No. 14-55633

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

TODD SCHUENEMAN, on behalf of himself and all others similarly situated,

Plaintiff-Appellant,

v.

ARENA PHARMACEUTICALS, INC., et al.,

Defendants-Appellees,

On Appeal from the United States District Court for the Southern District of California
Honorable Cathy Ann Bencivengo
Case No. 3:10-cv-01959-CAB-BLM

ANSWERING BRIEF OF DEFENDANTS-APPELLEES

William E. Grauer
Koji F. Fukumura
Mary Kathryn Kelley
Ryan E. Blair
Cooley LLP
4401 Eastgate Mall
San Diego, CA 92121-1909
(858) 550-6139

Attorneys for Defendants-Appellees

CORPORATE DISCLOSURE STATEMENT PURSUANT TO FED. R. APP. P. 26.1

Pursuant to Federal Rule of Appellate Procedure 26.1, counsel for Appellee Arena Pharmaceuticals, Inc. certifies the following: Appellee Arena Pharmaceuticals, Inc. has no parent corporations, and no publicly held company owns 10 percent or more of its stock.

Dated: October 24, 2014

COOLEY LLP

By /s/ William E. Grauer
William E. Grauer

TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF AUTHORITIES

Page

Cases

TABLE OF AUTHORITIES
(continued)

Page

TABLE OF AUTHORITIES
(continued)

Page

TABLE OF AUTHORITIES
(continued)

Page

Statutes

TABLE OF AUTHORITIES
(continued)

Page

Other Authorities

INTRODUCTION

This case involves a drug, lorcaserin, that has been approved by the U.S. Food and Drug Administration ("FDA") and is now in use throughout the United States to combat the obesity epidemic. In clinical trials involving over 8,500 humans, as well as in nonclinical trials involving mice and monkeys, Appellee Arena Pharmaceuticals, Inc. ("Arena") administered the drug for lengthy periods of time with no increased cancer risk.

Mid-way through a single nonclinical study involving a rat species highly susceptible to tumors (the "Rat Study"), however, Arena identified a possible increase in tumor rates. Arena immediately reported these findings to the FDA, even though the data was preliminary and had not been vetted by independent pathologists. At no point after receiving these interim findings did the FDA halt the then-ongoing clinical trials involving nearly 7,200 humans. Instead, the FDA permitted the clinical trials to continue, acknowledging in April 2008 that the interim Rat Study findings could change and that it was "plausible" these findings resulted from a rat-specific mechanism involving an increase in a hormone called prolactin that causes mammary tumors in rats but not humans.

In December 2009, Arena submitted its New Drug Application ("NDA") for lorcaserin to the FDA. In addition to results from its "pivotal" Phase III human trials that met all efficacy and safety endpoints established by the FDA and other

clinical and nonclinical trials, the NDA included the final Rat Study results, which showed that the cancerous tumors were confined to extremely high doses of the drug that the FDA has deemed not relevant to humans. The NDA also included the results of a series of six mechanistic studies conducted by Arena (the "Prolactin Studies") demonstrating that lorcaserin increased prolactin levels in rats.

On the basis of these results, as well as the positive results from more than 100 other clinical and preclinical studies, Arena had reason to be optimistic about the drug's potential for approval. However, at all times while the FDA considered lorcaserin, Arena provided extensive warnings that FDA approval could be delayed or denied. Lead Plaintiff-Appellant ("Plaintiff") makes no mention of these extensive risk warnings in his Opening Brief (the "Appeal" or "AOB"). Nor does Plaintiff mention that he affirmatively disavowed in writing before the district court the precise theory of fraud that is now the centerpiece of his Appeal – *i.e.*, that Arena knew the Rat Study would derail or delay FDA approval. (SER 149.)[1]

In September 2010, the FDA publicly disclosed a briefing document in advance of the FDA's Endocrinology and Metabolic Advisory Committee ("Advisory Committee") meeting to discuss lorcaserin. It was only then – ***more than 30 months after Arena met with the FDA in April 2008*** – that Defendants first learned they had a temporary disagreement with the FDA over the

[1] "SER __" refers to Defendants-Appellees' ("Defendants") Supplemental Excerpts of Record. "ER __" refers to Plaintiff's Excerpts of Record.

interpretation of the Rat Study data. Specifically, (1) Arena and the FDA viewed the results of the Prolactin Studies differently, and (2) due to "diagnostic uncertainty," the FDA had provisionally combined the malignant and benign tumor findings in the Rat Study pending a new review of the tissue slides by a group of independent pathologists. When this group examined the Rat Study data, it confirmed Arena's interpretation and actually showed that Arena had overreported the cancer findings – *i.e.*, there was *less* cancer than Arena had reported. The FDA thereafter agreed with Arena's interpretation of the Rat Study and approved the drug for human use (a fact admitted by Plaintiff but not mentioned until page 41 of his Appeal). (AOB at 41.)

After giving Plaintiff four opportunities to state a claim, the district court dismissed the case with prejudice because Plaintiff could not (and still cannot) plead scienter. In the end, the district court found that "Defendants had a legitimate scientific opinion that their data supported both the Prolactin Hypothesis and Arena's NDA when making statements about lorcaserin during the class period." (ER 4.) Indeed, nowhere does Plaintiff identify a single document or witness even hinting that any Defendant viewed the Rat Study or the Prolactin Studies negatively or believed the results would interfere with or delay lorcaserin's approval. And nowhere does Plaintiff allege a single communication from the FDA expressing a concern about the final results of the Rat Study or the Prolactin

Studies until publication of the FDA's September 2010 briefing document (near the very end of the Class Period).

For these reasons and other reasons set forth below, Plaintiff has failed to satisfy the pleading requirements of Federal Rule of Civil Procedure ("Rule") 9(b) and the Private Securities Litigation Reform Act of 1995 ("PSLRA"). The district court's dismissal of the case should be affirmed.

STATEMENT OF JURISDICTION

Defendants agree with Plaintiff's statement of jurisdiction.

STATEMENT OF THE ISSUES

1. Did the district court properly conclude that Plaintiff failed to plead with particularity a strong, cogent, and compelling inference of scienter where Defendants reasonably believed lorcaserin's overall safety profile to be positive, favorable, and encouraging, and where Plaintiff alleges no facts showing that the FDA expressed its view of the final results of the Rat Study and the Prolactin Studies before September 14, 2010, when it publicly disclosed its briefing document for lorcaserin?

2. Did the district court properly conclude that further amendment of Plaintiff's Second Consolidated Amended Class Action Complaint ("SAC") would be futile?

STATEMENT OF THE CASE

I. Nature of the Case

This is a securities fraud class action brought under Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 ("Exchange Act") and U.S. Securities and Exchange Commission ("SEC") Rule 10b-5 promulgated thereunder. 15 U.S.C. §§ 78j(b), 78t(a); 17 C.F.R. § 240.10b-5. Plaintiff alleges Defendants made material omissions and misleading statements regarding lorcaserin in Arena press releases SEC filings, and other public statements. After initially seeking a class period spanning March 17, 2008 through January 27, 2011 (ER 109, SAC ¶1), Plaintiff's proposed Third Consolidated Amended Class Action Complaint ("TAC") sought damages for all persons who acquired Arena securities between May 11, 2009 and January 27, 2011 (the "Class Period") (ER 49, TAC ¶1).[2]

II. Statement of Facts

A. Defendants

Arena is a San Diego biopharmaceutical company "focused on discovering, developing and commercializing drugs for cardiovascular, central nervous system, inflammatory, and metabolic diseases." (ER 118, SAC ¶49.) Individual defendants Jack Lief, Robert Hoffman, Dominic Behan, William Shanahan, Jr.,

[2] To aid the Court, record cites to a specific paragraph of the SAC or TAC are indicated by a citation following the record cite and use the format "SAC ¶__" or "TAC ¶__."

and Christy Anderson are, or were during the Class Period, members of Arena's management team. (ER 118-19, SAC ¶¶51-55.)

B. The FDA Approval Process

Before a drug can be approved, the FDA requires both nonclinical (*i.e.*, animal and lab) studies and clinical trials in humans. (ER 120-21, SAC ¶62.) Nonclinical studies include long-term studies on animals of a drug's toxicity and carcinogenicity. (*Id.*) Clinical trials are designed to determine whether a drug is safe and effective in humans. (*Id.*) There are three phases of human clinical trials – Phases I, II, and III – and each phase involves increasingly larger patient pools. (*Id.*) Phase III trials are commonly referred to as "pivotal" because they provide most of the efficacy and safety information used by the FDA to evaluate a drug's overall risk/benefit profile. (ER 121, SAC ¶¶62-63; ER 200.)

The FDA approval process involves periodic communications between the FDA and a drug sponsor. *See, e.g.*, 21 C.F.R. §§ 312.32, 312.47, 314.102. For example, drug sponsors are required to notify the FDA of any potential safety issues. *See* 21 C.F.R. § 312.32. Recognizing the preliminary and uncertain nature of ongoing drug trials, however, the regulations expressly state:

> A safety report or other information submitted by a sponsor under this part . . . does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event.

21 C.F.R. § 312.32(e).

The FDA approval process is fraught with uncertainty. Only 10-16% of new drugs successfully pass through the NDA process. (SER 136 (*Martin v. Maxim Pharms., Inc.*, No-00-cv-2507, slip op. at 9 (S.D. Cal. Dec. 1, 2003) (citation omitted).) *See also* J.A. DiMasi, *Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs*, 87 Clinical Pharmacology & Therapeutics 272, 273-74 (2010); Dana Ziker, *Reviewing Informed Consent: Using Risk Perception in Clinical Trials*, 2003 Duke L. & Tech. Rev. 15 (2003). Consistent with this uncertainty, Arena repeatedly cautioned investors that "[o]btaining approval of an NDA can be a lengthy, expensive, and uncertain process," that "[r]egulatory approval of an NDA . . . is not guaranteed," that "FDA officials may not find the data from preclinical studies and clinical trials sufficient," that "[p]reclinical . . . results are frequently susceptible to varying interpretations that may delay, limit, or prevent regulatory approvals or commercialization," and that "failure can occur at any stage." (*See, e.g.*, ER 207-09, 224-28, 334-39, 356-59.)

C. Lorcaserin

Lorcaserin is intended for weight loss and maintenance of weight loss, representing the "first in a new class of selective serotonin 2C receptor agonists." (ER 120, SAC ¶61.) By stimulating the serotonin 2C receptor, patients taking

lorcaserin feel less hungry and eat less. (*Id.*) Since at least 2003, Arena worked with the FDA to establish efficacy and safety endpoints and to complete all testing necessary to submit the lorcaserin NDA. (ER 120-21, SAC ¶62.)

1. Arena's "Pivotal" Phase III Studies

Between September 2006 and February 2009, Arena conducted two "pivotal" Phase III clinical trials - known as "BLOOM" (Behavioral modification and Lorcaserin for Overweight and Obesity Management) and "BLOSSOM" (Behavioral modification and LOrcaserin Second Study for Obesity Management) – involving nearly 7,200 patients treated with lorcaserin for up to two years. (ER 121, SAC ¶¶63-64; ER 155, SAC ¶209).

Arena, like other pharmaceutical companies, disclosed data from these "pivotal" Phase III human trials. (*See, e.g.*, ER 231-92.) The efficacy and safety data generated by these human trials is typically the FDA's focus. (ER 121, SAC ¶62; ER 200.) Plaintiff does not (and cannot) dispute that Defendants accurately reported the BLOOM and BLOSSOM trial results, all of which met the FDA's efficacy and safety endpoints. (AOB at 9; ER 231-92.)[3]

[3] Plaintiff correctly notes that the FDA would carefully scrutinize any cardiovascular side effects due to the 1997 withdrawal of Fen-Phen from the market because of a heart-valve condition called "valvulopathy." (ER 121, SAC ¶65; ER 205.) Plaintiff also concedes that the trial results for BLOOM and BLOSSOM showed that lorcaserin "did not increase cardiovascular risk." (AOB at 19 (citing ER 250, 253, 276).)

2. The Rat Study

In 2006, Arena began the Rat Study, in which lorcaserin was administered to male and female rats at three dosage levels up to 82 times the human dose. (SER 171.) The female rats involved in the Rat Study historically had a high incidence of tumors (SER 177), rendering carcinogenicity studies difficult to interpret. *See* Robert A. Squire, *The Interpretation of Equivocal or Marginal Animal Carcinogenicity Tests*, 4 Cell Biology and Toxicology 371 (1989).[4]

Mid-way through the Rat Study, Arena received interim data indicating an increased rate of malignant and/or benign tumors. (ER 56, TAC ¶32.) Arena promptly submitted a safety report to the FDA on May 31, 2007. (ER 57, TAC ¶35) It is undisputed that the FDA, upon receiving the safety report, did not issue a "clinical hold" or otherwise halt Arena's ongoing Phase III trials involving nearly 7,200 patients. Rather, the FDA, pursuant to its own guidelines, requested bi-monthly updates to stay apprised of the ongoing Rat Study. (ER 59, TAC ¶47). *See* 21 C.F.R. § 312.32(c)(1)(v)(3) ("FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph.").

Arena fully complied with this request, submitting several bi-monthly updates between September 2007 and early 2009. (ER 60, TAC ¶50; SER 66-67.)

[4] Arena also conducted a 2-year carcinogenicity study in mice which revealed "no drug-related tumors." (SER 96.)

Aside from the April 2008 meeting between the FDA and Arena (described in detail below), there are no allegations that the FDA commented on these bi-monthly updates or otherwise communicated with Arena about these updates during this time. Arena also updated its investigator brochure and patient informed consent forms associated with the ongoing clinical trials (which was readily available on the Internet) to include the interim Rat Study results. (SER 66.)

Because of the ongoing nature of the Rat Study, the bi-monthly updates only included "initial reads" of data not yet reviewed by a team of outside pathologists. (ER 71, TAC ¶103.) When Arena submitted its final report to the FDA around February 2009, it included a peer-reviewed analysis by "three [non-Arena] veterinary pathologists" who concluded there were fewer malignant tumors than Arena initially reported to the FDA in the bi-monthly reports. (*Id.*; SER 178-79.) The final Rat Study results demonstrated that increases in cancerous tumors only occurred in rats given extremely high doses of lorcaserin far in excess of what the FDA has deemed to "reflect a relevant risk to humans." (ER 58, TAC ¶38; SER 232.) Further, as Arena was aware, many drugs have been approved by the FDA despite similar rat or mouse tumor findings. (SER 244-52.)

3. The Prolactin Studies

Defendants believed the mammary tumors in rats "were caused by increases [in] serum prolactin levels," a rat-specific mechanism that does not occur in

humans (the "Prolactin Mechanism"). (ER 58, TAC ¶42.) This belief was well-grounded in academic studies (*id.*), and the FDA has acknowledged that "[p]rolactin is known to be an intermediary hormone in development of mammary tumors in rodents" (SER 179). The FDA has also acknowledged that even a small prolactin increase in rats can cause tumors: "***[T]here is no threshold of exposure*** to prolactin identified in the literature beyond which results" in mammary tumors in rats. (SER 101 (emphasis added).)

To test the Prolactin Mechanism, Defendants conducted the six Prolactin Studies between July 3, 2007 and December 19, 2008. (ER 3; ER 59, TAC ¶44; SER 7-10.) After some early trial-and-error, the Prolactin Studies demonstrated 3.4-4.2-fold and 2-fold increases in prolactin levels in male and female rats, respectively. (SER 7-10, 194-195.) Plaintiff does not (and cannot) challenge the results of the Prolactin Studies.

4. The April 2008 FDA Meeting

On April 9, 2008, Arena met with the FDA to discuss the ongoing Rat Study and Prolactin Studies. (ER 61, TAC ¶55.) In advance of the meeting, Arena "provided a background package containing information not included in prior [bi-monthly] updates." (SER 67.) While Plaintiff offers no factual allegations about what the FDA said at this meeting, it is undisputed that the FDA did not halt Arena's Phase III clinical trials involving thousands of humans. To the contrary,

the FDA itself set out several reasons why it believed that the Phase III trials should continue:

> Our decision to allow the clinical program to proceed following our meeting with [Arena] was based on the following: 1) the updated informed consent forms included the nonclinical [Rat Study] findings; 2) we learned that drug exposure in rats was nearly twice as high as predicted, which increased the safety margin to clinical exposure; 3) preliminary data showed a modest increase in serum prolactin levels after a single dose in male rats; 4) we acknowledged that the interim tumor incidence would change (e.g., might be less worrisome) . . .; 5) only with continued clinical study was it possible to assess whether long-term dosing with lorcaserin increased serum prolactin levels in humans; 6) only with continuation of clinical dosing would we obtain an accurate assessment of lorcaserin's weight-loss efficacy and safety in diabetes; and 7) given that lorcaserin is non-genotoxic, we believed that cancer risk was low under the conditions of use in the ongoing clinical trials . . . .

(*Id.*; *see also* SER 97.) Aside from this meeting, where the FDA expressly permitted Arena's clinical trials involving nearly 7,200 humans to continue, Plaintiff does not provide any evidence that the FDA criticized the methodology of the Rat Study or the Prolactin Studies, or provided its opinion on the final results of those studies until the FDA disclosed its briefing document for lorcaserin in September 2010, more than 30 months after this April 2008 meeting. (ER 68, TAC ¶95.)

5. Arena's NDA Submission

After spending almost $1 billion and nearly ten years developing the drug, Arena submitted the lorcaserin NDA in December 2009. (ER 118, SAC ¶50; ER

126, SAC ¶99; ER 211; ER 229; ER 115, SAC ¶30.) The NDA, which includes over 4 million pages, reports on 18 Phase I, II, and III clinical trials involving over 8,500 human patients, as well as over 100 hundred nonclinical studies, including the final Rat Study and the Prolactin Studies. (ER 155, SAC ¶211; ER 231; ER 115, SAC ¶30.)

6. The FDA Advisory Committee Meeting and Complete Response Letter

The FDA scheduled a meeting of its Advisory Committee to consider whether to recommend lorcaserin for FDA approval for September 16, 2010. (ER 382.)[5] Before the meeting, Arena spent months preparing "thousands of slides" and retaining numerous independent experts, including Dr. Gary Williams, M.D., one of the nation's preeminent toxicologists (and an expert in carcinogenicity), "to address questions almost instantaneously" that the Advisory Committee might raise at the meeting. (ER 158, SAC ¶223; ER 396.)

