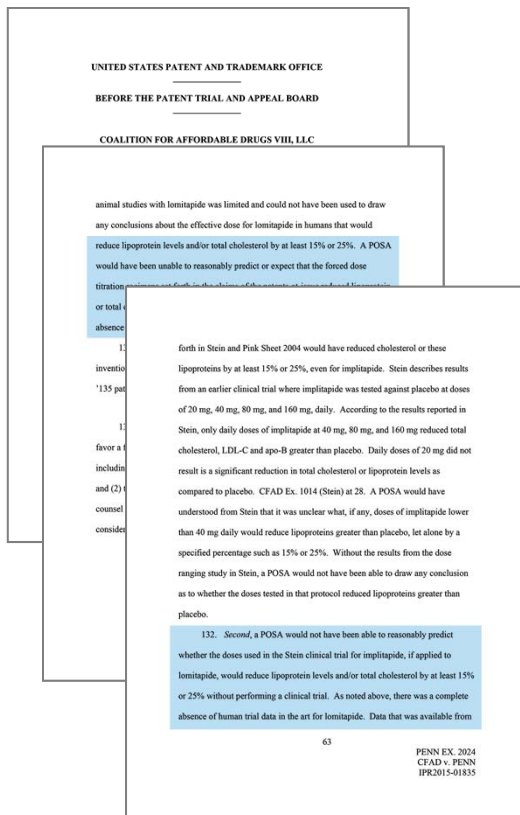
Source: Ex. 2023, Sacks Decl., ¶ 136; POR at 53-54

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



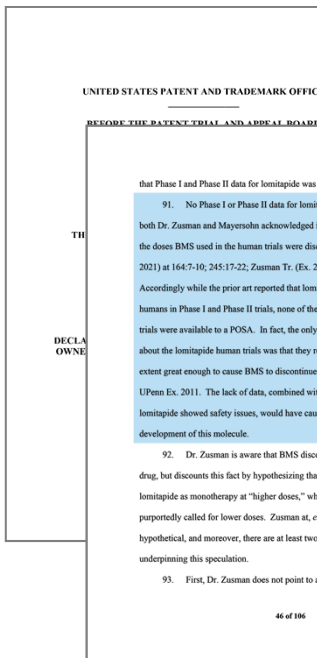
“ . . . a POSA would not have been able to reasonably predict whether the doses used in the Stein clinical trial for implitapide, if applied to lomitapide, would reduce lipoprotein levels and/or total cholesterol by at least 15% or 25% without performing a clinical trial. . . . there was a complete absence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

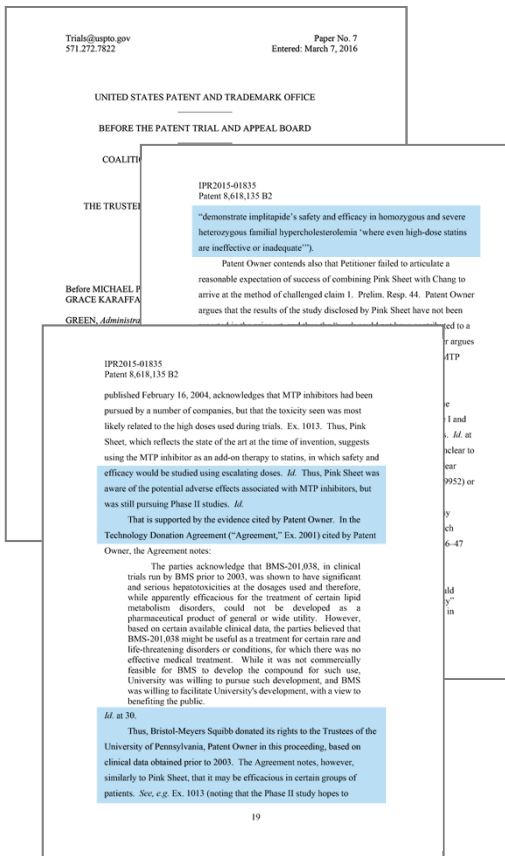
The Only Prior Art Disclosure Regarding Lomitapide's Clinical Trials Was That BMS Discontinued Development



“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)



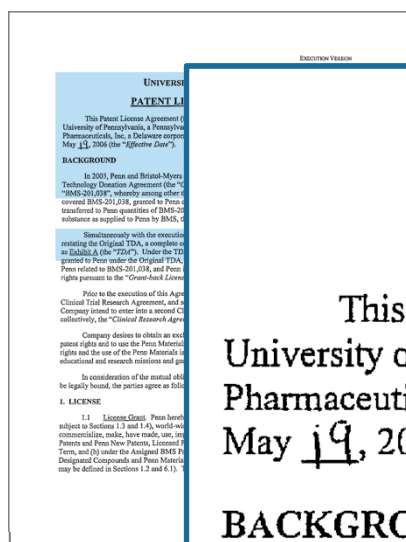
“Thus, Pink Sheet was aware of the potential adverse effects associated with MTP inhibitors, but was still pursuing Phase II studies. . . . That is supported by the evidence cited by Patent Owner. In the Technology Donation Agreement (‘Agreement,’ Ex. 2001)

* * *

. . . Thus, Bristol-Meyers Squibb donated its rights to the Trustees of the University of Pennsylvania, Patent Owner in this proceeding, based on clinical data obtained prior to 2003. The Agreement notes, however, similarly to Pink Sheet, that it may be efficacious in certain groups of patients. *See, e.g.* Ex. 1013 (noting that the Phase II study hopes to ‘demonstrate implitapide’s safety and efficacy in homozygous and severe heterozygous familial hypercholesterolemia “where even high-dose statins are ineffective or inadequate”).”

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

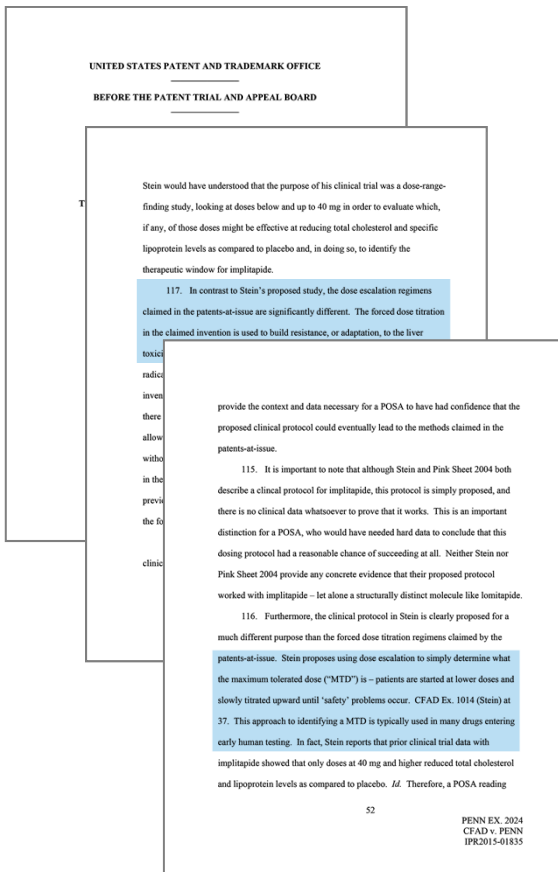
In 2003, Penn and Bristol-Myers Squibb Company ("*BMS*") entered into that certain Technology Donation Agreement (the "*Original TDA*") concerning a compound designated "BMS-201,038"

* * *

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



“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

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

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. DMS-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 1/2-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).

18

PENN EX. 2026
CFAD v. PENN
IPR2015-01835

“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.”

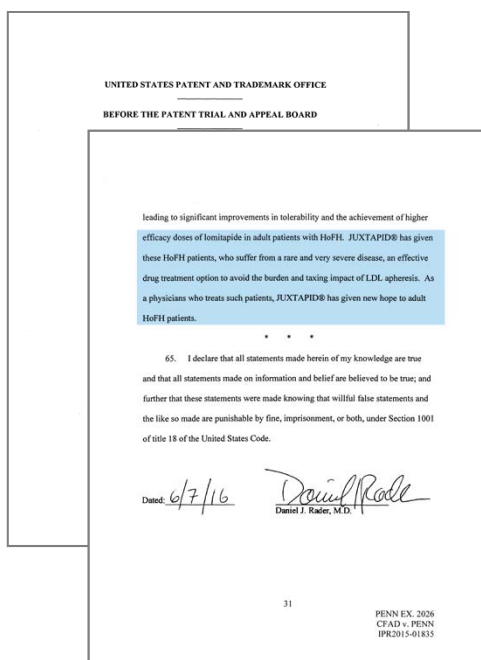
Source: Ex. 2026, Rader Decl., ¶ 40; POR at 36

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

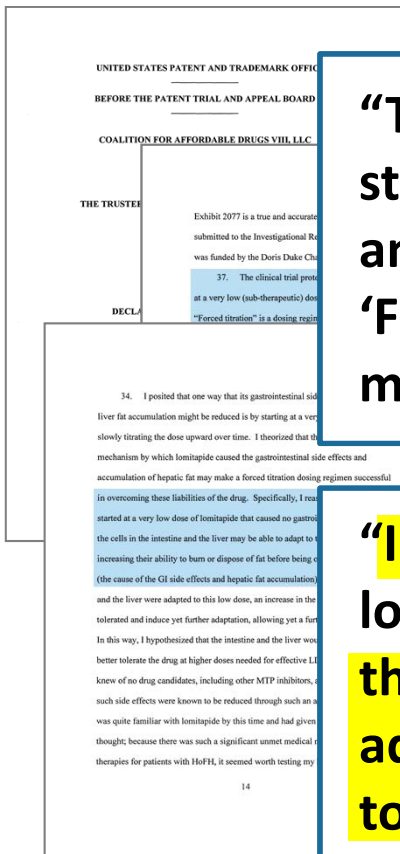
JUXTAPID® Has Given Hope to HoFH Patients



“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



“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 least 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

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:

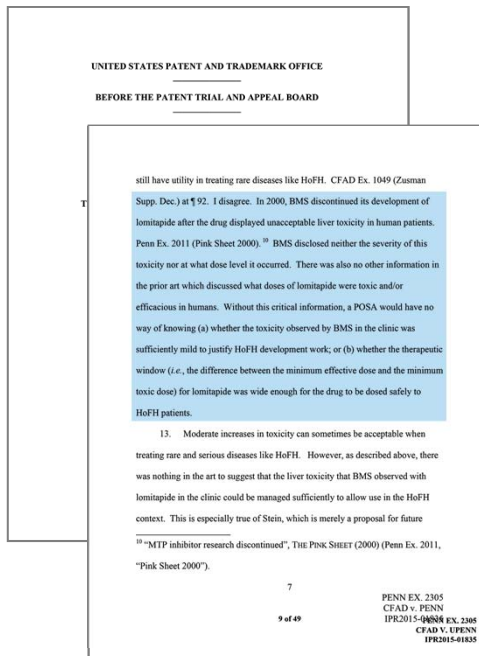
The method of claim 1 wherein one or more of Total Cholesterol, LDL, fasting triglycerides (TG), VLDL, lipoprotein (a) (Lp(a)), and apolipoproteins A-I, A-II, B, and E are reduced by at least 25%, compared to control levels.