On September 14, 2010, the FDA publicly disclosed on its website for the first time its own and Arena's briefing documents for lorcaserin, submitted in advance of the Advisory Committee meeting. (ER 116, SAC ¶36; ER 129, SAC ¶114; SER 160-99.) Both briefing documents addressed many topics related to

[5] The FDA may (but is not obligated to) to follow an advisory committee's recommendation. *See* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm (last visited October 23, 2014).

lorcaserin, including statistical interpretations of the Rat Study and the Prolactin Studies. (SER 171-84, 193-99.)

At the Advisory Committee meeting, a small portion of the presentations addressed the Rat Study and the Prolactin Studies. (SER 206-09, 211-15.) Under Arena's interpretation of those results: (1) lorcaserin was only associated with a statistically significant increase in malignant tumors in rats at the highest doses (up to 82 times human exposure) (SER 193-99, 206-09, 211), doses the FDA agrees do not "reflect a relevant risk to humans" (SER 232); and (2) the increase in mammary tumors resulted from the rat-specific Prolactin Mechanism (SER 193-99, 206-09).[6]

Under the FDA's preliminary interpretation, however, further independent pathologist review of the raw Rat Study data was needed. Pending this additional review, the FDA provisionally combined the benign and malignant mammary tumors, inflating the statistical tumor rate. (SER 176-77.) The FDA also observed that the Prolactin Studies did not show a "robust" and "sustained" prolactin increase. (SER 168, 179, 212.) The FDA unquestionably agreed with Arena, however, that there were no differences in "reports of cancer between lorcaserin and placebo-treated [human] subjects in the phase 3 clinical studies." (SER 165.)

[6] Regarding the increase in prolactin levels, Dr. Williams explained that a key focus is the timing of the prolactin increase relative to rat mammary development, not the amount of the increase. (SER 207-08.)

Acknowledging the difference of opinion between Arena and the FDA, Advisory Committee members expressed uncertainty about how to interpret the results from the Rat Study. (SER 217-18 ("I do feel a bit unqualified to make a judgment as to how we translate risk from rat study to humans . . . . I have absolutely no idea now [sic] to translate from animals to people.").) Ultimately, the Advisory Committee voted 9-5 against recommending approval of lorcaserin. (ER 130, SAC ¶118.) Of note, more than one-third of the Advisory Committee's experts believed lorcaserin should have been approved. (*Id.*)

In October 2010, the FDA issued a Complete Response Letter ("CRL") to Arena, requesting, among other things, an independent pathological review of the rat mammary tumor slides to demonstrate "that the Rat Study is not relevant to humans." (ER 131-32, SAC ¶¶120-22.)

7. The FDA's Subsequent Approval of Lorcaserin

In August 2011, after working with the FDA to select a group of independent pathologists to clarify the "diagnostic uncertainty in the classification of mammary masses in female rats" (ER 296), Arena announced the results of the re-adjudication of the mammary tumors from the Rat Study (SER 86-87). The results of this re-adjudication revealed – now for a second time – that Arena had overreported the incidence of malignant tumors. (SER 86-87.)

With the independently re-adjudicated data in hand, Arena resubmitted the lorcaserin NDA in December 2011. (SER 105.) The FDA thereafter released a second briefing document in advance of a May 2012 Advisory Committee meeting which found, among other things, that: (1) malignant and benign mammary rat tumors should be evaluated separately (SER 98-100); (2) there was at least a 24-fold safety margin for all cancerous mammary tumors in the Rat Study (*id.*), which the FDA interpreted as "of negligible risk to human subjects" (SER 101; SER 232); (3) "it is plausible that the minimal increase in exposure to prolactin induced by lorcaserin contributes to the emergenc[e] of [mammary tumors] in . . . rats" (SER 101); and (4) lorcaserin demonstrated virtually no risk in humans for brain tumors (SER 95). Thus, the Advisory Committee recommended lorcaserin for approval (SER 105), the FDA approved lorcaserin on June 27, 2012, and it is now on the market and being used to combat the obesity epidemic. (SER 112-13.)

III. Procedural History of This Litigation

A. The District Court Dismissed the CAC for Failure to Plead Scienter

Four days after the first Advisory Committee meeting in September 2010, Plaintiff filed his securities class action complaint naming Arena and others as Defendants. (Dkt. No. 1.) After the district court consolidated other related actions, Plaintiff was allowed to file a Consolidated Amended Class Action Complaint ("CAC") on November 1, 2011. (Dkt. No. 43.) Contrary to Plaintiff's

"theory of fraud" asserted in his Appeal (AOB at 30-31), Plaintiff made clear that the CAC did "not allege that the Defendants made false representations about lorcaserin's approval prospects or its 'future performance.' Rather the [CAC] allege[d] Defendants made materially false and misleading statements concerning lorcaserin's safety and the results of nonclinical studies." (SER 149.)[7]

On March 28, 2013, the district court dismissed the CAC for failing to plead scienter, without addressing Defendants' arguments that Plaintiff also failed to plead falsity. (ER 22-31.) The district court was "not persuaded that the [CAC] sufficiently ple[d] each Defendant knew or were [sic] deliberately reckless in not knowing about the Rat Study data or Arena's communications with the FDA about it." (ER 28.) The district court also held that:

> There are no factual allegations about how any Defendant interpreted or reacted to the Rat Study data or the FDA's request for bi-monthly updates on the data during the Class Period . . . [a]nd, as pled, Defendants only learned of the FDA's opinion on the Rat Study data two days before the September 16, 2010 Advisory Committee meeting. Further, while the FDA's March 2008 request for bi-monthly updates was unusual, there are no facts pled to infer that each Defendant should have known . . . that the updates suggested a risk to humans (or even to the NDA). In sum, the facts alleged do not demonstrate that there was a red flag that Defendants knew or deliberately disregarded when they chose to speak about lorcaserin's safety.

[7] Plaintiff now concedes that Defendants did not mislead the market about the objective safety of lorcaserin. (AOB at 41.)

(ER 29.) As such, the district court found it "more plausible" that Defendants "believed the [Rat Study] results to be [favorable] with regard to what the study was designed to test. Namely, the potential risk that drug candidates may be toxic or cause cancer ***in humans***." (ER 30 (citations omitted) (emphasis in original).) The district court concluded its scienter analysis by stating: "There is nothing to suggest that it would have been unreasonable for [Defendants] to interpret the Rat Study results as favorably contributing to lorcaserin's safety profile for humans and [the] NDA." (*Id.*)

B. The District Court Dismissed the SAC for Failure to Plead Scienter

On May 15, 2013, Plaintiff filed his SAC (his third complaint). (ER 106-173.) The SAC amended the CAC by: (1) including six purported confidential witnesses ("CWs"), none of whom are alleged to have had any discussions with Defendants or the FDA regarding the potential human risk created by the Rat Study results and four of whom were not even involved in the lorcaserin program; (2) asserting that Arena met with the FDA in April 2008, without offering relevant details about what was actually said at the meeting; (3) alleging that, in early 2009, Arena enacted budget cuts and employee layoffs in the face of the greatest economic downturn since the Great Depression; and (4) alleging that, as part of the review process, the FDA inspected a facility associated with Arena's nonclinical

studies and issued a form describing the visit, without providing a single detail about the inspection itself or the contents of the form given to Arena. (*Id.*)

Following oral argument on November 4, 2013 (Dkt. No. 82), the district court dismissed the SAC, again on the ground that Plaintiff failed to raise a strong inference of scienter. (ER 8-20.)[8] The district court's analysis focused on two statements made by Defendants in March 2009 and September 2009.[9] (ER 12-19.) The district court noted that "[p]rior thereto, the allegations of this case fail to show that Defendants had a duty to disclose the interim information about the Rat Study or their dialogue with the FDA about it or that they made deliberately reckless misleading statements about the Rat Study." (ER 12-13.)

Regarding Defendant Lief's March 12, 2009 conference call statement that his confidence in lorcaserin was based, in part, on "the preclinical studies that was [sic] done, all the animal studies that have been completed" (ER 14 (citing ER 140, SAC ¶144)), the district court concluded that "the record supports the more plausible inference that Defendants, when speaking about lorcaserin's overall

---

[8] The district court properly dismissed the claims against Defendant Hoffman, Arena's chief financial officer, with prejudice because the SAC failed to "sufficiently plead his knowledge of the Rat Study data." (ER 12 n.5.)

[9] Plaintiff suggests that Defendants improperly "steered the hearing toward the scientific implications" of the Rat Study and the Prolactin Studies. (AOB at 25-26.) Not so. In fact, in each of its orders, the district court was keenly focused on whether Defendants' favorable view of the Rat Study was reasonable in assessing scienter. (ER 4-6, 15, 18-19, 30.) As such, it was necessary to discuss the results of the Rat Study and the Prolactin Studies in assessing scienter.

safety profile and potential, reasonably believed it to be positive, favorable, or encouraging." (ER 15.) The district court also found that FDA's approval of lorcaserin "further supports an absence of scienter." (*Id.*)

Regarding Defendant Anderson's September 19, 2009 statement that "[w]e have favorable results on everything that we've compiled so far" (*id.*), the district court held that to plead scienter Plaintiff had to "show facts from the current record supporting a conclusion that it was more than just a difference of scientific opinion that led to the FDA's conclusion that Defendants failed to demonstrate that the Rat Study was irrelevant to humans." (ER 16.) In addressing the Prolactin Studies, the district court held that the SAC did not "plead what Defendants should have understood to be the threshold showing to satisfy the FDA's request that Arena substantiate" its belief that the mammary tumors in the Rat Study were due to the rat-specific Prolactin Mechanism. (ER 18.)[10]

In its order, the district court instructed Plaintiff to file a motion to amend the SAC and to attach the proposed TAC (his fourth complaint). (ER 16.)[11]

---

[10] The district court held that Plaintiff's allegations regarding "the FDA inspection, confidential witnesses . . . and budget cuts [ ] do not meaningfully contribute to a strong inference of scienter with respect to the overall safety statements." (ER 15 n.8.)

[11] The district court also instructed Plaintiff to "dramatically limit" the TAC "to the alleged materially false and misleading statements that support Plaintiff's theory that Defendants knew they had to and failed to substantiate their hypothesis that the tumors found in the Rat Study were due to a rat-specific mechanism . . . ." (ER 16-17 n.9.)

C. The District Court Denied Plaintiff's Motion to Amend the SAC

On November 27, 2013, Plaintiff filed his motion to amend the SAC and attached his proposed TAC. (ER 43-95.)[12] On March 20, 2014, the district court denied Plaintiff's motion to amend. (ER 1-7.) In its order, the district court carefully detailed the TAC's incurable defects regarding the Rat Study and the Prolactin Studies (which the district court referred to as the "mechanistic studies"):

- "[T]here are no facts before the Court suggesting Defendants knew they had to show that lorcaserin caused a sustained and robust increase in prolactin to obtain FDA approval." (ER 5.) (As noted above, it is the timing of any prolactin increase, not the amount, that matters (*see* SER 207-08).)
- "[T]here are no facts pled [ ] suggesting that the FDA commented about the mechanistic study data or results prior to its Advisory Committee's September 2010 public meeting." (ER 5.)
- "There are no facts pled showing Defendants presented the FDA with an unreasonable scientific interpretation of the mechanistic studies." (*Id.*)
- "There are also no facts pled suggesting Defendants must have believed the mechanistic studies failed to support the Prolactin Hypothesis." (*Id.*)
- "Plaintiff has not come forward with alleged facts that give rise to an inference that Defendants made statements knowing or turning a blind-eye to facts showing the NDA for lorcaserin lacked, or that the FDA would reject, the scientific data that was specifically requested by the FDA." (ER 6-7.)

The district court held that without these facts, any amendment would be futile because the "more cogent and compelling inference is that Defendants had a

[12] While the TAC narrows the Class Period, it remains strikingly long at 90 weeks, from May 11, 2009 through January 27, 2011. (ER 49, TAC ¶1.)

legitimate scientific reason to believe that the final Rat Study data, including the mechanistic studies' data, was sufficient to address the FDA's concerns." (ER 7.)

The district court thereafter entered its final judgment (ER 37-38), and on April 18, 2014, Plaintiff filed his notice of appeal. (ER 32-36.)

SUMMARY OF ARGUMENT

The district court properly dismissed this case because Plaintiff did not and cannot plead a strong, cogent, and compelling inference of scienter as required under Section 10(b) of the Exchange Act. Plaintiff argues that the "district court misapplied the scienter requirement because it erroneously believed that Defendants' scienter turned on subjective beliefs about lorcaserin's safety." (AOB at 32.) But even if, as Plaintiff contends, "scienter turns on Defendants' objective awareness of the negative results of the Rat Study and the FDA's expressed concerns about those results" (*id.*), Plaintiff's "theory of fraud" rests on two faulty assumptions that are fatal to his scienter allegations.

The first faulty assumption is that the final results from the Rat Study and the Prolactin Studies were "negative." (*Id.*) In fact, the overwhelming evidence is that by early February 2009 (3 months before the start of the TAC's Class Period and 9 months before Arena submitted the lorcaserin NDA), the final Rat Study showed there was no statistically significant increase in malignant tumors in "groups that would be clinically relevant to an assessment of human risk or use."

(ER15.) Further, by this time Arena had completed the Prolactin Studies, which showed prolactin increases in both male and female rats, supporting Defendants' longstanding view that the mammary tumors (which unambiguously did not occur in mice, monkeys, or humans) were caused by the rat-specific Prolactin Mechanism. Tellingly, Plaintiff omits from his Appeal and Excerpts of Record all reference to the documents that detail these results, even though Plaintiff himself put many of them before the district court.

The second faulty assumption is that the FDA "repeatedly expressed concerns" about the final results of the Rat Study and the Prolactin Studies. (AOB at 31.) However, nowhere in the Appeal or in any of the four complaints does Plaintiff identify a single FDA communication, email or memorandum to Arena indicating its position on the Rat Study or the Prolactin Studies before releasing its September 2010 briefing document. Moreover, at the April 2008 meeting between Arena and the FDA – held 10 months before Arena completed those studies and 30 months before it submitted the NDA – the FDA expressly allowed the ongoing Phase III trials involving nearly 7,200 humans to continue. The FDA would never have allowed this if it believed the Rat Study showed an increased risk that lorcaserin caused cancer in humans. The FDA also expressly noted at that meeting that the Prolactin Mechanism was a "plausible" mechanism of action and that the final results of the Rat Study could change. (SER 67.) Given that the FDA now

agrees with Arena's interpretation of the Rat Study and the Prolactin Studies and has approved lorcaserin for public use, at most Plaintiff has alleged a temporary disagreement between Arena and the FDA over these studies (which, again, Defendants did not learn of until September 2010), not scienter.

Notably, the Appeal abandons nearly all statements attributed to six purported CWs, none of which have any information bearing on the results of the final Rat Study or the Prolactin Studies. This omission inherently recognizes that those witnesses did not support Plaintiff's allegations of fraud. Further, Plaintiff's remaining scienter allegations – Arena's raising of capital, Arena's reduction in operating expenses during the greatest economic downturn since the Great Depression, and an FDA inspection of an Arena-related facility – similarly do not raise the slightest inference of scienter, especially in light of the fact that the Defendants did not sell a single share of Arena stock during the Class Period and instead increased their personal holdings by 25%.

By far, the more compelling inference is that Defendants genuinely believed their disclosures and warnings about lorcaserin's prospects for FDA approval. There is no evidence of any intent to defraud anyone.

Plaintiff's claim for violation of Section 20(a) of the Exchange Act is deficient because the claim requires a primary violation under Section 10(b), and none has been pled.

Finally, the district court afforded Plaintiff numerous opportunities to address the deficiencies identified, and he failed to do so. As such, leave to amend was properly denied.

The district court's decision should be affirmed.

ARGUMENT

I. STANDARD OF REVIEW

This Court reviews a dismissal under Rule 12(b)(6) *de novo*. *In re Rigel Pharms., Inc. Sec. Litig.*, 697 F.3d 869, 875 (9th Cir. 2012) (citation omitted). The Court may affirm a dismissal "on any proper ground, even if the district court did not reach the issue or relied on different grounds or reasoning." *Steckman v. Hart Brewing Co.*, 143 F.3d 1293, 1295 (9th Cir. 1998) (citation omitted).

II. Legal Standards Governing Defendants' Motion to Dismiss

A. Federal Rule of Civil Procedure 12(b)(6)

The Court must dismiss a complaint under Rule 12(b)(6) where it fails to allege facts sufficient to "plausibly" state a claim for relief. *Bell Atl. Corp. v. Twombly*, 127 S. Ct. 1955, 1965-66 (2007). While a court must accept all well-pleaded factual allegations as true, it need not consider "mere conclusory statements." *Ashcroft v. Iqbal*, 129 S. Ct. 1937, 1949 (2009). Nor should it accept legal or factual allegations based on unwarranted deductions, unreasonable inferences, or allegations that contradict matters properly subject to judicial notice

or exhibits incorporated by reference. *See Clegg v. Cult Awareness Network*, 18 F.3d 752, 755 (9th Cir. 1994).

B. Section 10(b) of the Securities Exchange Act of 1934 and Rule 10b-5

To state a claim under Section 10(b) of the Exchange Act and SEC Rule 10b-5 promulgated thereunder, a plaintiff must allege: (1) a misstatement or omission; (2) of material fact; (3) made with scienter; (4) on which he relied; and (5) proximately causing injury. *See DSAM Global Value Fund v. Altris Software, Inc.*, 288 F.3d 385, 388 (9th Cir. 2002) (citation omitted). Because fraud allegations harm livelihoods and reputations, Rule 9(b) requires that "a party must state with particularity the circumstances constituting fraud or mistake." Fed. R. Civ. P. 9(b).

The PSLRA significantly heightens the "particularity" requirement by imposing stringent requirements for pleading falsity and scienter in private securities litigation. 15 U.S.C. § 78u-4(b)(1)-(3). With regard to falsity, a plaintiff must identify specifically each statement alleged to have been false or misleading and to provide the reasons why the statement was false or misleading ***when made***. *Rigel*, 697 F.3d at 877. Further, if a plaintiff claims a defendant omitted a material fact, it must show that the defendant had a duty to disclose the omitted information. *See Basic v. Levinson*, 108 S. Ct. 978, 987 (1988). Rule 10b-5 does not require the disclosure of all material information. *See Matrixx Initiatives, Inc.*

v. Siracusano, 131 S. Ct. 1309, 1321-22 (2011). Rather, "[t]o be actionable under the securities laws, an omission . . . must affirmatively create an impression of a state of affairs that differs in a material way from the one that actually exists." *Brody v. Transitional Hosps. Corp.*, 280 F.3d 997, 1006 (9th Cir. 2002) (citation omitted). If a statement is incomplete but not false or misleading, it is not actionable under the securities laws. *Id.*[13]

To plead scienter, a complaint must "state with particularity facts giving rise to a strong inference" that a defendant was deliberately reckless or engaged in conscious misconduct. 15 U.S.C. § 78u-4(b)(2). To plead deliberate recklessness, "the plaintiff must plead a highly unreasonable omission, involving not merely simple, or even inexcusable negligence, but an ***extreme departure*** from the standards of ordinary care . . . ." *Zucco Partners, LLC v. Digimarc Corp.*, 552 F.3d 981, 991 (9th Cir. 2009) (citation and internal quotation marks omitted; emphasis added).[14] Moreover, a complaint will survive a motion to dismiss only "if a reasonable person would deem the inference of scienter cogent and at least as compelling as any opposing inference one could draw from the facts alleged." *Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 127 S. Ct. 2499, 2510 (2007). A court

[13] Because Plaintiff's Appeal only addresses scienter, Defendants' Answering Brief focuses on that element of a Section 10(b) claim as well. However, given the *de novo* nature of the Court's review, Defendants include the legal standard for pleading falsity and argue, in the alternative, that Plaintiff cannot show that any statement at issue in the SAC or TAC was misleading *when made*.