Claim 8:

The method of claim 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]

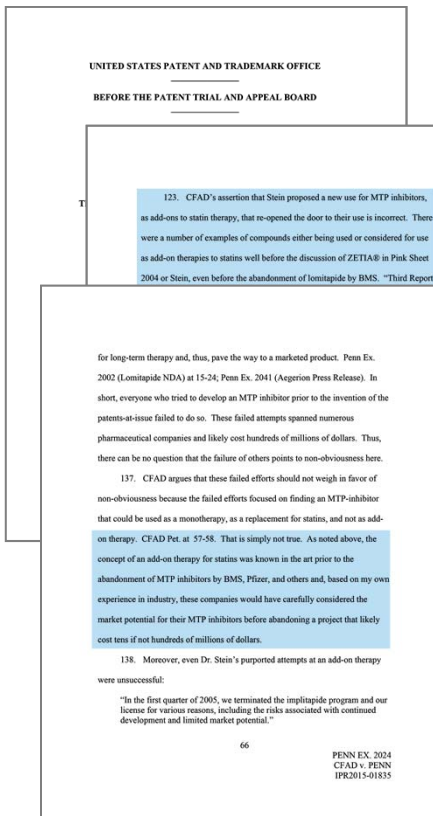
It Would Not Have Been Obvious to Develop Lomitapide for HoFH



“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



“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.”

“... 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.**

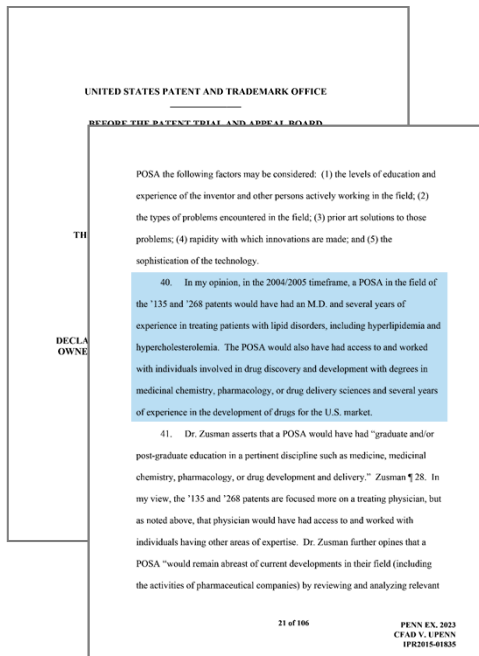
Source: Ex. 2022, Zusman Tr., 171:17-172:6 (Objection Omitted); MTA at 18

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



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.

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

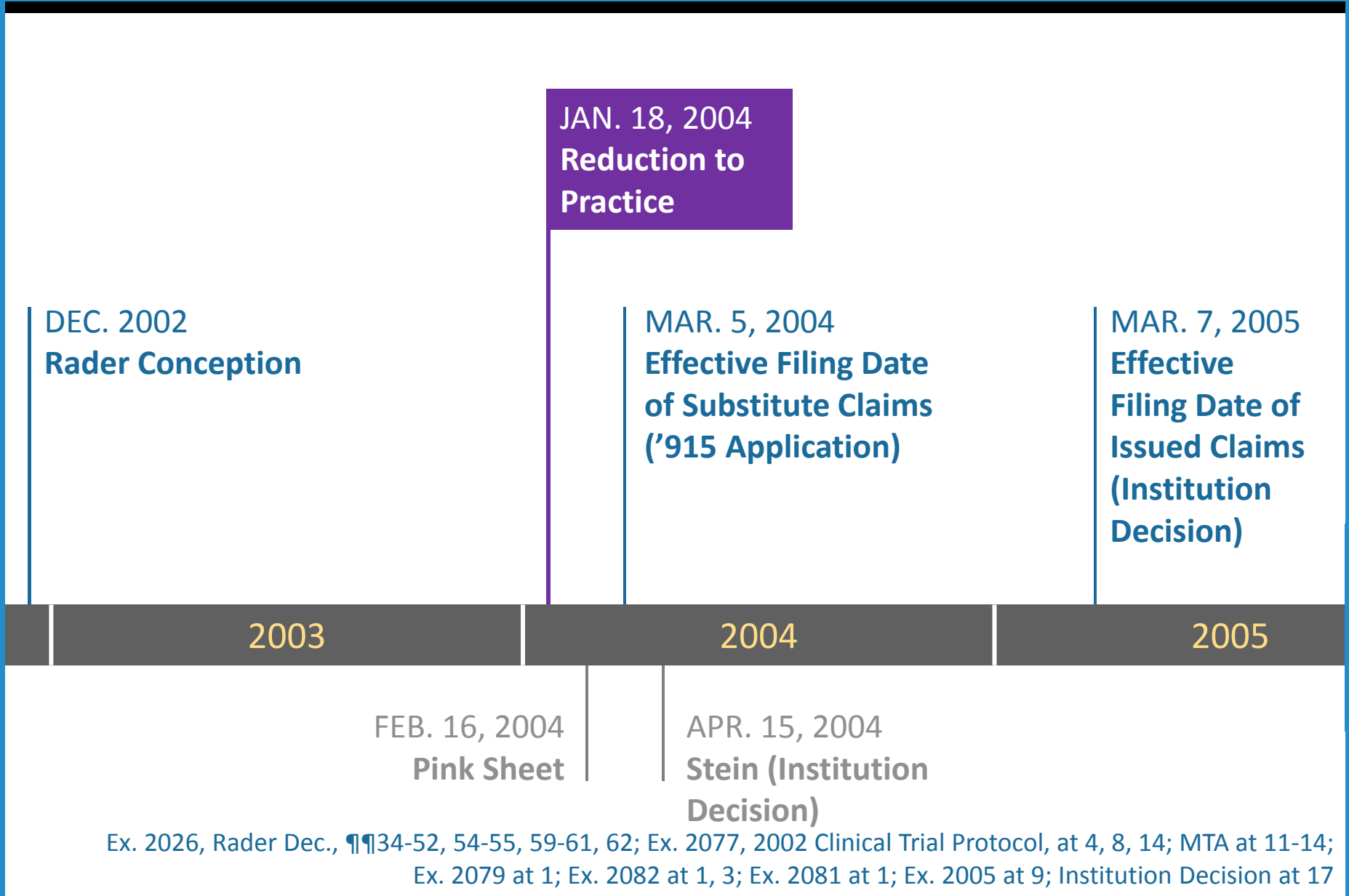
(2) The substitute claims present additional bases for patentability over the issued claims

- 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

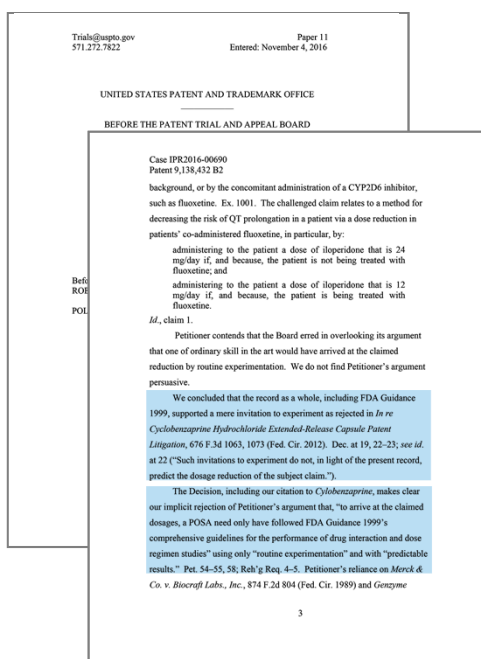
- The substitute claims are narrower than the issued claims and supported by the written descriptions

The Substitute Claims Pre-Date Pink Sheet And Stein



Mere Invitations To Experiment From General Guidance Documents Is Not Enough

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

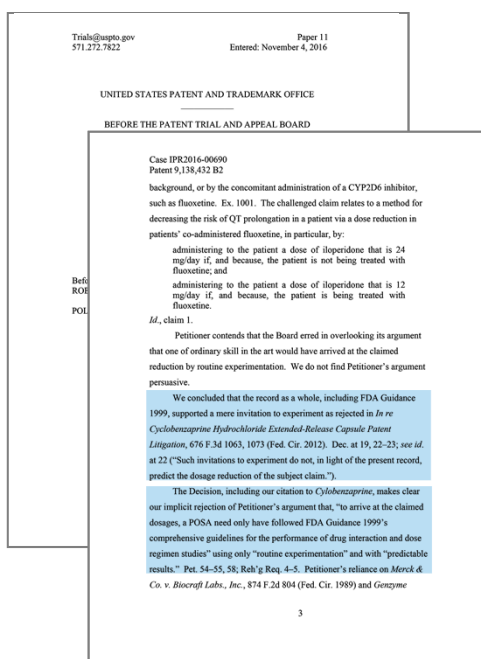


“We concluded that the record as a whole, including FDA Guidance 1999, supported a mere invitation to experiment as rejected in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012). Dec. at 19, 22–23; see *id.* at 22 (“Such invitations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

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

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



“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.”

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 piperidiny]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

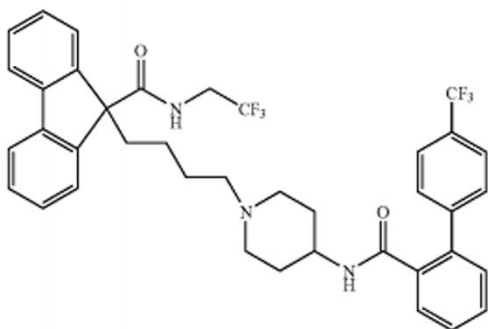
Patent Owner's Contingent Motion To Amend Should Be Granted

- **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

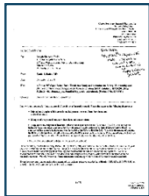
Patent Owner's Contingent Motion To Amend Should Be Granted

- **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 <u>upward dose titration</u> 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 Reduced To Practice By January 18, 2004