[14] Plaintiff agrees that this is the correct standard in assessing scienter. (SER 17.)

must take into account plausible nonculpable explanations for the defendant's conduct, and "omissions and ambiguities count against inferring scienter." *Id.* at 2511. In making this analysis, "courts must consider . . . documents incorporated into the complaint by reference, and matters of which a court may take judicial notice." *Id.* at 2509.

III. Plaintiff Fails to Raise a Strong Inference of Scienter

In assessing scienter, the district court correctly noted that "the hurdle" for Plaintiff to overcome "was to show that Defendants knew or were deliberately reckless in making certain statements about Arena's drug lorcaserin because the statements were seriously undermined by scientific data concerning Arena's Rat Study." (ER 3.) In short, Plaintiff "needed to show that this case is about more than a difference of scientific opinion between Defendants and the FDA on the relevant data." (*Id.*) In four tries, he was not able to do so, and the district court properly dismissed the case.

A. Defendants Were Reasonable in Viewing the Results of the Rat Study and Prolactin Studies as Favorable

The crux of Plaintiff's appeal rests on his conclusory contention that the results of the Rat Study and the Prolactin Studies were "negative." (AOB at 32-33.) This contention, however, is belied by the allegations on the face of Plaintiff's complaints and by the record before the Court. As the TAC alleges, "in order to demonstrate that the tumors observed in the Rat Study were irrelevant to human

risk, [Arena] would have to demonstrate ***either*** a safety margin (*i.e.*, a showing that the drug exposure level needed to cause the tumor in rodents is substantially greater than human exposure at recommended dose), ***or*** a rodent-specific mechanism." (ER 57, TAC ¶37 (emphasis added).) The most "cogent" and "compelling" inference in the record is that, by the start of the Class Period, Defendants believed they had established both a safety margin and a rat-specific mechanism.

First, there is no dispute that "[t]he final Rat Study showed there was no significant cancer in any of the groups that would be clinically relevant to an assessment of human risk or use." (ER 15.) Indeed, a statistically significant increase in malignant tumors at issue only occurred at doses 82 and 55 times the human lorcaserin dose in female and male rats, respectively. (SER 171.) The FDA expressly states that "if a drug is only positive in rodents at doses above those producing a 25-fold exposure over exposure in humans, such a finding ***would not be considered likely to reflect a relevant risk to humans***." (SER 232 (emphasis added); ER 58, TAC ¶38.) Therefore, by the start of the Class Period, by far the most plausible inference is that Defendants believed they had demonstrated a more than sufficient safety margin for the malignant tumors in the Rat Study, negating scienter.

Second, with respect to the mammary tumors (both benign and malignant) in the Rat Study, Plaintiff concedes that Defendants completed the Prolactin Studies by December 2008. (ER 59, TAC ¶44; ER 62, TAC ¶65.) As noted above, when Arena completed this series of six studies, they unequivocally showed a 3.4-4.2-fold increase in prolactin in male rats and a 2-fold increase in prolactin in female rats. (SER 7-10, 194-95.)[15] Thus, the Prolactin Studies supported Arena's view that the Prolactin Mechanism caused the mammary tumors in rats. Considering the FDA stated that Defendants' view was "plausible" even before Arena completed these studies, (SER 67, 101), these findings also negate any inference of scienter.

Importantly, Plaintiff does not contend that Defendants miscalculated, manipulated, or improperly conducted these studies in any way. Moreover,

[15] Showing disregard for the scientific process, Plaintiff complains that the first of the Prolactin Studies did not support the Prolactin Mechanism. However, as clearly shown in the record, the six studies reflected an ongoing trial-and-error process to accurately record increases in prolactin levels. (*Id.*) Further, in claiming that the "Follow Up Tests . . . disclosed that lorcaserin had no effect on prolactin in female rats and in fact reduced prolactin in males by 50 percent" (AOB at 11-12 (citing ER 63, TAC ¶ 67)), Plaintiff has confused the results of the Prolactin Studies – which were specifically designed to measure prolactin increases – with the results of a single, exploratory "TK" arm of the Rat Study. (SER 171.) The TK arm was a preliminary part of Arena's investigation of prolactin, whereby a small number of rats were given lorcaserin for an additional 2 to 4 weeks after one year of original dosing to monitor "serum analysis of prolactin" and "immunohistochemical staining of prolactin." (*Id.*) In any event, even the TK arm of the Rat Study showed "a slight increase in prolactin immunoreactivity" in female rats. (SER 181.) In other words, even the data underlying Plaintiff's incorrect use of the TK arm of the Rat Study supported increased prolactin, not to mention the Prolactin Studies that Plaintiff neither addresses in his Appeal nor includes in his Excerpts of Record.

Plaintiff does not make a single particularized factual allegation that Defendants, much less each of them, did not believe that they had demonstrated both a safety margin and a rat-specific mechanism for the Rat Study results. *See In re AstraZeneca Sec. Litig.*, 559 F. Supp. 2d 453, 471 (S.D.N.Y. 2008) ("[T]here is nothing what[so]ever to indicate that the statements made did not reflect the honest belief of the authors . . . [or] that there was a consensus of management that the risks of [the drug] made the drug unlikely to be approved."). As to the clinical trials involving over 8,500 humans, Plaintiff has never alleged the slightest error or misrepresentation of data.

The authorities cited in Plaintiff's Appeal are inapposite. For example, in *Warshaw v. Xoma Corp.*, plaintiffs alleged particularized facts that defendants knew their Phase III trial results had a "glaring safety issue" and "actually increase[d] mortality in a large percentage of . . . patients" even though they publicly disclosed that "everything [was] going fine." 74 F.3d 955, 957 (9th Cir. 1996). Similarly, in *In re Connetics Corp. Sec. Litig.*, No. C 07-02940 SI, 2008 WL 3842938, at *1 (N.D. Cal. Aug. 14, 2008), plaintiff pled detailed facts that defendants' own panel of experts concluded that no drug with similar problems to their drug candidate had *ever* been approved by the FDA. In stark contrast here, numerous drugs with prolactin increases and similar tumor findings in rats had been approved prior to the start of the Class Period. (SER 179, 244-52.) *See*

Rigel, 697 F.3d at 883 (no scienter where defendants were aware of drugs that had been approved by the FDA with similar trial results). Further, it is undisputed that one of the nation's preeminent experts in rodent carcinogenicity agreed with Defendants' view that "lorcaserin does not pose a cancer risk to humans . . . ." (SER 209.)[16]

Finally, the Rat Study and the Prolactin Studies must be considered along with the dozens of other preclinical mouse and monkey studies and the clinical trials involving over 8,500 human patients, none showing the slightest increase in tumors or prolactin. (SER 165, 168-70, 208-09.) As such, the district court correctly held that the more "cogent" and "compelling" inference is that the Defendants "had a legitimate scientific reason to believe that the final Rat Study data, including the [Prolactin Studies], was sufficient to address the FDA's safety concerns." (ER 7.)

B. The FDA Did Not Disclose Its Interpretation of the Rat Study and Prolactin Studies Until It Published the September 2010 Briefing Document

Plaintiff contends that Defendants committed fraud because the FDA "repeatedly expressed concerns" about the Rat Study and the Prolactin Studies.

[16] *In re Immune Response Sec. Litig.*, 375 F. Supp. 2d 983 (S.D. Cal. 2005), is of no help to Plaintiff. In that case, the plaintiff alleged "corroborating details of [ ] internal reports" regarding the company's Phase III clinical trial that "proved that [the drug] had no effect on secondary markers, while Defendants repeatedly assured the public otherwise." *Id.* at 1019-20. No such factual allegations have been made here.

(*See, e.g.*, AOB at 31.) This is completely unsupported by the record. As the district court held, "there are no facts . . . suggesting that the FDA commented about the" final results of the Rat Study or the Prolactin Studies "prior to [the] Advisory Committee's September 2010 public meeting . . . ." (ER 5.)

The extent of the FDA's communications with Arena regarding the Rat Study and the Prolactin Studies in the record can be broken into three distinct time periods, each of which is discussed below. Taken together, this evidence powerfully illustrates the absence of any contemporaneous "red flags" from the FDA during the Class Period from which this Court could infer scienter.

Pre-April 2008 Communications with the FDA: At all times before April 2008, the FDA viewed Arena's position that the mammary tumors in the Rat Study were caused by the Prolactin Mechanism as "reasonable" and "plausible." (SER 31, 66, 101.) Moreover, while the FDA requested in the fall of 2007 that Arena "substantiate[ ]" its view "with data on prolactin levels" (SER 66), nowhere is it alleged that the FDA required Arena to meet some "generally accepted standard" regarding the prolactin increase. (ER 18.) To the contrary, the FDA itself stated that "there is no threshold of exposure to prolactin identified in the literature beyond which results" in mammary tumors in rats (SER 101), and that even a "modest increase in . . . prolactin . . . len[t] support to the" Prolactin

Mechanism (SER 67). This is exactly what Dr. Williams explained at the September 2010 Advisory Committee meeting without rebuttal. (SER 207-08.)

Further, in September 2007 the FDA requested that Arena send bi-monthly updates regarding the interim results of the Rat Study, and Arena did so. (ER 59-60, TAC ¶¶47, 50.) At most, this shows the "give and take" between the FDA and a pharmaceutical company that "is the essence of the . . . license application process," not scienter. *In re MedImmune, Inc. Sec. Litig.*, 873 F. Supp. 953, 966 (D. Md. 1995); *see also id.* ("Mere questioning by the FDA imposed no duty upon Defendants . . . to report to the public the FDA staffers' questions as they arose."). (*See also* ER 12 ("[T]he allegations of this case fail to show that Defendants had a duty to disclose interim information about the Rat Study or their dialogue with the FDA about it . . . .").)

April 2008 FDA Meeting with Arena: Plaintiff concedes that at the April 2008 FDA meeting with Arena, the FDA did not halt or delay the ongoing Phase III trials (ER 125, SAC ¶¶87-88), even though Plaintiff claims the FDA "continued to believe that the Rat Study's adverse results were relevant to humans" (ER 61, TAC ¶56). But, it is not disputed that FDA allowed lorcaserin to be administered to nearly 7,200 humans for over two years thereafter, strongly undermining any inference that the FDA believed the Rat Study posed a risk to humans (or any inference of scienter). (ER 125, SAC ¶¶87-88)

In fact, the FDA noted that: "1) the rat study was not yet complete and tumor incidence could change further, 2) the reclassified interim tumor data suggested that malignancies were confined to the highest dose of lorcaserin, [and] 3) preliminary data in male rats suggested that lorcaserin may modestly increase prolactin . . . ." (SER 97; *see also* SER 67 (citing additional reasons).)[17] The FDA's reasons for permitting the Phase III trials to continue in April 2008 are precisely the same reasons why Arena believed it had demonstrated both a safety margin and a rat-specific mechanism upon completion of the Rat Study and the Prolactin Studies. In any event, in light of the FDA allowing the Phase III trials to continue (and its approval of the drug), there simply is no basis to infer scienter because of a single FDA meeting occurring more than a year before the Class Period began and a full 18 months before Arena submitted the lorcaserin NDA. (*See* SER 138 (*Maxim*, slip op. at 11 (rejecting inference of scienter based on "what [defendants were] allegedly told two years earlier by the FDA")).)

[17] The FDA also noted that "[i]nvestigator brochure and patient informed consent documents were updated to include the tumor findings in rats." (SER 97.) The patient consent form was publicly available during the Class Period. *See, e.g.*, http://www.weightcenter.org/images/BLOSSOM-ICF-AbbrText-031308.pdf (last visited Sept. 24, 2014). *See Berry v. Valence Tech., Inc.*, 175 F.3d 699, 703 n.4 (9th Cir. 1999) ("A reasonable investor is presumed to have information available in the public domain, and therefore . . . is imputed with constructive knowledge of this information.") (citation omitted). If Defendants were trying to hide the results of the Rat Study, why did they put it in the public domain for all to see?

Post-April 2008 Communications with the FDA: After the April 2008 FDA meeting, there is not a scrap of evidence in the SAC, TAC, or elsewhere that the FDA expressed any concern to Arena about the design or results of the Rat Study or the Prolactin Studies until September 2010, when it disclosed its briefing document.[18] There are no emails, reports, or other communications from the FDA to Arena regarding the Rat Study after April 2008. There are no documents, confidential witness statements, or FDA meeting minutes reflecting communications from the FDA commenting on Arena's draft of the final Rat Study and Prolactin Studies, which Arena sent the FDA on February 3, 2009. (ER 62, TAC ¶65.) Even the FDA's own October 2010 internal "Chronology of Events Related to Nonclinical Assessments" – which Plaintiff himself put before the district court – reflects no FDA communications in the 30-month span between the April 2008 FDA meeting and the September 2010 Advisory Committee meeting. (SER 65-67.) Plaintiff claims Defendants committed fraud because they withheld "the very existence of their scientific disagreement with the FDA." (AOB at 42 (emphasis removed).) *But, until September 2010 Arena did not know any such*

[18] The TAC refers to a "mid-2008" meeting with the FDA "at which one of two topics on the agenda was the ongoing Rat Study." (ER 62, TAC ¶61.) Plaintiff offers no details whatsoever of this meeting. Similarly, in alleging an August 9, 2009 pre-NDA meeting with the FDA to discuss lorcaserin, there is absolutely no evidence that the FDA offered its view of the Rat Study or the Prolactin Studies at this meeting. (ER 64, TAC ¶74.) Indeed, the TAC states that the FDA "told Defendants that [mammary tumors] . . . should be analyzed in the NDA." (*Id.*) Defendants did so and, as shown above, their analysis was highly favorable.

scientific disagreement existed. Further, this scientific disagreement was only temporary and the FDA approved lorcaserin with no further issues relating to the Rat Study.

The absence of contemporaneous FDA communications about the Rat Study and the Prolactin Studies during the Class Period fatally undercuts Plaintiff's authorities. For example, in *In re CV Therapeutics, Inc. Sec. Litig.*, the district court found that plaintiff established scienter because after defendants submitted their NDA but months before the FDA's decision, the company received a "Discipline Review Letter" containing "four pages of very specific concerns that the FDA had regarding [the drug]." No. C 03-03709 SI, 2004 WL 1753251, at *5-7 & n.5 (N.D. Cal. Aug. 5, 2004). Ignoring this letter, the defendant falsely stated to the public that it had received "NOTHING" relevant from the FDA. *Id.* at *7 (emphasis in original). *Connetics* also does not help Plaintiff because in that case the plaintiff alleged detailed facts of an FDA conference call where the FDA informed the company that the results of a transgenic mouse study was a "serious issue" and that "it did not look good for obtaining approval," the same thing the company had been told by its own panel of experts. 2008 WL 3842938, at *1. Finally, in *In re Sepracor, Inc. Sec. Litig.*, scienter was established because the defendants did not disclose side effects for which the FDA had clearly established

a "zero tolerance" FDA policy.[19] 308 F. Supp. 2d 20, 25, 30-31 (D. Mass. 2004).[20] In contrast here and as noted above, the FDA has approved numerous drugs with similar rat tumor findings. (SER 244-52.) *See Rigel*, 697 F.3d at 883; *see also In re Vertex Pharms, Inc., Sec. Litig.*, 357 F. Supp. 2d 343, 352 (D. Mass. 2005) (no scienter for failure to disclose animal toxicity because "many drugs currently on the market are toxic depending on dosage levels and concentrations"). Therefore, Plaintiff's own authorities negate any inference of scienter.

C. Arena's and the FDA's Differing Initial Interpretations of the Rat Study and Prolactin Studies Do Not Show Scienter

Given Defendants' "reasonable" view of the Rat Study and Prolactin Studies as "favorable" and the absence of "facts pled that suggest[ ] that the FDA commented about the [studies] prior to its Advisory Committee's September 2010 public meeting," the district court properly held that Plaintiff had not adequately alleged scienter because "the more plausible inference is that Defendants had a

[19] Importantly, and contrary to Plaintiff's argument that affirming the district court's decision would establish a threshold for pleading scienter that requires "'smoking gun' evidence" (AOB at 55), *Sepracor* specifically noted that "[t]he Complaints do not present a 'smoking gun' in the form of internal [company] memoranda or evidence of insider trading." *Id.* at 31. Indeed, that the complaints in *Sepracor*, *Warshaw*, *Connetics*, *CV Therapeutics*, and *Immune Response* all survived motions to dismiss based on circumstantial evidence demonstrates the fallacy of Plaintiff's argument.

[20] The SAC and TAC allege that the FDA's key area of focus regarding lorcaserin's safety was heart-valve disease side effects – *i.e.,* valvulopathy. (ER 55, TAC ¶¶26-28; ER 121-22, SAC ¶¶65-68.) As noted above, Plaintiff concedes that lorcaserin "did not increase cardiovascular risk." (AOB at 9 (citing ER 250, 253, 276).)

legitimate and unanticipated scientific disagreement with the FDA." (ER 5-6.) Indeed, as the Ninth Circuit has recognized, "[a]lthough Plaintiffs may have established a legitimate difference in opinion as to the proper statistical analysis, they have hardly stated a securities fraud claim." *Rigel*, 697 F.3d at 879 (quoting *DeMarco v. DepoTech Corp.*, 149 F. Supp. 2d 1212, 1225 (S.D. Cal. 2001)); *see also AstraZeneca*, 559 F. Supp. 2d at 471. Moreover, as shown above, any such disagreement was only temporary and the FDA then agreed with Defendants' interpretation of the data.

Indeed, under Defendants' interpretation, Arena had established *both* a "safety margin" and a "rodent-specific mechanism" for the tumors observed in the Rat Study. (ER 57, TAC ¶37; SER 193-99, 206-07.)