Results from the clinical trial proved Dr. Rader's general hypothesis

UNITED STATES PATENT AND TRADEMARK OFFICE
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 1 mg/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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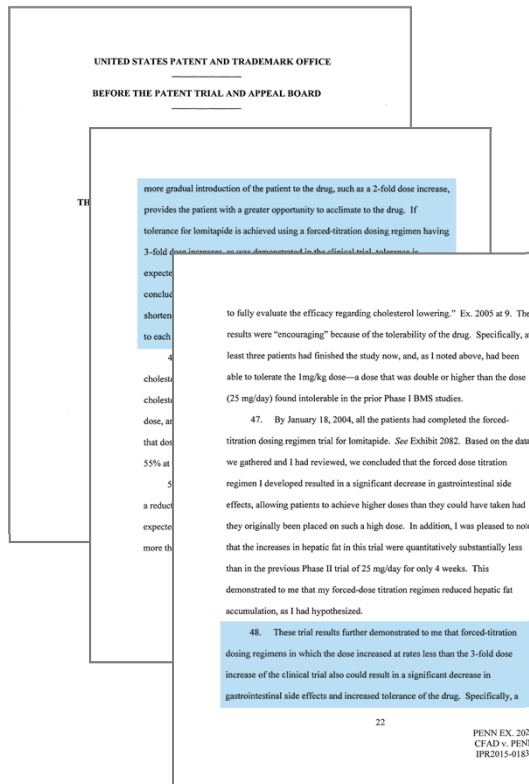
PENN EX. 2026
CPAD v. PENN
IPR2015-01835

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

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 <u>prior to</u> lomitapide's withdrawal from the clinic. WHHL rabbit study consisted of <u>five rabbits</u> at a <u>single dose</u> for <u>two weeks</u> ; 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 <u>dose-dependent</u> 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

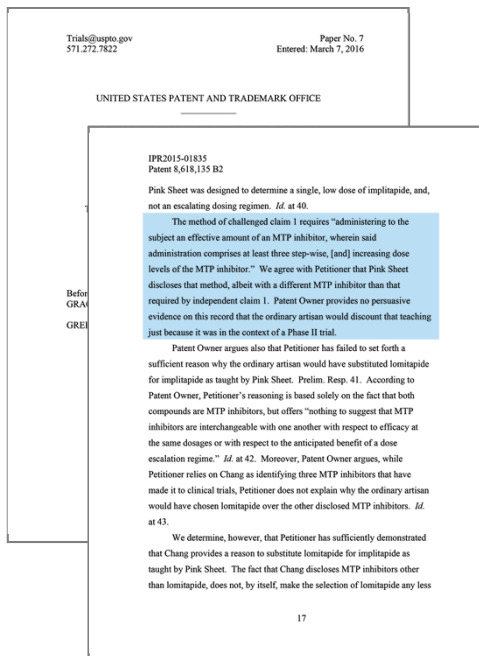
- **Pink Sheet and Stein do not teach the two-fold increasing dose regimen in the substitute claims**
 - Stein / Pink Sheet:
 - Conservative titration
 - Gradual dose increase of 5 mg per level over five week intervals
 - No specified target dose
 - Substitute claims:
 - Aggressive titration
 - Dose 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

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



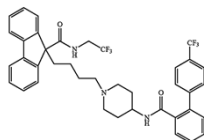
“The method of challenged claim 1 requires ‘administering to the subject an effective amount of an MTP inhibitor, wherein said administration comprises at least three step-wise, [and] increasing dose levels of the MTP inhibitor.’ We agree with Petitioner that Pink Sheet discloses that method, albeit 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:

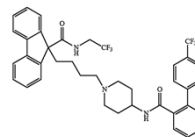


~~or a pharmaceutically acceptable salt thereof or the piperidine N-oxide thereof~~

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
<p>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,</p>	<p>[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.”</p> <p><i>See also</i> [0033] (hypercholesterolemia); ¶ [0001] (Abstract); Claim 2.</p> <p style="text-align: right;">Source: Ex. 1006, ’915 Appl., at [0020], [0033], [0001], Claim 2</p>	<p>[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.”</p> <p><i>See also</i> [0042]; [0027]</p> <p style="text-align: right;">Source: Ex. 1008, ’118 Appl., at [0024], [0042], [0027]</p>

The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
<p>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 <u>50% of the immediately following dose level</u>, and</p>	<p>[0046] “In some embodiments, each dose level is no more than 50% of the immediately following dose level.”</p> <p>[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.”</p> <p><i>See also</i> Claim 18: “A method of claim 17 wherein each said dose level is no more than 50% of the immediately following dose level.”</p> <p style="text-align: right;">Source: Ex. 1006, '915 Appl., at [0046], [0093], Claim 18</p>	<p>[0053] “In some embodiments, each dose level is no more than 50% of the immediately following dose level.”</p> <p>[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.”</p> <p>[0074] (50% escalation between doses 1-3)</p> <p style="text-align: right;">Source: Ex. 1008, '118 Appl., at [0053], [00112], [0074]</p>