At the September 2010 Advisory Committee meeting, the FDA initially took a different position, temporarily combining the benign and malignant mammary tumors pending an independent re-evaluation of the tumor slides. (SER 176-78; *see also* SER 236.)[21] The FDA also viewed the Prolactin Studies "as ***supporting***

[21] Drug sponsors (including Arena) and the FDA may sometimes combine cancer and non-cancer data for certain purposes (*e.g.*, trend analysis (SER 196)). However, at no point did Arena perform such a combination of data because of "diagnostic uncertainty" in interpreting the rat tissue slides (the very first reason given by the FDA for this combination of data) (SER 63-64). There are no facts alleged to indicate that Arena could have foreseen that the FDA would temporarily combine the data pending review by independent pathologists. (*See* SER 209 (Dr. Williams noting that benign and malignant mammary tumors are different types of neoplasms and that he could find "no support for combining these different tumor

Defendants' hypothesis," but "opined that it was weak support for the hypothesis" and not sufficiently "robust" or "substantial." (ER 6; SER 168, 179, 212-13.) Thus, at most Plaintiff has established a temporary disagreement between Arena and the FDA, but not scienter. *See MedImmune*, 873 F. Supp. at 966 ("Medical researchers may well differ over . . . the interpretation of test results. Although the [FDA] may have disagreed, there is nothing to suggest that Defendants could not reasonably have entertained the opinion [that their results were favorable] . . . .").

While Plaintiff tries to downplay *AstraZeneca*, the district court correctly found the case on-point in rejecting Plaintiff's scienter allegations. (ER 6-7.) In *AstraZeneca*, like here, plaintiff alleged that an FDA briefing document released two days before an FDA advisory committee meeting revealed "troubling, previously undisclosed data" regarding a drug's safety results. 559 F. Supp. 2d at 462. Relying on this negative safety data, the advisory committee recommended against approval of the drug (*id.* at 463), and plaintiff filed suit based on defendants' failure to disclose the safety data (*id.* at 457). After reviewing both the FDA's and AstraZeneca's briefing documents and "concluding that both present the honest analysis and conclusions of their authors" (*id.* at 471), the court held

---

types").) And, after re-adjudication, it turned out Arena had overreported the caner rate. Does a company and its officers acting with scienter overreport the amount of cancer in a study?

that plaintiff did not establish scienter even though defendants were in possession of "previously undisclosed data":

> As of the time when the FDA Advisory Committee met . . . AstraZeneca had its side of the case and the FDA staff had its side. The FDA staff view prevailed before the Advisory Committee. This does not mean that AstraZeneca was not conscientious in advocating the drug Exanta before the FDA, nor does it mean that the information issued publicly over the course of more than year was dishonest or recklessly disseminated.

Id. at 462, 471.[22]

Here, the lack of scienter is even more apparent because it is undisputed that after the independent pathologists re-adjudicated the rat tissue slides, the FDA evaluated the benign and malignant tumors separately, agreed with Arena that this data was not relevant to humans, and approved lorcaserin. (SER 98-101, 112.) The FDA also accepted Arena's interpretation that even "the minimal increase in exposure to prolactin induced by lorcaserin contributes to the emergence" of the mammary tumors in the Rat Study. (SER 101.) The FDA's post-September 2010 actions demonstrate that Defendants' view of the Rat Study and Prolactin Studies

[22] *AstraZeneca* noted the inherent uncertainty of the drug development process and FDA approval: "[P]articularly in the testing and development stage, the possible beneficial effects of a drug may be accompanied by adverse side effects, and there may be uncertainty as to how the risk-benefit balance ultimate turns out, and how it will be viewed by regulators. But if the management of the company releases positive reports about the drug to the public along the way which the management honestly believes to be true, and where there is no reckless disregard for the truth, then that is not securities fraud, even thought at a later point some event occurs which prevents the marketing of the drug . . . ." *Id.* at 470 (citation omitted).

was undeniably reasonable – and correct – undercutting any inference of scienter. *Kovtun v. VIVUS, Inc.*, No. C 10-4957 PJH, 2012 WL 4477647, at *10 (N.D. Cal. Sept. 27, 2012) (FDA's post-class period approval of drug "vitiate[d] plaintiff's theory" of scienter); *In re Cyberonics, Inc. Sec. Litig.*, Civil Action No. H-05-2121, 2006 WL 2050696, at *8 (S.D. Tex. Jul. 20, 2006) (scienter allegations based on failure to disclose safety concerns were "greatly undermined" by issuance of FDA approvable letter).

D. Plaintiff's Remaining Allegations Do Not Give Rise to a Strong Inference of Scienter

In the SAC and TAC, Plaintiff's additional scienter allegations focus on: (1) CW statements; (2) Arena's need for capital; (3) Arena's reduction in expenses in early 2009; and (4) an FDA inspection of an Arena-related facility. As shown below, the district court correctly ruled (twice) that these allegations "do not meaningfully contribute to a strong inference of scienter with respect to the overall safety statements." (ER 8; ER 15 n.8.)

1. Confidential Witness Statements, Even if Credited, Do Not Show Scienter

As this Court has explained, a complaint relying on confidential witness statements must pass two hurdles to satisfy the PSLRA's requirements:

> First, the confidential witnesses whose statements are introduced to establish scienter must be described with sufficient particularity to establish their reliability and personal knowledge . . . Second, those statements which are reported by confidential witnesses with

> sufficient reliability and personal knowledge must themselves be indicative of scienter.

Zucco, 552 F.3d at 995 (citations omitted). Plaintiff fails to satisfy either requirement, which is likely why the Appeal barely refers to the allegations from the six CWs identified in the SAC and TAC.[23] In any event, the CW allegations are even weaker in the TAC because not a single CW even mentions the Prolactin Studies, much less that he or she discussed those studies with Defendants or offered any information "indicative of scienter" with respect to those studies. *Id.* The district court properly recognized this when it held that the CW allegations "do not meaningfully contribute to the Court's scienter analysis." (ER 6.)

Only CW1 and CW2 are alleged to have been involved with the lorcaserin program. CW1 is alleged to have "handled correspondence with the FDA and prepared meeting packages, safety reports and carcinogenicity updates for the lorcaserin project" (although it is unclear whether he or she did so in a clerical or substantive way). (ER 53, TAC ¶19 n.1). Notably, however, CW1 is conspicuously silent as to Defendants' or the FDA's interpretation of the Rat Study or the Prolactin Studies. CW1 certainly does not suggest or even imply that any

[23] The TAC removed all allegations regarding CW6, who left Arena well before his purported discussion with another Arena employee in April 2010 and who provided no meaningful information regarding the Rat Study or the Prolactin Studies, much less regarding scienter. (*Compare* ER 127, SAC ¶104 *with* ER 66, TAC ¶¶85-86). *See Zucco*, 552 F.3d at 996-97 (disregarding CW allegations relating to events that took place after he or she left the company).

Defendant believed these studies posed an impediment to or would delay FDA approval. *See VIVUS*, 2012 WL 4477647, at *18 (dismissing complaint, in part, because "the allegations regarding the [CWs] provide no details of any fact that contradicted Defendants' public statements about" the drug). Similarly, CW2 is alleged to have attended a "mid-2008" meeting between Arena and the FDA to discuss lorcaserin. (ER 62, TAC ¶61.) But neither CW2 nor the TAC offers any information from the meeting bearing on scienter, or anything about what the FDA said at that meeting (or even if this "mid-2008" meeting was, in fact, the same April 2008 meeting between Arena and the FDA described above). (SER 67.) At most, CW1 and CW2 simply show what was already known – the interim Rat Study results were promptly reported to and discussed with the FDA, and Arena provided the FDA with bi-monthly interim updates until Arena completed the Rat Study and the Prolactin Studies. *VIVUS*, 2012 WL 4477647, at *18 ("[T]here is nothing ominous or even surprising about employees of a pharmaceutical company that is developing a new drug engaging in discussions about safety issues.").

The remaining allegations by CWs 3-6 are all based on hearsay, rumor, and speculation and should not be credited. (*See, e.g.*, ER 56-57, TAC ¶¶33-34 (CW3's statements all based on conversations with another Arena employee who allegedly participated in a lorcaserin team meeting long before the Class Period "in 2006 or 2007" but is not alleged to have had any role in the lorcaserin program);

ER 59, TAC ¶45 (CW4 "was told by Barbara Koozer . . ."); ER 62-64, TAC ¶¶62-63, 72 ("Based on discussions with Koozer and other Arena employees, C[W] 5 believed . . ."); AOB at 18-19 n.59 ("Another employee heard that the layoffs were likely linked to management's concerns about the future of lorcaserin."); ER 127, SAC ¶104 (CW6, who left Arena in 2009, "was told" by a former colleague in April 2010 about unrelated mouse data.) Without personal and first-hand knowledge or communications with Defendants, the Court cannot infer scienter. *Zucco*, 552 F.3d at 997 ("A majority of the [CWs] base[d] their knowledge on vague hearsay, which is not enough to satisfy *Daou*'s reliability standard."); *see also In re Metawave Commc'ns Corp. Sec. Litig.*, 298 F. Supp. 2d 1056, 1058 (W.D. Wash. 2003) ("The Court must be able to tell whether a [CW] is speaking from personal knowledge, or merely regurgitating gossip and innuendo.") (citation and internal quotation marks omitted); *In re Wachovia Equity Sec. Litig.*, 753 F. Supp. 2d 326, 352 (S.D.N.Y. 2011) ("The absence of [a CW's] communication [with Defendants] undermines the inference that Defendants recklessly disregarded the truth . . . ").

Further, because a CW's personal knowledge is limited to his or her corporate department, the allegations by CWs 3-6 should be disregarded entirely. *See VIVUS*, 2012 WL 4477647, at *17 (disregarding allegations by CWs not alleged to have had any involvement in a drug's development program). For

example, CW4 and CW5 worked in Arena's purchasing department (ER 59, TAC ¶45 n.4; ER 62, TAC ¶62 n.5), and therefore had no basis to opine on the Rat Study or the Prolactin Studies. CW3 and CW6 also are not alleged to have had any role in the lorcaserin program. (ER 56, TAC ¶33 n.3; ER 115, SAC ¶31 n.6.) *See Applestein v. Medivation, Inc.*, No. C 10-0998 EMC, 2011 WL 3651149, at *5 (N.D. Cal. Aug. 18, 2011) (adequate basis for CW reliability depends on CW's position in the company).

Finally, when utilizing CWs, a plaintiff must rely on facts and not conclusions. *See In re Hypercom Corp. Sec. Litig.*, No. CV-05-0455-PHX-NVW, 2006 WL 1836181, at *6-7 (D. Ariz. Jul. 5, 2006). For example, Plaintiff alleges that back "in 2006 or 2007" – again, long before the Class Period – it was CW3's opinion that the "FDA is going to look into" the Rat Study results and "take a poor view of where the data stands." (ER 56-57, TAC ¶34.) Notwithstanding that the FDA was fully informed about the interim results from the Rat Study, allowed the Phase III trials to continue in humans, and thereafter approved the drug, CW3 was engaging in pure speculation about what the FDA would do years later. *See In re Elan Corp. Sec. Litig.*, 543 F. Supp. 2d 187, 217 (S.D.N.Y. 2008) ("Plaintiffs allege no facts indicating that [the CW] was qualified to make this or any medical diagnosis.") For the same reason, CW5's conclusions about the reasons for

Arena's budget cuts and her termination are not grounded in facts and therefore should not be considered. *Zucco*, 552 F.3d at 1000.

2. Arena's Capital Needs Do Not Show Scienter Particularly When Considered with the Lack of Stock Sales

This Court expressly rejects scienter allegations based on a general motive to raise capital. *See Rigel*, 697 F.3d at 884 ("[T]he desire to obtain good financing . . . [is] not, without more, sufficient to allege scienter; to hold otherwise would support a finding of scienter for any company that seeks to enhance its business prospects.") (citing *Lipton v. Pathogenesis Corp.*, 284 F.3d 1027, 1038 (9th Cir. 2002); *Zucco*, 552 F.3d at 1006; *see also In re Portal Software Inc. Sec. Litig.*, No. C 03-5138, 2005 WL 1910923, at *12 (N.D. Cal. Aug. 10, 2005) (no scienter inference where company raised $60 million in a secondary offering less than two months before alleged corrective disclosure even where financing was needed to keep company a going concern); *In re Metricom Sec. Litig.*, No. C 01-4085 PJH, 2004 WL 966291, at *6, *35 (N.D. Cal. Apr. 29, 2004) (no scienter where plaintiffs alleged defendants engaged in public offering to raise "huge amounts of capital" even where company filed for bankruptcy less than 18 months after offering). To hold otherwise would mean that every development stage pharmaceutical company *a fortiori* has a motive to commit fraud. Such generalized allegations do not satisfy the PSLRA.

Moreover, Plaintiff's generalized motive allegations must be balanced against the fact that Defendants are not alleged to have sold a *single* share of Arena stock during the Class Period. This Court has repeatedly held that the absence of insider trading by a defendant is highly relevant and undermines any inference of scienter. *See Rigel*, 697 F.3d at 884 (the absence of stock sales "is inconsistent with Plaintiff's theory that financial motive establishes scienter here"); *Metzler Inv. GMBH v. Corinthian Colls., Inc.*, 540 F.3d 1049, 1067 (9th Cir. 2008) (stating that where one individual "sold nothing at all" it suggests "that there was no insider information from which to benefit"); *Lipton*, 284 F.3d at 1037. In this case, the judicially noticeable facts establish that Defendants ***increased*** their personal Arena holdings by 25% during the Class Period, losing over $15.5 million in the value of their holdings when the FDA delayed approving lorcaserin. (SER 323-34.) Plaintiff does not attempt to explain why Defendants would make themselves the victims of their own alleged fraud. *See In re PMI Group, Inc. Sec. Litig.*, No. C 08-1405, 2009 WL 1916934, at *10 (N.D. Cal. Jul. 1, 2009) (increasing holdings in company during class period is inconsistent with intent to defraud); *Zack v. Allied Waste Indus., Inc.*, 2005 WL 3501414, at *14 (D. Ariz. Dec. 15, 2005) ("[T]he individual defendants increased their stock holdings during the class period, which gives rise to an inference of good faith conduct, instead of the requisite scienter."), *aff'd*, 275 Fed. App'x 722 (9th Cir. 2008).

3. Arena's Business Decisions Do Not Show Scienter

Relying on CW5's conjecture alone, Plaintiff contends that Arena's budget cuts and employee layoffs in early 2009 were due to uncertainty about the lorcaserin NDA. (ER 62-64, TAC ¶¶62-63, 72.) Plaintiff offers no basis for CW5's conclusion about the reason for Arena's business decisions. *See In re ESS Tech., Inc. Sec. Litig.*, No. C 02-4497, 2004 WL 3030058, at *4 (N.D. Cal. Dec. 1, 2004) (disregarding CW allegations where there was "no foundation upon which to conclude . . . that the layoffs meant that defendants knew they could not produce and obtain the numbers represented").

Moreover, CW5's view ignores that at that time the United States was in the midst of a significant economic downturn. (SER 121 ("Given the challenging economic environment, we believe it is necessary to reduce our cash usage and provide Arena with additional financial flexibility to support our expected filing of a[n NDA] . . . for lorcaserin.").) Indeed, the layoffs and budget cuts actually rebut an inference of scienter because they show Defendants focusing on lorcaserin at the expense of other programs. *Accord Oppenheim Pramerica Asset Mgmt. S.A.R.L. v. Encysive Pharms., Inc.*, No. Civ.A. H-06-3022, 2007 WL 2720074, at *5 (S.D. Tex. Sept. 18, 2007) (no scienter inference where defendants "used a large part of the money it acquired from stock sales to finance the development of

[its device], indicating defendants' belief that [the device's] potential as a successful and lucrative produce for the company justified the expenditures").

4. The FDA Inspection of an Arena-Related Facility Does Not Show Scienter

The TAC does not offer a single detail about a purported FDA inspection in June 2010 – 6 months after Arena submitted the lorcaserin NDA – at an Arena-related facility where certain nonclinical studies were conducted. (ER 67, TAC ¶¶90-91.) Plaintiff ignores that the FDA conducts inspections of facilities all the time. *See, e.g.*, 21 U.S.C. § 374. As to the purported inspection here, what were the results? What were the FDA's observations?[24] More importantly, how did (or could) any such inspection impact Defendants' favorable view of the Rat Study or the Prolactin Studies, particularly where the FDA is not alleged to have communicated with Arena about these studies until it disclosed its September 2010

[24] Plaintiff removed from the TAC all allegations regarding Arena's receipt of a Form 483 following the FDA's inspection. (*Compare* ER 67, TAC ¶¶ 90-91 *with* ER 128-29, SAC ¶110.) Even if these allegations remained in the TAC, Form 483s are not indicative of scienter because they are merely "inspectional observations and do not represent a final agency determination regarding [a company's] compliance." *In re Genzyme Corp. Sec. Litig.*, Civil Action No. 09-11267-GAO, 2012 WL 1076124, at *10 (D. Mass. Mar. 30, 2012) ("Given the FDA's own warnings and enforcement policies regarding its issuance, one can safely conclude that the immateriality [of] the Form 483 negates any inference of scienter."), *aff'd*, 754 F.3d 31 (1st Cir. 2014). *See also id.* ("Since, given the FDA's own view of the significance of the form, it is of questionable materiality in a securities law context, the complaint would have to be far more specific in its allegations about why defendants' omission to disclose it was done with the requisite intent to deceive.")

briefing document? Plaintiff's inability to answer these and may other key questions refutes any inference of scienter.

E. Viewed "Holistically," the Most Cogent and Compelling Inference Is That Defendants Lacked Scienter

The Court must view Plaintiff's allegations "holistically." *Tellabs*, 127 S. Ct. at 2511; *Rigel*, 697 F.3d at 884-85. In this case, a holistic review strongly favors Defendants. By far the more compelling (and the only cogent) inference is that Defendants acted in good faith throughout the Class Period and were as surprised and disappointed as Arena stockholders by the temporary disagreement with the FDA in September 2010 over the interpretation of the results of the Rat Study and the Prolactin Studies.

Moreover, the facts in the record unambiguously establish that: (1) long before the Class Period, rather than hiding the Rat Study, Defendants immediately reported the interim data to the FDA (ER57, TAC ¶35); (2) the FDA thereafter allowed the human clinical trials involving nearly 7,200 humans to continue for nearly two more years (SER 66-67); (3) the FDA agreed in April 2008 that the rat-specific Prolactin Mechanism was a "reasonable" mode of action and that a "modest increase" in prolactin lent support to that mode of action (*id.*); (4) the Prolactin Studies showed an increase in prolactin in both female and male rats (SER 7-10, 194-95); (5) the increase in malignant tumors in the Rat Study occurred only at dosage levels not "clinically relevant to an assessment of human risk or

use" (ER 15); (6) there were no increases in tumors in the preclinical mouse and monkey studies (including a long-term carcinogenicity study in mice) or in human clinical trials involving over 8,500 patients (SER 165, 169-70, 193, 206, 208-09); (7) the FDA has approved numerous drugs despite prolactin increases and similar rat tumor findings (SER 244-52); (8) Defendants repeatedly warned investors that its preclinical and clinical lorcaserin trials were subject to different interpretation by the FDA (*see, e.g.*, ER 207-08, 226-28, 334-39, 356-59); (9) after resolving certain diagnostic uncertainties, the FDA agreed with Arena's interpretation of the Rat Study and approved the drug (SER 112); and (10) Defendants significantly increased their personal Arena holdings during the Class Period (SER 323-34).

In the face of this overwhelming evidence refuting any inference of scienter, Plaintiff cannot allege a single contemporaneous internal communication, email, memorandum, or confidential witness statement suggesting that anyone at Arena believed or said that the Rat Study or the Prolactin Studies would delay or impede FDA approval. Plaintiff also cannot allege a single contemporaneous FDA communication, email, or meeting where the FDA expressed to Arena its concern about or interpretation of the final results of the Rat Study or the Prolactin Studies before publishing its September 2010 briefing document. Plaintiff's remaining scienter allegations are "certainly not as strong as the inference that Defendants had a non-fraudulent intent." *Rigel*, 697 F.3d at 885; *VIVUS*, 2012 WL 4477647,

at *23 ("[A] 'collective' view of plaintiff's allegations does not approach a cogent and compelling inference of scienter, and certainly not one that is more plausible than that defendants genuinely believed in the promise of [their drug].")

IV. Plaintiff's View of Scienter Runs Counter to the Federal Securities Laws.

Plaintiff believes that investors should have had "the opportunity to independently evaluate how the FDA might act in light of the Rat Study." (AOB at 31.)[25] However, this ignores the irrefutable fact that rats only developed cancer at extremely high doses deemed irrelevant to humans. In any event, if pharmaceutical companies were obligated to ensure that investors could independently evaluate all details of a drug candidate at every stage of the drug development process, then nothing short of the complete and full disclosure of all interim results, all FDA questions and communications, and every page of a

[25] To the extent Plaintiff is arguing that Defendants had an independent obligation to disclose the Rat Study, the Supreme Court has soundly rejected that argument. *See Matrixx*, 131 S. Ct. at 1322 ("Even with respect to information that a reasonable investor might consider material, companies can control what they have to disclose under these provisions by controlling what they say to the market.") Here, Defendants chose to disclose data from its "pivotal" Phase III human trials because such trials are what the FDA "used in evaluating [a drug's] overall risks and benefits." (ER 53, TAC ¶16.) Because the Rat Study had nothing to do with the Phase III results, Defendants had no duty to disclose it. *Rigel*, 697 F.3d at 880 n.8 ("[A] company is not required to disclose every safety-related result . . . even if investors would consider the information significant"); *see also Sec. Police and Fire Prof'ls of Am. Ret. Fund v. Pfizer, Inc.*, Civil Action No. 10-cv-3105 (SDW), 2013 WL 1750010, at *7 (D.N.J. Apr. 22, 2013) ("Defendants did not make an affirmative statement about the [clinical] data, and therefore did not put the subject of the [clinical] data 'in play.'").

company's NDA (here, more than 4 million pages) would suffice. A pharmaceutical company's SEC filings could be thousands of pages long, deluging the market.

Just as an example, here Arena could not have disclosed the Rat Study results without also disclosing, at a minimum, each bi-monthly update sent to the FDA, the mouse, monkey, and human studies, and each of the six Prolactin Studies so an investor could consider the Rat Study in context. This would defeat the purpose of the federal securities laws by overwhelming potential investors in an avalanche of information. *See Twinde v. Threshold Pharms., Inc.*, No. C 07-4972 CW, 2008 WL 2740457, at *9 (N.D. Cal. Jul. 11, 2008) ("An excess of disclosure can have the same net effect as a dearth of it – the shareholder misses the relevant information.") (citation omitted). Further, consider a hypothetical investor who sold his or her Arena holdings based on his or her interpretation of the first report to the FDA about the interim Rat Study results, only to see Arena's stock price zig-zag based on each subsequent interim report in the ongoing study, the final Rat Study results, the Prolactin Studies, and then watch it rise significantly when the FDA approved lorcaserin.

Especially in the pharmaceutical industry, public companies must make frequent judgments about where to draw the line on disclosure issues because they cannot know in advance what the FDA may later consider important in conducting

its risk/benefit analysis of a drug. Liability under Section 10(b) of the Exchange Act is limited to those cases where the disclosure judgment is not just wrong and not just negligent. *See In re Geopharma, Inc. Sec. Litig.*, 411 F. Supp. 2d 434, 436-37 (S.D.N.Y. 2006) ("It is entirely possible for a defendant to make an honest but negligent mistake in judging how much detail needs to be included in public statements to avoid misleading the market."). Rather, Section 10(b) requires an "extreme departure" from ordinary standards of care amounting to "deliberate recklessness" or an actual intent to defraud. *Zucco*, 552 F.3d at 991. As noted in Section III., above, Plaintiff has made no such showing.

V. The Control Person Claim Necessarily Fails

Because Plaintiff fails to plead a primary violation of Section 10(b) of the Exchange Act, his claim under Section 20(a) fails as well. *Id.* at 990 (citations omitted). (ER 7.)

VI. The District Court Properly Denied Leave to Amend

The district court was within its discretion to deny Plaintiff's motion to amend the SAC and dismiss the case with prejudice. The proposed TAC was Plaintiff's fourth attempt to plead a claim under the Exchange Act. The district court previously identified specific deficiencies in both the CAC and the SAC and gave Plaintiff the opportunity to correct them. *See Zucco*, 552 F.3d at 1007 (no error in denying leave to amend as "it was clear that the plaintiffs had made their best case and had been found wanting"); *Metzler*, 540 F.3d at 1072. Plaintiff's

inability to do so after four tries is a "strong indication that the plaintiffs have no additional facts to plead." *In re Vantive Corp. Sec. Litig.*, 283 F.3d 1079, 1098 (9th Cir. 2002).

CONCLUSION

For the foregoing reasons, the Court should affirm the district court's decision dismissing the SAC, denying Plaintiff's motion to amend the SAC, dismissing the case with prejudice, and entering judgment for Defendants.

Dated: October 24, 2014

Respectfully submitted,

/s/William E. Grauer

William E. Grauer
Koji F. Fukumura
Mary Kathryn Kelley
Ryan E. Blair
Cooley LLP
4401 Eastgate Mall
San Diego, CA 92121-1909
Phone: (858) 550-6000
Facsimile: (858) 550-6420

Attorneys for Defendants-Appellees

CERTIFICATION OF COMPLIANCE PURSUANT TO FED. R. APP. P. 32(a)(7)(C) AND CIRCUIT RULES 32-1 FOR CASE NO. 14-55633

I certify that, pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C) the attached answering brief (1) complies with the length limits set forth at Fed. R. App. P. 32(a)(7)(B) because it contains 13,997 words, excluding the parts of the brief exempted by Fed. R. App. Ap. 32(a)(7)(B)(iii); and (2) complies with Fed. R. App. P. 32(a)(5) and (6) because the brief is proportionally spaced using 14-point Times New Roman Type.

Dated: October 24, 2014

/s/William E. Grauer
William E. Grauer

CERTIFICATION PURSUANT TO CIRCUIT RULE 28-2.6

Pursuant to Ninth Circuit Rule 28-2.6, I certify that there are no known related cases pending in this Court.

Dated: October 24, 2014

/s/William E. Grauer
William E. Grauer

CERTIFICATE OF SERVICE

I hereby certify that, on October 24, 2014, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit using the appellate CM/ECF system. Participants in the case who are registered CM/ECF users will be served by the appellate CM/ECF users. Upon acceptance by the Clerk of the Court of the electronically filed document, one copy of the following will be served, via U.S. Mail, postage prepaid on:

Eirk D. Peterson
Kessler Topaz Meltzer & Check LLP
One Sansome Street
Suite 1850
San Francisco, CA 94104

Dated: October 24, 2014

/s/William E. Grauer
William E. Grauer

No. 14-55633

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

TODD SCHUENEMAN, on behalf of himself and all others similarly situated,

Plaintiff-Appellant,

v.

ARENA PHARMACEUTICALS, INC., et al.,

Defendants-Appellees,

On Appeal from the United States District Court for the Southern District of California
Honorable Cathy Ann Bencivengo
Case No. 3:10-cv-01959-CAB-BLM

DEFENDANTS-APPELLEES' SUPPLEMENTAL EXCERPTS OF RECORD
VOLUME I OF II
(PAGES 1-242)

William E. Grauer
Koji F. Fukumura
Mary Kathryn Kelley
Ryan E. Blair
Cooley LLP
4401 Eastgate Mall
San Diego, CA 92121-1909
(858) 550-6139

Attorneys for Defendants-Appellees

TABLE OF CONTENTS
VOLUME I OF II

Page

Page

TABLE OF CONTENTS
VOLUME II OF II

Page

COOLEY LLP
WILLIAM E. GRAUER (84806)
(grauerwe@cooley.com)
KOJI F. FUKUMURA (189719)
(kfukumura@cooley.com)
MARY KATHRYN KELLEY (170259)
(mkkelley@cooley.com)
RYAN E. BLAIR (246724)
(rblair@cooley.com)
4401 Eastgate Mall
San Diego, CA 92121
Telephone: (858) 550-6000
Facsimile: (858) 550-6420

Attorneys for Defendants Arena Pharmaceuticals, Inc., Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situation,

Plaintiff,

v.

ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON,

Defendants.

Case No. 10-CV-1959-CAB (BLM)

THIRD SUPPLEMENTAL DECLARATION OF RYAN E. BLAIR IN SUPPORT OF DEFENDANTS' OPPOSITION TO LEAD PLAINTIFF'S MOTION TO AMEND SECOND CONSOLIDATED AMENDED CLASS ACTION COMPLAINT

Date: January 3, 2014
Time: 2:30 p.m.
Judge: Hon. Cathy Ann Bencivengo
Ctrm: 4C

[Oral argument requested subject to Court approval]

WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situation, Plaintiffs, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, and WILLIAM SHANAHAN, JR. Defendants.	Case No. 10-CV-1961-CAB (BLM)
WILLIAM PRATT, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1977-CAB (BLM)
CRAIG RUBENSTEIN, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1984-CAB (BLM)

RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2026-CAB (BLM)
THONG VU, Individually and on behalf of all others similarly situated Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2086-CAB (BLM)
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 10-cv-2335-CAB (BLM)

I, Ryan E. Blair, declare as follows:

1. I am an attorney with the law firm of Cooley LLP, counsel for defendants Arena Pharmaceuticals, Inc. ("Arena"), Jack Lief, Robert E. Hoffman (who has been dismissed from this action with prejudice per the Court's Order (Dkt. No. 71 at 13)), Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson (collectively, "defendants"). I have personal knowledge of the following facts and, if called upon to testify, I could and would testify competently thereto.

2. Attached hereto as Exhibit BF is a true and correct copy of 4 pages of the Pharmacology/Toxicology NDA Review and Evaluation of the lorcaserin drug by the U.S. Food and Drug Administration ("FDA") dated October 20, 2010. Portions of Exhibit BF have already been introduced into the record by plaintiff. (*See* Dkt. No. 61-4.) Plaintiff, however, omitted from his exhibit the four pages that expressly discuss the results of the prolactin mechanistic studies and the dates of those studies. Accordingly, Exhibit BF is a proper subject of judicial notice under both the "incorporation by reference" doctrine and the doctrine of completeness. *See In re CNET Networks, Inc.*, 483 F. Supp. 2d 947, 953 (N.D. Cal. 2007) (considering the full text of documents).).

3. Attached hereto as Exhibit BG is a true and correct copy of a 9-page excerpt of Arena's NDA for lorcaserin (which is over 4 million pages and includes many terabytes of scientific data), submitted to the FDA in December 2009 and located within the section of the NDA titled "2.6.6. Toxicology Written Summary." Plaintiff's proposed Third Consolidated Amended Complaint ("TAC") and Motion to Amend ("Motion") repeatedly refer to statements purportedly contained in the NDA. (*See, e.g.*, TAC, ¶¶ 78-81; Motion at 11:10-21.) Accordingly, because Exhibit BG is part of the NDA and shows what Arena actually said in the NDA, it is relevant, helpful, and clearly incorporated by reference into the TAC and subject to judicial notice under the incorporation by reference doctrine. *See CNET*, 483 F. Supp. 2d at 953.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 20th day of December, 2013, at San Diego, California.

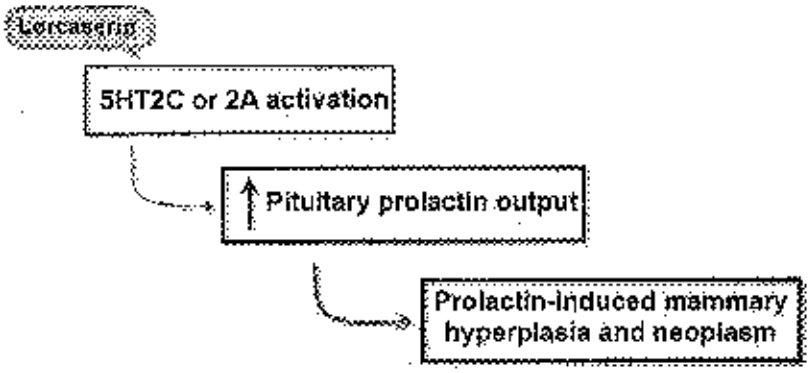
Ryan E. Blair

Exhibit BF

10 Special Mechanistic Studies

Mechanistic Studies Designed To Explore the Role of Prolactin in Lorcaserin Induced Mammary Neoplasia in Rats

The sponsor had performed series of mechanism studies to support the hypothesis that lorcaserin induced increase in mammary gland neoplasia in rats was due to lorcaserin related increase in serum prolactin levels. The studies were designed to show that the lorcaserin effect is via prolactin similar to several approved antipsychotic drugs which are recognized to increase prolactin and prolactin-related increase in mammary tumors in rats.



Lorcaserin is a $5HT_{2C}$ selective agonist (Ki=13 nM). Binding and functional tests have shown lorcaserin to be at least 5 and 11 fold more selective to $5HT_{2C}$ than to $5HT_{2A}$ (Ki=92 nM) and $5HT_{2B}$ (Ki=147 nM), respectively. The EC_{50} for human $5HT_{2A}$, $5HT_{2B}$ and $5HT_{2C}$ is estimated to be 133, 811 and 9 nM, respectively. Lorcaserin had no notable binding to dopamine receptors in the [redacted] assay. Oral administration of lorcaserin (36 mg/kg) did not alter intracellular dopamine or serotonin in nucleus Accumbens in rat while dexfenfluramine (2.6 mg/kg), a nonselective serotonin agonist increased intracellular serotonin but not dopamine, suggesting both compounds may low abuse potential (a dopamine effect in nucleus accumbens). Lorcaserin is extensively metabolized in all species but the prominent inactive metabolites are M1 (lorcaserin sulfamate) and to some extent M5 (N-carbamoyl glucuronide).

Study Title: Acute Effects of Lorcaserin on Serum Prolactin Levels in Rats (DBR-08-031)

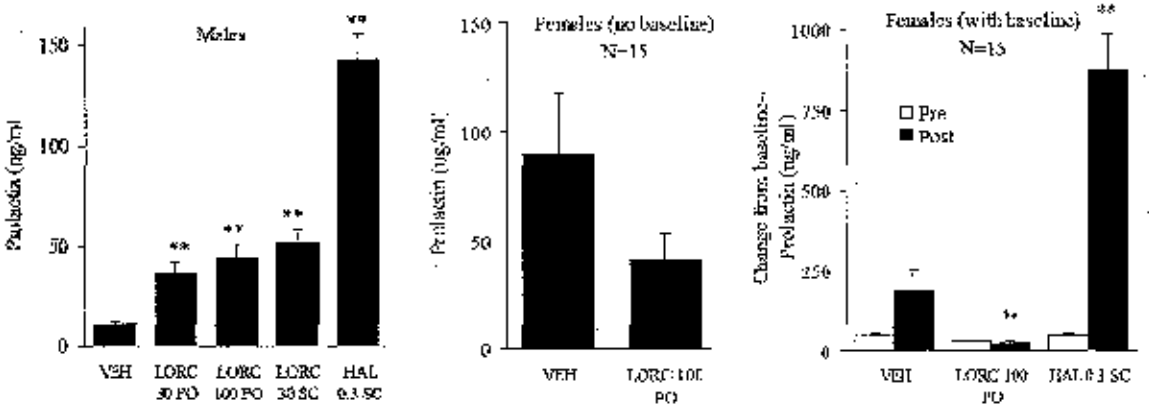
In an acute non-GLP study, single dose of lorcaserin (30-100 mg/kg, PO) and neuroleptic haloperidol (positive control,0.3 mg/kg, SC) were administered to 12 week old male and female SD rats (Arena Discovery Labs, March 20, 2008). Haloperidol is a dopamine antagonist known to increase serum prolactin levels. Prolactin levels were measured 30 min after administration of each compound via cardiac puncture under CO_2 anesthesia. A subset of females were bled (1 ml) prior to drug administration via

tail vein. Serum samples were sent to [redacted] for prolactin analysis.

In this single dose study, lorcaserin increased prolactin levels in male rats but not in females. In female rats, serum prolactin levels appeared to decrease while haloperidol consistently increased serum prolactin levels in both male and female rats suggesting that haloperidol is a very potent stimulator of prolactin release. Since the lorcaserin induced increase in prolactin in male rats was relatively weak compared to haloperidol, the finding may be related to an a acute effect possible stress related. For example, even administration of vehicle increased prolactin in females by ~5 fold. However, based on the study, the sponsor concluded that ovarian hormones may have been interfering with the prolactin release in female rats. Since haloperidol was able to increase prolactin levels in males by 15 fold and in females by as much as 80 fold, the role of lorcaserin in prolactin release in male rats thus was likely incidental.