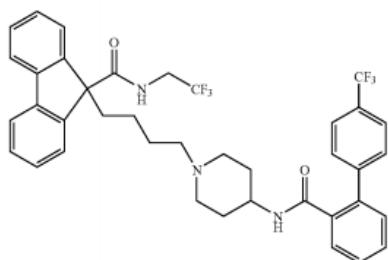
The Substitute Claims Are Supported

Element	Ex. 1006 ('915 Appl.) Cites	Ex. 1008 ('118 Appl.) Cites
<p><u>wherein a third dose level is from about 0.2 to about 50 mg/day-0.59 mg/kg/day based on a weight between 62.5 and 74.9 kg; and</u></p>	<p>[0047] “In some embodiments, the third dose level is from about 0.2 to about 0.59 mg/kg/day.”</p> <p>[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.”</p> <p>[0097] (Example 6): “70 kg man”</p> <p style="text-align: right;">Source: Ex. 1006, '915 Appl., at [0047], [0093], [0097]]</p>	<p>[0054] “In some embodiments, the third dose level is from about 0.2 to about 0.59 mg/kg/day.”</p> <p>[00112] (Example 7): “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.”</p> <p>[00116] (Example 8): “70 kg man”</p> <p style="text-align: right;">Source: Ex. 1008, '118 Appl., at [0054], [00112], [00116]]</p>

The Substitute Claims Are Supported

Element

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

Ex. 1006 ('915 Appl.) Cites

[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-Trifluoroethyl)-9-[4-[4-[[4'-(trifluoromethyl)[1,1'biphenyl]-2-Yl]carbonyl]amino]-1-piperidinyl]butyl]9H-fluorene-9-carboxamide, methanesulfonate.”

Source: Ex. 1006, '915 Appl., at [0043]

Ex. 1008 ('118 Appl.) Cites

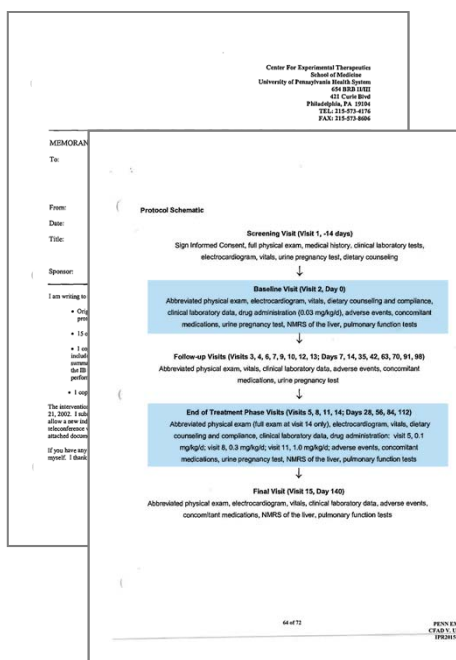
[0034] “In some embodiments, the MTP inhibitor is BMS-20 1038. As used herein, the phrase ‘**BMS-201038**’ refers to a compound known as N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[4'-(trifluoromethyl)[1, 1'biphenyl]-2Yl]carbonyl]amino]-l-piperidinyl]butyl]9H-fluorene-9-carboxamide, methanesulfonate”

Source: Ex. 1008, '118 Appl., at [0034]

The Substitute Claims Are Supported

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

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

Center For Experimental Therapeutics
School of Medicine
University of Pennsylvania Health System
421 Curie Blvd
Philadelphia, PA 19104
TEL: 215-875-4176
FAX: 215-875-4866

MEMORANDUM

To: _____

From: _____

Date: _____

Title: _____

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 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 (20°-25°) 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

Page 13 of 57
34 of 72
PENN EX 2077
CRF 13-13200
09/26/14/003

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 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.

2. Investigate the molecular etiology of inherited high HDL, chole candidate gene and linkage analysis approaches.

We have been aggressively recruiting probands, siblings, and high HDL cholesterol levels. Currently, we have DNA samples in HDL levels above or equal to the ninetieth percentile for the subject. We also have DNA samples from 171 relatives of these probands who have HDL levels above or equal to the ninetieth percentile. Samples recently arrived in the lab, whose final results are pending to obtain DNA from about 120 individuals (both probands and relatives) who have been sent kits for collecting blood samples. We have several extended families with evidence of a dominantly transmitted high HDL-C phenotype in us to collect additional family members. Dr. Marina Costantini and I will be investigating the etiology of this phenotype in the lab.

3. Develop methods for assessment of the rate of reverse cholel and apply them to the investigation of novel therapies targeted toward HDL metabolism.

We have been actively collaborating with Dr. George Roth of Philadelphia to assess variation in the ability of sera to promote cholesterol efflux and will correlate serum cholesterol, other serum parameters and with the presence of cardiovascular disease in a study of the effect of the Thapsigargin inhibitor.