Effects of lorcaserin and haloperidol on serum prolactin levels in male Sprague Dawley rats

Effects of lorcaserin and haloperidol on serum prolactin levels in female Sprague Dawley rats. **p<0.01 compared to vehicle controls



In summary acute administration (single dose) of lorcaserin increased prolactin levels in male rats but not in female rats. In contrast, haloperidol, a dopamine antagonist, robustly increased prolactin levels in both males and female rats.

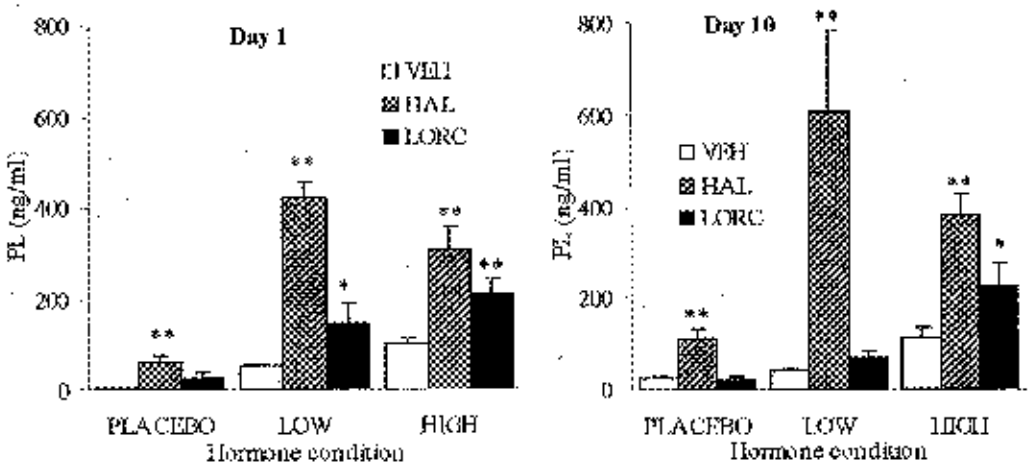
Study Title: Sub-chronic Effects of Lo on Serum Prolactin Levels in Ovariectomized Female Rats (DBR 08-032)

In a follow up sub-chronic non-GLP study, the role of multiple doses lorcaserin on prolactin levels was evaluated in ovariectomized female rats (May 28, 2008, Area Discovery Labs). The study was similar to the single dose study described above except that lorcaserin dose of 100 mg/kg was administered by gavage for 10 days to ovariectomized rats replenished with ovarian hormones (0.1 mg estradiol-β + 15 mg progesterone or 2.5 mg estrodial-β+35 mg progesterone). Haloperidol (0.3 mg/kg, SC) served as positive control.

As expected, haloperidol increased serum prolactin levels after acute and 10 day dosing in ovariectomized female rats replenished with ovarian hormones regardless of hormone replacement regimen. In contrast, lorcaserin increased prolactin levels only in animals receiving hormone replacement and not in placebo implanted ovariectomized

rats. Since lorcaserin's effect was minimal with low dose hormone replacement (normal levels) and only increased with supra-pharmacological doses of estradiol and progesterone, the relevance of this finding is questionable. The normal estradiol levels in female rats is about 2 to 50 pg/ml vs. estradiol levels with mega dose of implanted pellets. The reviewer estimated estradiol levels were up to 20x the normal levels. The study conditions do not resemble the conditions in the carci study. The estradiol levels in the ovariectomized rats were closer to high normal (next study) than it should have been and hormone replenishment itself produced a significant increase in serum prolactin.

Effect of lorcaserin and haloperidol on serum prolactin levels after acute and sub-chronic treatment in ovariectomized female rats implanted with placebo or hormone pellets *p<0.05; **p<0.01

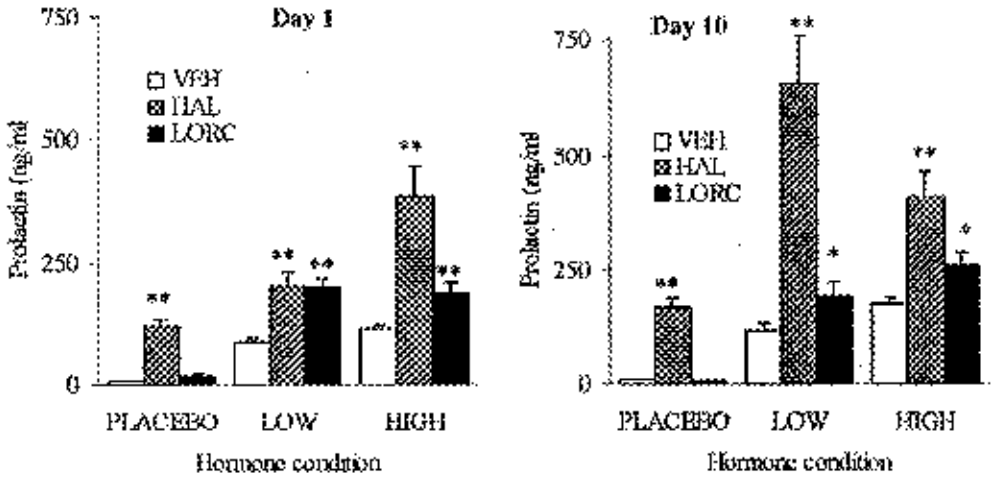


Study Title: Sub-chronic Effects of Lorcaserin on Serum Prolactin Levels in Ovariectomized Female Rats (DBR-09-001)

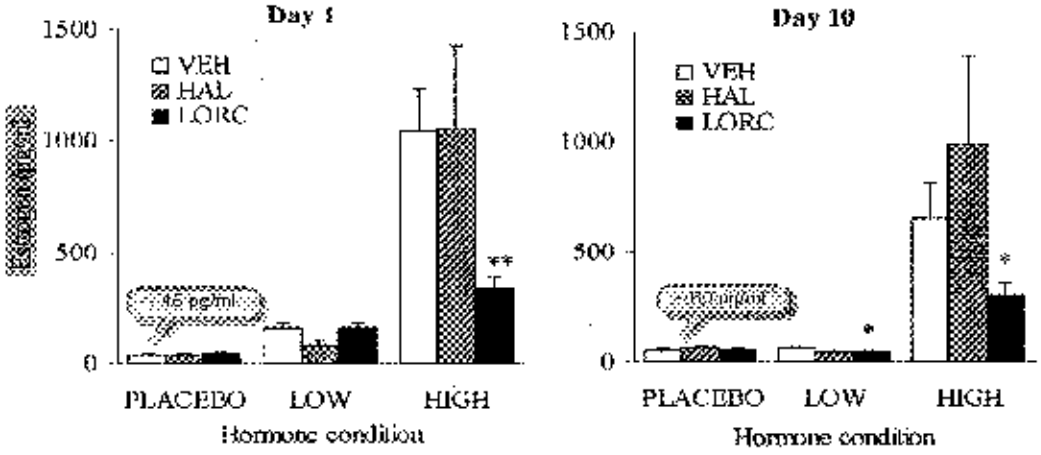
The sponsor repeated the same study above (Nov 4, 2008) in the same animal model as described in study # DBR-08-032 (Arena Discovery Labs). The study findings were pretty much similar to those in the earlier study. As discussed earlier, the relevance of ovariectomized rats replenished with supra- pharmacological doses of estradiol/ progesterone is questionable and not similar to rats in the carci study. For prolactin to be the intermediary hormone between lorcaserin and mammary tumors there should have been persistent elevation in prolactin levels in intact rats in the chronic studies as was the case for most antipsychotic drugs.

Effect of lorcaserin and haloperidol on serum prolactin levels after acute and sub-chronic treatment in ovariectomized female rats implanted with placebo or hormone pellets

*p<0.05; **p<0.01 vs. vehicle



Serum estrogen levels in ovariectomized female rats implanted with hormone pellets



Study Title: A preliminary pharmacokinetic evaluation of prolactin release and concentration of other hormones in female SD rats after treatment with APD356 (679001 & TX08001)

In a mechanistic study, the effects of single and multiple doses of APD356 (100 mg/kg, 10 days) on several endogenous hormones were evaluated in ovariectomized Crl:CD(SD) rats. The positive control groups (intact and ovariectomized) received S^+ fenfluramine (10 mg/kg, IP), a nonselective serotonin agonist. This GLP study was

Laurence D. King (SBN 206423)
Mario M. Choi (SBN 243409)
KAPLAN FOX & KILSHEIMER LLP
350 Sansome Street, Suite 400
San Francisco, CA 94104
Telephone: 415-772-4700
Facsimile: 415-772-4707
lking@kaplanfox.com
mchoi@kaplanfox.com

Robert N. Kaplan (admitted *pro hac vice*)
Jeffrey P. Campisi (admitted *pro hac vice*)
KAPLAN FOX & KILSHEIMER LLP
850 Third Avenue, 14th Floor
New York, NY 10022
Telephone: 212-687-1980
Facsimile: 212-687-7714

Lead Counsel for Lead Plaintiff Carl Schwartz and the Proposed Class

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situated,

Plaintiff,

vs.

ARENA PHARMACEUTICALS, INC., JACK LIEF, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON,

Defendants.

Case No. 3:10-cv-01959-CAB

LEAD PLAINTIFF'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF LEAD PLAINTIFF'S MOTION TO AMEND SECOND CONSOLIDATED AMENDED CLASS ACTION COMPLAINT

Judge: Hon. Cathy Ann Bencivengo
Courtroom: 4C
Hearing Date: January 3, 2014
Hearing Time: 2:00 p.m.

[Oral argument requested, subject to Court approval]

captions continue on next page

WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF and WILLIAM SHANAHAN, JR. Defendants.	Case No. 3:10-cv-01961-CAB
WILLIAM PRATT, Individually and on Behalf of All Others Similarly Situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01977-CAB
CRAIG RUBENSTEIN, Individually and on Behalf of All Others Similarly Situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01984-CAB

captions continue on next page

RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02026-CAB
THONG VU, individually and on behalf of all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02086-CAB
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02335-CAB

TABLE OF CONTENTS

I. INTRODUCTION

The Court's November 4, 2013 Order (ECF. No. 71) (the "Order") permitted Lead Plaintiff to amend his complaint because the record before the Court contained enough facts to show that Defendant Christy Anderson's representation to investors on September 18, 2009 that "[w]e've I think put together pretty much all of the data that we now need for this N[ew] D[rug] A[pplication]. We have *favorable results on everything* that we've compiled so far. . . " was materially false and misleading and was made under circumstances that may have given rise to a strong inference of scienter. (Order, at 8-9 (emphasis in original).) As noted by the Court, "this statement, having been made by the Company's Vice President for Lorcaserin Development and the person in charge of putting together the NDA communicated to investors that Arena had checked all the boxes that it needed to for its NDA submission." (*Id.*) But, Defendants[1] had not "checked all the boxes and they knew it" because that the FDA required Defendants to substantiate their hypothesis that the tumors found in the Ray Study were due to a rat-specific mechanism with data" showing an increase in prolactin levels in rats, and by the beginning of the Class Period (May 11, 2009) Defendants knew that their mechanistic studies on rats failed to show such an increase. (*Id.* at 9.) The Court concluded that the "factual record may give rise to the more plausible inference that defendant Anderson knew or deliberately disregarded facts that seriously undermined any belief Defendants may have had regarding the sufficiency of the data." (*Id.*)

[1] The "Defendants" are Arena Pharmaceuticals, Inc. ("Arena" or the "Company"); Jack Lief ("Lief"), Arena's President, CEO and Chairman; Dominic P. Behan ("Behan"), Arena's Senior Vice President and Chief Scientific Officer; William R. Shanahan, Jr. ("Shanahan"), Arena's Senior Vice President and Chief Medical Officer; and Christy Anderson ("Anderson"), Arena's former Vice President of Clinical Development. The Court dismissed with prejudice claims against Robert E. Hoffman, Arena's CFO. (Order at 5, n.5.)

Consistent with the Order, the proposed Amended Complaint[2] pleads facts that demonstrate that, by the beginning of the Class Period, Defendant Anderson, as well as Defendants Lief, Shanahan, and Behan, knew of the Rat Study's adverse results and discussed them with the FDA, and that Defendants hypothesized that the cancer observed in rats was not relevant to humans because the cancer was caused by an increase in prolactin, a hormone secreted by the pituitary gland and a known rat carcinogen (the "Prolactin Hypothesis"). (¶ 42.)[3] Through correspondence and meetings with the FDA, Defendants learned that the FDA required Defendants to submit data from the Rat Study showing that lorcaserin caused an increase in prolactin in rats in order to support their Prolactin Hypothesis, and in order to demonstrate to the FDA that there was no risk to humans. (¶ 43.) Between July 2007 and December 2008, Defendants conducted six mechanistic studies that were designed to show that lorcaserin increased prolactin in mammary tumors in rats, and submitted the data to the FDA in February 2009. (¶¶ 44, 65.) However, the Rat Study data did not show an increase in prolactin as required by the FDA. (¶ 66.) In Defendants' mechanistic studies, haloperidol (an antipsychotic unrelated to lorcaserin) increased prolactin levels in male rats by 15 fold and in females by as much as 80 fold. (*Id.*) In sharp contrast, Defendants' mechanistic studies showed that lorcaserin had ***no effect*** on serum prolactin in female rats, and ***reduced*** prolactin in males by 50% in the rat carcinogenicity study. (¶ 67.) Further, the single and multiple doses of lorcaserin (10 to 100 mg/kg) consistently failed to show a significant rise in serum prolactin levels in female rats at any time period. (*Id.*) Thus, by the beginning of the Class Period, Defendants knew that they failed to develop data required by the FDA to substantiate the Prolactin Hypothesis.

[2] For the Court's convenience, Exhibit A to the accompanying Declaration of Laurence D. King, dated November 27, 2013 is the proposed Amended Complaint. Exhibit B is a highlighted and redlined version of the Complaint that reflects Lead Plaintiff's amendments to the Second Consolidated Amended Class Action Complaint (ECF No. 59).

[3] "¶_" and "¶¶_" refer to paragraphs of the proposed Amended Complaint.

(¶ 68.) As a result, Defendants did not have evidence to show that the Rat Study's adverse results were irrelevant to human risk.

Accordingly, it was an extreme departure from ordinary standards of conduct for Defendant Anderson to represent on a September 18, 2009 conference call with investors that "[w]e have favorable results on everything that we've compiled so far" (¶¶ 75, 109) when internally she knew at that time that the mechanistic studies on rats were not favorable, and in fact, had failed to demonstrate an increase in prolactin as required by the FDA. Therefore, Defendants failed to show that the Rat Study's adverse results were not relevant to humans. Similarly, Defendants Lief, Shanahan, and Behan's representations to investors that Defendants had demonstrated lorcaserin's "long-term safety" and that lorcaserin's "mechanism" was safe (¶¶ 106, 112, 115, 119, 135, 138-39, 151-52) were false and misleading and they knew it because Defendants' mechanistic studies had failed to show that the cancer observed in the Rat Study was caused by a rat-specific mechanism. (¶¶ 66-70.) Like Anderson, by the beginning of the Class Period, Defendants Lief, Behan, and Shanahan knew that the FDA required them to substantiate the Prolactin Hypothesis with data showing an increase in prolactin levels in rats exposed to lorcaserin, and that Defendants' mechanistic rat studies had failed to do so. (¶¶ 57-60.) The data collected by Defendants did not show an increase in prolactin as required by the FDA. (¶ 66.) As such, it was an extreme departure from ordinary standards of conduct for Lief, Shanahan, and Behan to represent that lorcaserin's mechanism was safe for human use and that lorcaserin's safety had been demonstrated.

When read holistically, *Matrixx Initiatives, Inc. v. Siracusano*, 131 S. Ct. 1309, 1324 (2011), the Complaint's new allegations, along with the existing allegations, strongly support an inference of scienter. *See, e.g.*, *In re Amylin Pharms., Inc. Sec. Litig.*, No. 01CV1455 BTM (NLS), 2003 WL 21500525, at *8 (S.D. Cal. May 1, 2003) (denying motion to dismiss where "concerns raised by the

FDA . . . were much more significant than a 'bump on the road' and shed serious doubt on the sufficiency of the trials. Accordingly, Defendants were obligated to disclose the FDA's concerns to render their statement not misleading") ("*Amylin II*"). In the face of these material negative facts, Defendants could not have reasonably believed that the results of the Rat Study were positive, "favorable" or "encouraging" or that they had developed data showing an increase in prolactin in rats as required by the FDA.

For these reasons, and as further articulated below, the Court should grant Lead Plaintiff's Motion to Amend the Second Consolidated Amended Class Action Complaint.

II. BACKGROUND AND FACTS

The March 28, 2013 and November 4, 2013 Orders (ECF Nos. 56 and 71) set forth the background of this matter. The new facts alleged in the proposed amended Complaint are set forth above, highlighted in the "redlined" version of the proposed Amended Complaint attached as Exhibit B to the King Declaration, and are further discussed below.

III. DISCUSSION

A. Legal Standard

Fed. R. Civ. P. 15(a) provides that amendment of a complaint after a responsive pleading has been filed may be allowed by leave of the court and "shall freely be given when justice so requires." *Foman v. Davis*, 371 U.S. 178, 182, (1962); *Larios v. Nike Retail Servs., Inc.*, No. 11cv1600-GPC-NLS, 2013 WL 4046680, at *2 (S.D. Cal. Aug. 9, 2013). Granting leave to amend rests in the sound discretion of the trial court. *Int'l Ass'n of Machinists & Aerospace Workers v. Republic Airlines*, 761 F.2d 1386, 1390 (9th Cir. 1985). This discretion must be guided by the strong federal policy favoring the disposition of cases on the merits and permitting amendments with "extreme liberality." *DCD Programs, Ltd. v. Leighton*, 833 F.2d 183, 186 (9th Cir. 1987) (citations omitted). As

Laurence D. King (SBN 206423)
Mario M. Choi (SBN 243409)
KAPLAN FOX & KILSHEIMER LLP
350 Sansome Street, Suite 400
San Francisco, CA 94104
Telephone: 415-772-4700
Facsimile: 415-772-4707
lking@kaplanfox.com
mchoi@kaplanfox.com

Robert N. Kaplan (admitted *pro hac vice*)
Jeffrey P. Campisi (admitted *pro hac vice*)
KAPLAN FOX & KILSHEIMER LLP
850 Third Avenue
New York, NY 10022

Lead Counsel for Lead Plaintiff Carl Schwartz and the Proposed Class

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situated,

Plaintiff,

vs.

ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON,

Defendants.

[Additional Captions on Following Pages]

Case No. 3:10-cv-01959-CAB-BLM

DECLARATION OF LAURENCE D. KING IN OPPOSITION TO DEFENDANTS' MOTION TO DISMISS THE SECOND CONSOLIDATED AMENDED CLASS ACTION COMPLAINT

Judge: Hon. Cathy Ann Bencivengo
Courtroom: 4C
Hearing Date: Aug. 2, 2013
Hearing Time: 2:30 p.m.

[Oral argument requested, subject to Court approval]

WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF and WILLIAM SHANAHAN, Defendants.	Case No. 3:10-cv-01961-CAB-BLM
WILLIAM PRATT, on behalf of himself and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01977-CAB-BLM
CRAIG RUBENSTEIN, on behalf of himself and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01984-CAB-BLM

RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02026-CAB-BLM
THONG VU, individually and on behalf of all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-2086-CAB-BLM
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-2335-CAB-BLM

I, Laurence D. King, declare as follows:

1. I am a partner with the law firm of Kaplan Fox & Kilsheimer LLP, counsel for Lead Plaintiff Carl Schwartz and the Proposed Class. I have personal knowledge of the following facts and, if called upon to testify, I could and would testify competently thereto.

2. Attached hereto as Exhibit A is a true and correct copy of the redlined version of the Second Consolidated Amended Class Complaint ("Complaint") (ECF No. 56), reflecting Lead Plaintiff's amendments to the Complaint.

3. Attached hereto as Exhibit B is a true and correct copy of a chronology of events showing when Defendants Arena Pharmaceuticals, Inc. ("Arena"), Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, and Christy Anderson (collectively, "Defendants") learned of the adverse results observed in the Rat Study and the dates of meetings and correspondence with the Federal Food & Drug Administration ("FDA") about the adverse results of the Rat Study.

4. Attached hereto as Exhibit C is a true and correct copy of excerpts of the Pharmacology/Toxicology NDA Review and Evaluation of the lorcarserin drug by the FDA, signed by Dr. Fred Alavi (with concurrence by Dr. Todd M. Bourcier) on October 20, 2010.

5. Attached hereto as Exhibit D is a true and correct copy of the Summary Review for Regulatory Action by the FDA concerning the lorcaserin drug, signed by Dr. Eric Colman on October 21, 2010.

6. Attached hereto as Exhibit E is a true and correct copy of Prescribing Information concerning BELVIQ (lorcaserin).

7. Attached hereto as Exhibit F is a true and correct copy of the letter signed June 27, 2012 from the FDA to Arena approving Arena's New Drug Application dated December 18, 2009 for Belviq (lorcaserin).

8. Attached hereto as Exhibit G is a true and correct copy of Arena's Form 8-K filed with U.S. Securities and Exchange Commission ("SEC") on January 22,

2013, noting objections by the European Medicines Agency concerning approval of lorcaserin in the European Union.

9. Attached hereto as Exhibit H is a true and correct copy of Arena's Form 8-K filed with the SEC on May 2, 2013, noting Arena's withdrawal of its request for approval of lorcaserin in the European Union.

10. Attached hereto as Exhibit I is a true and correct copy of the Order filed April 11, 2010, in *In re Fannie Mae 2008 Sec. Litig.*, No. 1:08-cv-07831-PAC (S.D.N.Y.) (ECF No. 269).

11. Attached hereto as Exhibit J is a true and correct copy of excerpts of the Notice of Motion and Motion to Dismiss Consolidated Complaint for Violation of the Federal Securities Laws; Memorandum of Points and Authorities in Support, dated October 14, 2008, in *In re The PMI Group, Inc. Sec. Litig.*, No. 3:08-cv-01405-SI (N.D. Cal.) (ECF No. 28).

12. Attached hereto as Exhibit K is a true and correct copy DSI Consult Request for Nonclinical Site Inspections, dated March 3, 2010.

13. Attached hereto as Exhibit L is a true and correct copy of Arena's Form 10-Q for the quarter ended September 30, 2010, filed with the SEC on November 9, 2010.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 15th day of July, 2013, in San Francisco, California.

/s/ Laurence D. King
Laurence D. King

CERTIFICATE OF SERVICE

I, Laurence D. King, hereby declare that on July 15, 2013, I caused the foregoing to be filed electronically using the Court's CM/ECF system which sent notifications of the filing to counsel of record.

/s/ Laurence D. King
Laurence D. King

EXHIBIT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22-529
Supporting document/s:	electronic NDA
Applicant's letter date:	Dec 22, 2009
CDER stamp date:	Dec 23-2009
Product:	LORQESS® (Lorcaserin HCl)
Indication:	treatment of obesity
Applicant:	Arena Pharmaceuticals
Review Division:	DMEP
Reviewer:	Fred Alavi, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director:	Mary Parks, MD
Project Manager:	Patricia Madara

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-529 are owned by Arena Pharmaceuticals or are data for which Arena has obtained a written right of reference.
Any information or data necessary for approval of NDA 22-529 that Arena does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Arena does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-529.

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability: Not recommended for approval until rodent carcinogenicity findings are clarified**.**

1.1.2 Additional Non-Clinical Recommendations:

The mode of action for mammary neoplasm and brain astrocytoma needs to be addressed. The reviewer recommends re-evaluation of mammary and brain tissue slides by an independent panel of pathologists. Since brain tumors are small and can be easily missed, more sectioning of brain tissue is recommended. The reviewer also recommends analysis of brain lorcaserin distribution in both male and female rats due to significant gender differences in lorcaserin kinetics in rats.

1.1.3 Labeling- Not applicable at this stage

1.2 Brief Discussion of Nonclinical Findings

Lorcaserin is a new molecular entity designed to selectively to bind serotonin 2C receptors ($5HT_{2C}$) in the brain. The sponsor is seeking approval of lorcaserin for a weight loss indication. To assess the safety of lorcaserin, standard toxicological assessments of lorcaserin were carried out. Evaluations included genotoxicity, rat and monkey toxicology and carcinogenicity studies in mice and rats. The reproductive toxicity of lorcaserin was assessed in rats and rabbits. The toxicological assessments identified two major findings of clinical concern, a) neoplastic tumors in male and female rats and b) renal tubular regeneration and degeneration in a 12-month monkey study.

The genotoxicity and carcinogenicity of lorcaserin was assessed in a standard battery of genotoxicity tests and 2-year rodent bioassays, respectively. Lorcaserin was not genotoxic nor mutagenic in the standard *in-vitro* and *in-vivo* genotoxicity assays. The mouse carcinogenicity study was initiated with lorcaserin doses of 0, 25, 50 and 100 mg/kg. Oral administration of 100 mg/kg of lorcaserin (7.5 and 15x the clinical dose of 10 mg BID based on AUC) resulted in acute increase in mortality in both male and female mice within 16 days of the study initiation leading to a reduction of the lorcaserin dose after consultation with eCAC. The cause of death at 100 mg/kg was not determined but suspected to be neuronal in origin since lorcaserin can partition into the mouse brain up to 25x the plasma levels. The sharp increase in deaths in mice was unexpected since 100 mg/kg and higher doses of lorcaserin were tolerated for as long as 13 weeks. The mouse study was continued (Day 19) with lower lorcaserin doses of 0, 5, 25 and 50 mg/kg. The top dose of 50 mg/kg (4 and 7x the MRHD) was without any further incidence of mortality. In fact, there were no statistically significant changes in

any of the parameters evaluated in the 2-year mouse study with lorcaserin doses up to 50 mg/kg. The incidence of mammary adenocarcinoma in control, 5, 25 and 50 mg/kg (2/75, 1/65, 1/65, 4/75 mice) were not significant. The NOAEL for mouse carcinogenicity was 50 mg/kg (4x the MRHD in female and 7x the MRHD in males, based on AUC).

The rat 2-year carcinogenicity study was carried out with 0, 10, 30 and 100 mg/kg of lorcaserin (C, LD, MD and HD, respectively). Lorcaserin significantly and dose-dependently increased mortality at all doses in females due to mammary tumors and in HD males due to various types of tumors. Lorcaserin dose-dependently increased the number of deaths by mammary tumor and decreased the survival time (latency) in female rats. Both fibroadenoma and adenocarcinoma were fatal in female rats.

Lorcaserin Dose, mg/kg	**0**	**10**	**30**	**100**
Number of death due to mammary tumors in female rats				
Number of animals per group	65	65	65	75
Due to fibroadenoma	2	9	14	10
Due to adenocarcinoma and or fibro	13	22	29	50
Combined	**15**	**31**	**43**	**68**

There were nearly twice as many dead female rats due to mammary tumors at LD than in control. Fatality due to tumors occurred earliest in HD females at WK 42 vs. WK 61 in HD males. Since deaths were caused by tumors and weight loss in the HD males is a function of pharmacological activity of lorcaserin, the top dose of 100 mg/kg did not exceed the maximum tolerated dose (MTD) and the rat study was accepted as valid by the reviewer and eCAC (meeting minutes in Appendix A).

Lorcaserin resulted in numerous tumors in both male and female rats. These tumors occurred much earlier in lorcaserin treated rats. The first appearance of nodules in lorcaserin treated female was 11 to 13 weeks earlier than control females while in males they occurred 10 to 23 weeks earlier than control males.

Lorcaserin Dose, mg/kg	**0**	**10**	**30**	**100**
First tumor appearance, Weeks				
Female rats	33	24	20	20
Male rats	50	40	38	27

The two prominent tumors were mammary (adenocarcinoma and fibroadenoma) and brain. In females, the incidence of mammary fibroadenoma alone or in combination with adenocarcinoma were increased at every dose level ($p<0.0001$) with no safety margin (< 7x the MRHD). The incidence of adenocarcinoma was increased only in the HD females but numerically, the number of adenocarcinoma in LD and MD females was

higher than control and historical background. In males, the combined incidence of mammary fibroadenoma and adenocarcinoma was also significantly increased in MD and HD groups with a 5 fold safety margin.

Incidence of mammary tumors in male and female SD rats in the 2-year carcinogenicity study

Lorcaserin Dose, mg/kg	0	10	30	100
Mammary Tumors in Male Rats				
AUC Exposure Multiples	-	5x	17x	55x
Adenocarcinoma @ (historical range: **0 - 2%**)	0	0	2/65 (**3%**)	2/75 (**3%**)
Fibroadenoma @ (historical range: **0 - 3.3%**)	0	1/65 (**1.5%**)	4/65 (**6%**)	6/75 * (**8%**)
Combined	**0**	**1**	**6 ***	**8 ****
Mammary Tumors in Female SD Rats				
Exposure multiples	--	7x	24x	82x
Adenocarcinoma @ (historical range: **8.3 - 37%**)	28/65 (**43%**)	34/65 (**52%**)	35/65 (**54%**)	60/75 ** (**80%**)
Fibroadenoma @ (historical range: **22 - 54%**)	20/65 (**31%**)	47/65 ** (**72%**)	53/65 ** (**82%**)	45/75 ** (**60%**)
Combined	**40**	**56 ****	**61 ****	**70 ****

* p value <0.05, ** p value <0.01

Although the incidences of mammary tumors in the interim TK female rats were not included in the analysis, the incidence of adenocarcinoma was common finding in lorcaserin treated female rats.

Lorcaserin Dose, mg/kg	0	10	30	100
Mammary tumors in TK female SD Rats (n = 5-14/group)				
Adenocarcinoma	**0**/5	**7**/14	**6**/14	**7**/10
Fibroadenoma	3/5	5/14	8/14	5/10

Both fibroadenoma and adenocarcinoma were fatal in female rats. Division and eCAC recommended combining tumors originating from the same tissue. The sponsor also had analyzed mammary tumors individually and in combination. Combining benign (fibroadenoma) with malignant (adenocarcinoma) for statistical analysis was justified and logical for several reasons: **a)** a number of adenocarcinoma cases in female rats were reclassified to fibroadenoma, suggesting that distinguishing adenocarcinoma from fibroadenoma was difficult for the reviewing pathologist, **b)** both mammary fibroadenoma and adenocarcinoma originate from the same tissue with epithelial lineage, **c)** mammary tumor development in rodents is generally recognized to progress from hyperplasia to benign to malignant, **d)** combining mammary tumors in rats is an accepted practice used by other sponsors and the sponsor of this application.

As shown in the table below, the number of adenocarcinoma in the lorcaserin treated groups started decreasing after WK 96 even though more animals remained to be analyzed, suggesting the distinction between adenocarcinoma and fibroadenoma is not clear cut.

Changes in diagnosis of adenocarcinoma and fibroadenoma over time (from Wk 55 until the final NDA submission)

Mammary Adenocarcinoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
Week 55 update	0/1	2 / 4	5 / 7	13 / 15
Week 68 update	2 / 5	6 / 6	16 / 18	45 / 46
Week 88 update	16 / 28	27 / 38	36 / 45	72 / 74
Week 96 update	20 / 39	34 / 50	43 / 57	72 / 75
Week 104 update	30 / 65	35 / 65	35 / 65	63 / 75
Final update	29 / 65	35 / 65	36 / 65	62 / 75
Final NDA	28 / 65	34 / 65	35 / 65	60 / 75

Mammary Fibroadenoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
Week 55 update	0 /1	1 / 4	3 / 7	2 / 15
Week 68 update	1 / 10	1 / 11	5 / 18	20 / 46
Week 88 update	4 / 28	16 / 38	24 / 45	35 / 74
Week 96 update	10 / 39	27 / 50	36 / 57	36 / 75
Week 104 update	20 / 65	47 / 65	60 / 65	53 / 75
Final update	20 / 65	48 / 65	56 / 65	51 / 75
Final NDA	20 / 65	47 / 65	53 / 65	45 / 75

The lorcaserin-related increase in mammary tumors were hypothesized by the sponsor to be mediated indirectly by action of lorcaserin on prolactin since prolactin is a known intermediary hormone in rodent mammary tumorogenesis for several drugs including antipsychotic anti-dopaminergic drugs, such as haloperidol. This mode of action sounded reasonable at the time; however, the mechanistic studies provided by the sponsor thus far have failed to persuasively demonstrate a link between lorcaserin-emergent mammary tumors and prolactin, as it has been demonstrated for haloperidol. Lorcaserin had no effect on serum prolactin in female rats and reduced prolactin in males by 50% in the rat carcinogenicity study.

Serum Prolactin at week 55 and 56 in TK rats in the carcinogenicity study		
Lorcaserin, mg/kg	Serum prolactin at WK 55 in male rats	Serum prolactin at WK 56 in female rats, ng/ml
0	57.8 ± 32 *	115 ± 80
10	28.2 ± 12	130 ± 56
30	29.9 ± 11	106 ± 68
100	23.6 ± 16	117 ± 63

* p vales < 0.05

In multiple supportive GLP studies, haloperidol robustly increased serum prolactin under all circumstances (intact, ovariectomized) while lorcaserin did not. When rats were ovariectomized and replenished with estradiol and progesterone, a minimal increase in prolactin was seen with lorcaserin. Since the conditions of the study were rather contrived and nothing like those present in the rat carcinogenicity study, the scientific value of the study is questionable.
Dexfenfluramine, a nonselective serotonin agonist, also mildly increased prolactin levels supposedly by increasing brain serotonin, which lorcaserin does not. Dexfenfluramine does not cause mammary tumors in rodents despite the mild increase in prolactin, suggesting that a small increase in prolactin is unlikely to lead to mammary tumors.

Serum Prolactin Analysis				Study: (b) (4) 570002/TX08007		
	Sexually Intact Female			Ovariectomized Females		
Group:	Vehicle	Lorc	D-Fen	Vehicle	Lorc	D-Fen
Prolactin, ng/ml						
Day 9	15.0	6.2	42.10	10.7	3.1	21.50
Day 20	11.7	9.1	98.1 *	4.6	4.7	12.6 *

With no role definitively attributable to prolactin, one has to conclude that lorcaserin increased mammary tumors in rats by a direct or indirect mechanism independent of prolactin.
The second prominent tumor identified was the increased incidence of brain astrocytoma in HD male rats ($p<0.0001$). Numerically, the number of astrocytoma in MD males was greater than control and the historical background, and the Division and eCAC consider this numerical increase related to drug treatment.

Incidence of adenocarcinoma and schwannoma (all sites) in male rats

Lorcaserin dose, mg/kg	**0** n=65	**10** n=65	**30** n=65	**100** n=75
AUC Exposure Multiples	-	**5x**	**17x**	**55x**
Nervous System Tumors in Male Rats				
Astrocytoma @ (historical range 0 to 5%)	**1 (1.5%)**	**0**	**4 (6%)**	**8 ** (10.7%)**
Malignant Schwannoma @ (historical range, 0-3.3%)	**0**	**0**	**2 (3%)**	**9** (12%)**

The sponsor has argued that astrocytoma in rats derive from a microglial lineage compared to an astrocytic lineage as occurs in humans, and therefore astrocytoma in rats does not have a human counterpart. The issue of cell lineage of rat astrocytoma has been known for more than 20 years and the issue is unsettled as they are still officially classified as astrocytoma in rats. The sponsor has also suggested that the absence of a significant increase in astrocytoma in female rats indicates that astrocytoma is gender specific. Although this is a plausible explanation, the fact that female rats were dying 7 to 17 weeks earlier than males and had significantly shorter

duration of exposure than males also bears consideration. Also, brain exposure in female rats may have differed from males, because there appears to be a significant gender difference in plasma drug exposure in rats. It should be noted that there was a total of 20 cases of astrocytoma in the rat study of which only one was found in the control group, suggesting that astrocytoma was indeed consistently more common in rats administered lorcaserin.

Incidence of astrocytoma in the main and the interim TK animals (WK 52) in the 2-year rat carcinogenicity study

Lorcaserin dose, mg/kg		**0** n=65	**10** n=65	**30** n=65	**100** n=75
Main study, astrocytoma	M	1	0	4	8
	F	0	2	0	1
TK study, astrocytoma	M	0	0	0	1
	F	0	0	1	2
Total astrocytoma (20)		**1**	**2**	**5**	**12**

Risk assessment for astrocytoma is complicated by the fact that human brain lorcaserin exposure is unknown. Lorcaserin is a CNS drug and highly partitions to brain relative to plasma (35x the plasma in rats and 10x the plasma in monkeys), so a safety margin based on plasma levels is less acceptable than a safety margin based on brain levels of drug. If the brain exposure data in monkeys extends to humans (10x the plasma), then a sufficient safety margin exists for astrocytoma (14x the MRHD). But if one assumes a human brain partition similar to rats, the safety margin is reduced to only 5x the clinical dose, which raises our level of concern.