1 of 2
PROTECTIVE ORDER MATERIAL

Progress Report Year 1 Oct, 2003

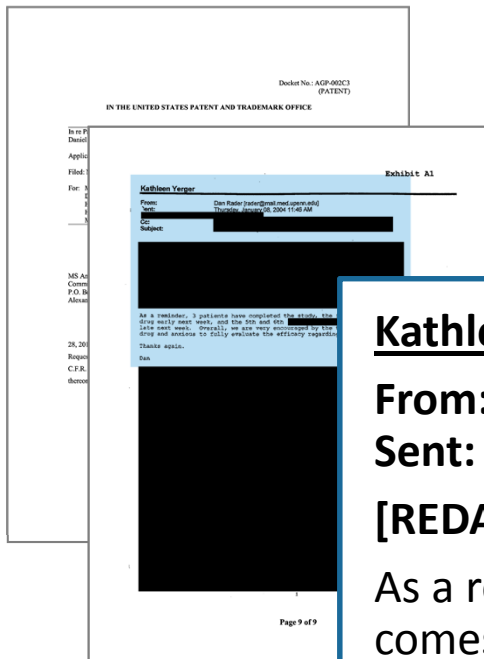
Results in Year 1

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

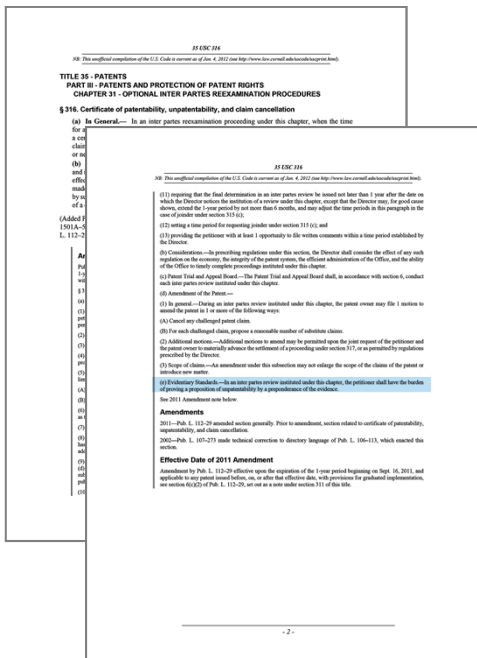
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The Substitute Claims Were Reduced To Practice By January 18, 2004

“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).

Petitioner Has The Burden On All Propositions Of Unpatentability



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.**

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 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

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to
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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 stratification 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,

ii

“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
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GUIDELINE FOR INDUSTRY¹ DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

I. INTRODUCTION

A. Purpose of Dose-Response Information

Knowledge of the relationship between drug concentration in blood, and of undesirable effects) is important for individual patients. This information is important for identifying the best 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. Dose-concentration, concentration-response, and concentration-effect relationships are used to prepare dosage and labeling. In addition, knowledge of these relationships is an important part of an economical approach to global drug registration.

¹This guideline was developed with the International Conference on Harmonization of Pharmaceutical Registration for Human Use. It was developed in consultation with the regulatory parties, in accordance with the ICH process, March 10, 1994. At Step 4 of the adoption to the regulatory bodies of the E.U. guideline was published in the Official Journal of the European Communities and is applicable to both drug and biological products. The ICH guidelines to state procedures or standards generally issued under § 10.90(b) (2) of the FDCA are acceptable to FDA. Therefore, this guideline is not subject to the requirements of FDCA § 10.90(b), and it does not create or confer any person, nor does it operate to bind FDA. For more information, contact the Executive Secretariat and Research, 7000 Standish Place, Rockville, MD 20852. Electronic version of this guideline is also available at: www.fda.gov/cder/ftp/iver/CDV02/CDER.FDA.GC

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

Guideline for Industry

Dose-Response Information to Re

A number of specific study designs can be used to assess dose-response. The same approaches can also be used to measure concentration-response relationships. Although not intended to be an exhaustive list, the following approaches have been shown to be useful ways of deriving valid dose-response information. Some designs outlined in this guidance are better established than others, but all are worthy of consideration. These designs can be applied to the study of established clinical endpoints or surrogate endpoints.

1. Parallel Dose-Response

Randomization

parallel dose-response

that has had an

dose is the final

immediately on

"forced" titration

dose should be

dose-response

in all cases, a 10

provides evidence

of the drug effect

limited effect on

Monoclonal (best

unequivocally it

can salvage, in

and, therefore,

all doses were

ected a statistic

between doses

(upward slope)

It should be de

tested, if it is to

clinically mean

The parallel dose

(population-ave

of individual do

It is all too com

dose-response, but

that doses did not

go high enough.

A formally planned

interim analysis (or

other multi-stage

design).

that has had extensive use and considerable success. The fixed dose is the final or maintenance dose; patients may be placed immediately on that dose or titrated gradually (in a scheduled "forced" titration) to it if that seems safer. In either case, the final

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

ES
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(CDER)

Guidance for Industry and Reviewers¹ Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

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I. INTRODUCTION
This guidance outlines a process (algorithm) and recommended starting dose (MRSD) for "first in man" clinical trials of new molecular entities 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.
The goals of this guidance are to (1) establish a dose, (2) provide common conversion factors for 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.

II. SCOPE
The process identified in this document pertains to determining the MRSD for adult healthy subjects when beginning a clinical investigation of any new drug or biological therapeutic that has been tested in animals. This document is not pertinent to prophylactic vaccines or 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.

¹ This guidance has been prepared by the Office of New Drugs (OND) in cooperation with the Center for Biologics Evaluation and Research (CBER).

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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

Guidance for Industry and Reviewers

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40 Although the process outlined in this document uses observed toxicities, administered doses, and
41 an algorithmic approach to calculate the MSRD, an alternative approach could be proposed that
42 places primary emphasis on animal pharmacokinetics and modeling rather than dose. In a
43 limited number of cases, animal pharmacokinetic data may be useful in determining initial
44 clinical doses.² However, in the majority of new INDs, animal data are not available in
45 sufficient detail to construct a scientifically valid, pharmacokinetic model whose aim is to
46 accurately project an MSRD.
47
48 Toxicity should be avoided at the initial dose. However, doses should be chosen that allow
49 reasonably rapid attainment of the phase 1 trial objectives (e.g., assessment of the therapeutic's
50 tolerability, pharmacodynamic or pharmacokinetic profile). All of the relevant preclinical data,
51 including information on the pharmacologically active dose, the full toxicologic profile of the
52 compound, and the pharmacokinetics (absorption, distribution, metabolism, and excretion) of the
53 therapeutic, should be considered when determining the MSRD. Starting with doses lower than
54 the MSRD is always a possible option and may be particularly appropriate to meet some clinical
55 trial objectives.
56
57 The remainder of this document will focus on the recommended algorithmic process for starting
58 dose extrapolation from animals to humans based on administered doses, since this method will
59 likely be useful for the majority of new INDs seeking to investigate new drugs in healthy
60 volunteers. Some classes of drugs (e.g., many cytotoxic or biological agents) are commonly
61 introduced into initial clinical trials in patient volunteers rather than healthy volunteers.
62 Typically, this occurs when a drug is suspected or known to be unavoidably toxic. Although this
63 document does not specifically address starting doses in patients, many principles and some
64 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 tolerability and metabolism may differ significantly from that of animals; (2) metabolism of toxicity may not be known for a toxic concentration in a particular concentration, 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 project starting doses would require multiple untested assumptions. Modeling may be more useful when plasma toxicity is measured during doses in special cases where the underlying assumptions would be necessary. Such cases are exemplified by large molecule weight proteins (like humanized monoclonal antibodies), which are immunologically untested, are derived from recombinant DNA technology, and have known immunogenic, local immunologic and desirable effects on blood cells, and have a volume of distribution limited to the plasma volume. Here, alternative, pharmacokinetic, and pharmacodynamic models have been useful in identifying the human single 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 response 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.

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“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

Guidance for Industry and Reviewers

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

308 When determining the MRSD for the first dose of a new therapeutic in humans, absorption,
309 distribution, and elimination parameters will not be known for humans. Comparative
310 metabolism data, however, might be available based on in vitro studies. These data are
311 particularly relevant when there are marked differences in both the in vivo metabolic profiles
312 and HEDs in animals. Class experience implies that previous studies have demonstrated that a
313 particular animal model is more appropriate for the assessment of safety for a particular class of
314 therapeutic. For example, in the nonclinical safety assessment of the phosphodiesterase
315 inhibitor class, the monkey is considered the most appropriate species because monkeys
316 experience the same dose limiting toxicity as humans, (i.e., complete atrioventricular block), whereas
317 rodents do not. For this class of therapeutic, the MRSD would usually be based on the HED for
318 the NOAEL in monkeys regardless of whether it was lower than that in rodents, unless unique
319 dose limiting toxicities were observed with the new antineoplastic compound in the rodent species.
320 Similarities of biochemistry and physiology between the species and humans that are relevant to
321 the limiting toxicities of the therapeutic should also be considered under class experience. If a
322 species is the most sensitive but has differences in physiology compared to humans that mitigate
323 it to the therapeutic, it may not be the most appropriate species for selecting the MRSD.
324
325 **VII. STEP 4: APPLICATION OF SAFETY FACTOR**
326
327 Once the HED of the NOAEL in the most appropriate species has been determined, a safety
328 factor is then applied in order to provide a margin of safety for protection of human subjects
329 receiving the initial clinical dose. This safety factor allows for the variability in extrapolating from
330 animal toxicity studies to studies in humans resulting from: (1) uncertainties due to enhanced
331 sensitivity to therapeutic activity in humans versus animals, (2) difficulties in detecting certain
332 toxicities in animals (e.g., headache, myalgia, mental disturbances), (3) differences in receptor
333 density or affinity, (4) interspecies toxicities, and (5) interspecies differences in absorption,
334 distribution, metabolism, and excretion of the therapeutic. These differences may be
335 accommodated by lowering the human starting dose from the HED of the selected species
336 NOAEL.
337
338 In practice, the MRSD for the clinical trial is determined by dividing the HED derived from the
339 animal NOAEL by the safety factor. The default safety factor used is 10. This is a historically
340 accepted value, but, as described below, should be evaluated based on available information.
341
342 While a safety factor of 10 can generally be considered adequate for protection of human
343 subjects participating in initial clinical trials, this safety factor may not be appropriate for all
344 cases. The safety factor should be raised when there is reason for increased concern, and
345 lowered when concern is reduced due to available data that provide added assurance of safety.
346 This can be visualized as a sliding scale, balancing findings that mitigate the concern for harm to
347 healthy volunteers with those that suggest greater concern is warranted. The extent of the
348 increase or decrease is largely a matter of judgment, using the available information. It is

“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

Common public guidance

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

308 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

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261 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 ($W^{0.75}$).

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264
265 • 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 anti-tumor oligonucleotides in humans is believed to be dependent upon C5a6 (Gray et al., 1997). For some anti-tumor drugs, the C5a6 correlates across nonclinical species with mg/kg dose and in such instances mg/kg scaling would be justified.

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272 • 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.

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VI. STEP 3: MOST APPROPRIATE SPECIES SELECTION

294 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).

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VI. STEP 3: MOST APPROPRIATE SPECIES SELECTION

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

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

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

Reigner Emphasizes Importance Of PK/PD Data



“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

COALITION

THE TRUSTEES

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)	?	?	?	

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

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PENN EX. 2023
CPAD V. UPENN
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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 REVISED DEMONSTRATIVE EXHIBITS** to be served electronically on December 7, 2016 on the counsel below:

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/Eric T. Romeo/
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