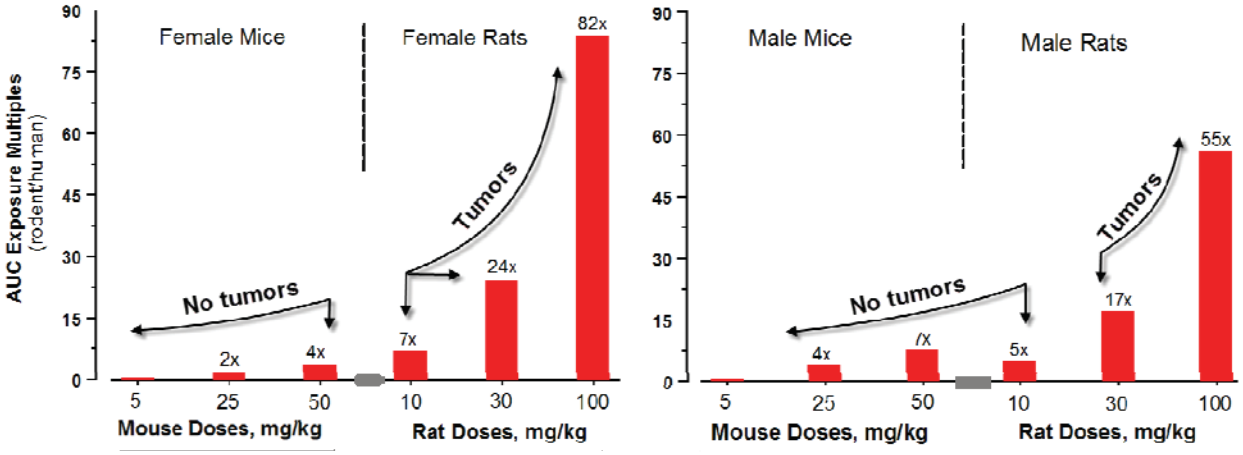
Exposure multiple based on estimated brain concentrations of lorcaserin in humans		
Brain : Plasma Ratio	10 mg/kg (No astrocytoma)	30 mg/kg (astrocytoma)
Assuming 10x →	**14 x**	50x
Assuming 25x →	**5 x**	17x

Other significant tumors associated with lorcaserin in male rats were skin (squamous cell carcinoma and subcutis fibroma) and malignant schwannoma, with drug-related increases occurring at 17-fold the clinical dose. The clinical relevance of these tumor types is uncertain. Also, hepatocellular adenoma and carcinoma occurred at 100 mg/kg, or 55x the clinical dose, which presents a minimal potential risk to human subjects.

Overall, lorcaserin was considered to be a non-genotoxic carcinogen in rats. Lorcaserin dose-dependently increased mammary tumors at all doses in female rats (<7x the MRHD) and at ≥ 30 mg/kg (≥ 17x the MRHD) in male rats. The incidence of astrocytoma was significantly increased in HD males (100 mg/kg) and was numerically

higher than the control and historical background in MD males (30 mg/kg). With no brain exposure data, the safety margin for astrocytoma is difficult to predict.

Lorcaserin exposure in mice and rats relative to the clinical dose of 10 mg BID, based on AUC (1.02 μg.h/ml)



The absence of significant increases in mammary tumors in mice at the maximum tolerated dose of 50 mg/kg is not considered evidence of a species specificity because the highest drug exposure in mice was equal to or less than the lowest drug exposure in rats. Furthermore, since lorcaserin partitions to the brain in mice (25x the plasma) less than that in rats (35x the plasma), the brain exposure to lorcaserin did not cover the same range seen in rats, suggesting that the absence of tumors in mice were primarily due to lower exposure to lorcaserin.

Renal Tubular findings in monkey

In the 12-month monkey study (2, 10, 50 and 125 mg/kg; 1, 6, 37 and 61x the clinical dose of 10 mg BID on AUC), lorcaserin resulted in minimal to moderate renal tubular regeneration and degeneration at ≥ 10 mg/kg in monkeys. The severity and incidence of tubular regeneration and degeneration increased with dose and persisted at the end of the 4-week recovery in some animals at 50 and 125 mg/kg. Lower doses were not included in the recovery phase. Examination of renal slides from the rodent studies were not consistent. Some early studies (i.e. 3-month rat) had identified a renal signal but there were no such findings in the 6-month or the 2-year rat carcinogenicity study. Although rats are prone to glomerulosclerosis, cynomolgus monkeys are not, thus making the renal signal in monkeys an important adverse effect. The reason for concern stems from the high concentration and function of $5HT_{2A}$ receptors in the kidney. Activation of $5HT_{2A}$ has been shown to result in tubular hypertrophy in rodents. The relevance of renal degeneration at this point is not certain since there has been no notable renal signal in clinical studies. Whether there are renal tubular changes in humans is currently unknown.

Nonclinical safety issues relevant to clinical use

The most prominent non-clinical finding of potential relevance to chronic use of lorcaserin in human subjects is the increased incidence of mammary and brain tumors in the 2-year rat carcinogenicity study. Prolactin as the intermediately hormone for mammary tumors is a plausible explanation but studies provided by the sponsor to date have failed to show a clear relationship between lorcaserin and prolactin. If the effect of lorcaserin on mammary tissue is by direct activation of off target receptors ($5HT_{2A}$ or $5HT_{2B}$), resembling that of $5HT_{2B}$ activation of heart valves, then the long-term risk to humans is substantial.

The high incidence of astrocytoma in male rats at $\geq$ 30 mg/kg is a concern due to the absence of a reliable estimate of safety margins. Although the cell lineage and site concordance of rat astrocytoma to humans remains unresolved, the fact that lorcaserin is a CNS active drug with significant partitioning to brain tissue makes it a long-term clinical risk unless a reliable safety margin can be established or a mode of action that is irrelevant to human biology is demonstrated.

2 Drug Information

2.1 Drug: Lorqess ®

2.1.1 CAS Registry Number: 856681-05-5

2.1.2 Generic Name: Lorcaserin hydrochloride

2.1.3 Code Name: APD356 hemihydrate, AR226173 hydrochloride hemihydrate

2.1.4 Chemical Name:

(R)-8-Chloro-1-methyl-2,3,4,5 tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate

2.1.5 Molecular Formula/Molecular Weight: $C_{11}H_{15}Cl_2N.5H_2O$, MW (b) (4) g/mol

2.1.6 Structure:

(b) (4)

2.1.7 Pharmacologic class: Serotonin receptor 2 C (5HT2C) agonist

2.2 Relevant IND/s, NDA/s:

IND 69888 (Arena pharmaceuticals),
Sibutramine (IND 27,624, NDA 20-632, Abbott/Knoll)
IND (b) (4)
Dexfenfluramine (NDA 20344)

2.3 Clinical Formulation: 10 mg lorcaserin hydrochloride tablets

2.3.1 Drug Formulation

Active ingredient: 10.4 mg of APD356 Hemihydrate (10.4 mg tablets)

Inactive ingredients: Silicified microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose Na, magnesium stearate and [redacted]

Component	Grade	Function	mg/tablet	%w/w
Core				
Lorcaserin HCl Hemihydrate	Arena	Drug substance	10.4[a]	10.4
Silicified microcrystalline cellulose[b]	[redacted]	[redacted]		
Hydroxypropyl cellulose	NF			
Croscarmellose sodium	NF			
Magnesium stearate	NF			
[redacted]				
	[redacted]			
	USP			

[a] Equivalent to 10 mg lorcaserin HCl.

2.3.2 Comments on Novel Excipients: All the excipient are GRAS

2.3.3 Comments on Impurities/Degradants of Concern: There are several very minor impurities in the product of which only the [redacted]) exceeded ≥ [redacted] The potential genotoxicity of the impurities were examined using MultiCASE software that evaluates for structural activity relationship of the impurities to the available database. Three of the 12 minor impurities [redacted] were found to have the potential for genotoxicity. Since the exposures to these impurities were less than the daily allowance of [redacted] under the genotoxic impurities guidance [redacted] no specific safety analysis is required and thus deemed to be safe. Residual solvents [redacted] in the drug substance were less than the accepted ICH limits.

2.4 Proposed Clinical Population and Dosing Regimen: [redacted]

2.5 Regulatory Background. Lorcaserin IND was submitted to FDA on May 25, 2004 with some clinical experience in trials carried out in the UK. The rat and mouse carcinogenicity study protocols were submitted on Jan 25 of 2005 and May 23, 2006,

respectively. Upon initiation of mouse carcinogenicity study, the unexpected rise in mortality within 16 days administration of 100 mg/kg of lorcaserin, the sponsor requested dose adjustment to 50 mg/kg. Mid-way (63 weeks) through the rat carcinogenicity study the sponsor submitted a 15-day safety report on May 31, 2007 (#0047), showing a high incidence of mammary tumors in females and brain tumors in male and female rats. At the time of the submission, the sponsor was 8 months to the 2-year clinical study #3182. The Division recommended changes to the consent form to reflect the preliminary data describing higher than normal incidence of mammary tumors and brain tumors in the ongoing study. The Division requested bimonthly updates of mammary and brain tumor incidence as histopathology evaluation of dead rats became available (page 148). In the 3rd bimonthly update on March 10, 08 (WK 96) with all the HD females necropsied, there was an apparent dose-dependent increase in incidence of malignant mammary tumors (adenocarcinoma) in female rats at all doses. The division met with the sponsor to discuss the mode of action for mammary tumors and the possibility of a clinical hold. The Division allowed the ongoing phase 3 studies to continue since the data from other groups in the rat study were still missing, prolactin was a reasonable explanation of mode of action, and there were no mammary tumors in mice. The Division requested a draft report of the rat and mouse carcinogenicity studies as soon as possible and requested changes to the clinical protocol to include analysis of human serum prolactin. The bimonthly updates continued until the rat study was completed and draft report of the rat study was submitted (Feb 3, 2009).

3 Studies Submitted:

Acute toxicology studies in rats and monkeys
PK, TK studies including brain distribution in mice, rats and monkeys
Standard battery of *in-vitro* and *in-vivo* genotoxicity tests
Mechanistic studies exploring role of prolactin
3- and 6-month SD rat toxicology studies
3-month dose ranging study in CD-1 mice
3- and 12-month cynomolgus monkeys studies
2-year rat and mouse carcinogenicity studies
Rat fertility and reproductive studies
Rat and rabbit embryofetal developmental studies
Rat pre- and post-developmental studies

3.1 Studies Reviewed: All the above

3.2 Studies Not Reviewed: None

3.3 Previous Reviews Referenced: Toxicology studies up to 3-months in mice, rats, and monkey studies, genotoxicity studies as well as some of the reproductive toxicology studies were review under lorcaserin IND 69,888.

4 Pharmacology

4.1 Primary Pharmacology

The FDA briefing document for the September advisory committee meeting reviews additional information regarding serotonin receptor selectivity and the nonclinical neurological and cardiac assessment of lorcaserin.

Lorcaserin is a chiral compound (r-racemate, purity >98%) isolated from S-racemate. *In-vivo* and *in-vitro* studies have not found any chiral inversion of lorcaserin. Rats pretreated with $5HT_{2C}$ antagonist (SB242084) had reduced response to lorcaserin suggesting that the appetite suppressant effect of lorcaserin is mediated via $5HT_{2C}$ receptor (Ki 23 nM). Lorcaserin (R-configuration) and its S-enantiomer binding have been tested for affinity to 76 other receptor types, ion channels and transporters (appendix B). The Neither enantiomers displayed significant inhibition of non-serotonergic receptors at tested concentrations of 1 μM. Lorcaserin has approximately 14 fold and 100 fold selectivity over $5HT_{2A}$ and $5HT_{2B}$ receptors, respectively. Lorcaserin was selective to $5HT_{2C}$ in rats but in monkeys, lorcaserin affinity to $5HT_{2C}$ and 5HT2A and $5HT_{2B}$ were similar. Since $5HT_{2C}$ are primarily located in the CNS, the potential non-CNS effect is likely to be a consequence of central effects of lorcaserin in rats.

Lorcaserin-mediated increase in inositol phosphate (IP) accumulation in HEK293 cells expressing 5-HT2 receptors.[1]

Compound	$5\text{-}HT_{2A}$ EC_{50} (nM) [± SEM]	$5\text{-}HT_{2A}$ Cmpd Max/5-HT Max [± SEM]	$5\text{-}HT_{2B}$ EC_{50} (nM) [± SEM]	$5\text{-}HT_{2B}$ Cmpd Max/ 5-HT Max [± SEM]	$5\text{-}HT_{2C}$ EC_{50} (nM) [± SEM]	$5\text{-}HT_{2C}$ Cmpd Max/ 5-HT Max [± SEM]
5-HT	122 [±4]	1.00	35 [±3]	1.00	22 [±1]	1.00
Lorcaserin	123 [±15]	0.84 [±0.12]	1,000 [±80]	1.0 [±0.004]	9 [±1]	1.0 [±0.004]

[1]Values represent the mean ± SEM of EC50 determinations. $5\text{-}HT_2$ Compound Max/5-HT Max refers to ratio of the maximal stimulation of inositol phosphate accumulation (percent control) observed with the highest concentration of test compound (10 μM) divided by the maximal stimulation of inositol phosphate accumulation observed in the presence of the highest concentration of 5-HT (10 μM) obtained in the same experiment.

Summary of lorcaserin binding affinities (K_i) for human and rat $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$ receptors

$h5\text{-}HT_{2A}$ K_i (nM) [±SD]	$r5\text{-}HT_{2A}$ K_i (nM) [±SD]	$h5\text{-}HT_{2C}$ Ki (nM) [±SD]	$r5\text{-}HT_{2C}$ K_i (nM) [±SD]
149 [±34]	150 [±35]	23 [±4]	15 [±3]

In addition to CNS, 5HT2A is also expressed in platelets, fibroblast and cardiovascular cells as well as the peripheral neuronal cells. Lysergic acid (LSD) exhibits agonist

exposure at the NOAEL dose of 50 mg/kg in the mouse carcinogenicity study was 4 to 7x the clinical dose of 10 mg/kg BID. As noted earlier, most of the changes in BW in rats and monkeys were seen at ≥ 50 mg/kg with exposure multiples of ≥ 22x the MRHD. The primary safety concern in the mouse study was the apparent and unanticipated steep dose response curve for toxicity. Whereas mice tolerated a 50mg/kg dose for 2 years without apparent adverse effects, a doubling of exposure to 100mg/kg resulted in rapid and unexplained deaths in a number of mice. As discussed earlier, 100 mg/kg had not resulted in sharp increase in mortality in earlier studies.

Rat Carcinogenicity Study

Sprague-Dawley rats were treated with 10, 30 and 100 mg/kg of lorcaserin for 2-years in the main study. After collection of plasma samples for TK analysis at WK 52, lorcaserin treatment was extended for 2 to 4 weeks for analysis of serum prolactin, estradiol, TSH and immunohistochemistry staining of prolactin positive cells in the mammary and pituitary gland. Lorcaserin exposure in male rats achieved a 5x, 17x, and 55x multiple at the LD, MD, and HD compared to the clinical dose. Exposure in female rats was higher, achieving a 7x, 24x, and 82x multiple of the clinical dose.

Oral administration of lorcaserin significantly decreased the survival rate in the male and female rats. The number of live rats and survival rate at the end of the 2-year rat carcinogenicity study is shown in table below.

2-Year Rat study	Sex	Lorcaserin Dose, mg/kg			
		Controls (H_2O)	10	30	100
Survival rate, %	M	33.8%	24.6%	30.7%	5.3%
	F	35%	18.4%	7.7%	0%

Surviving females of all dose groups and the HD males were necropsied around week 96/99, in accordance with ECAC's recommendations. Clonic convulsion occurred early in the study more in females (~1.5 fold higher exposure) than in males (2C male, 1 LD, 3 HD male, 1 LD female and 13 HD females), corresponding to higher lorcaserin exposure. Deaths in females were primarily due to mammary tumors palpable as early as WK 42 while the first evidence of palpable tumors in male rats occurred much later around WK 61. Deaths in HD males were due to brain, skin, mammary tissue, and neuronal tissue (schwannomas) tumors. These tumors occurred much earlier in lorcaserin treated rats. The first appearance of nodules in lorcaserin treated female rats was 11 to 13 weeks earlier than controls while in male rats they occurred 10 to 23 weeks earlier than control males.

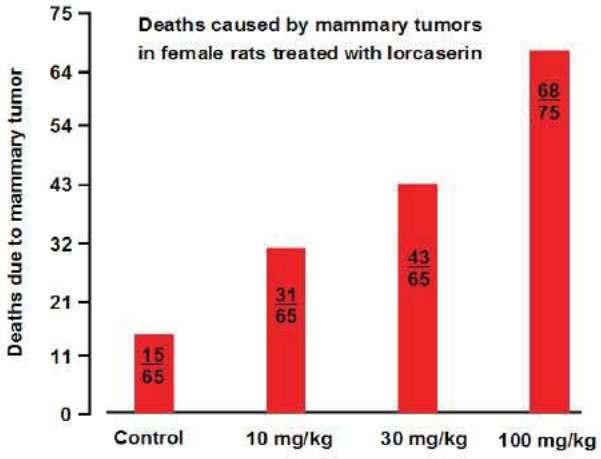
Lorcaserin Dose, mg/kg	0	10	30	100
First tumor appearance, Weeks				
Female rats	33	24	20	20
Male rats	50	40	38	27

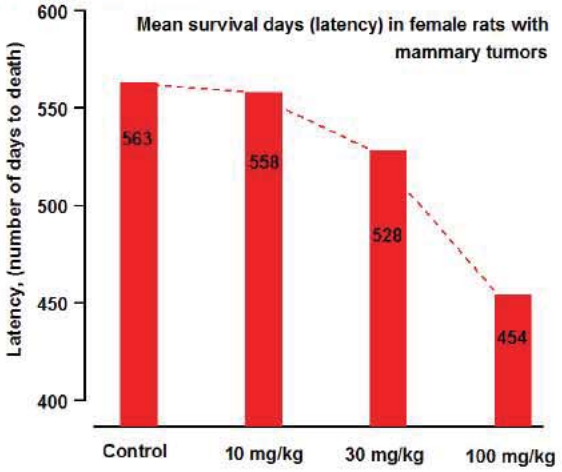
The number of deaths caused by mammary tumors increased in females in a dose-dependent manner while latency decreased with increase in lorcaserin dose. The higher the lorcaserin dose, the more females died of mammary tumor and at an earlier

time. Furthermore, higher doses were associated with multiple tumor cites for both fibroadenoma and adenocarcinoma in female rats. The number of deaths due to both fibroadenoma and adenocarcinoma in control, LD, MD and HD are shown in table below. Looking at the table below closer, one can readily see that even the low dose of lorcaserin (31 deaths) was causing significant more deaths than control females (15 deaths due to mammary tumor). Two HD females (#4202 and 4212) that were euthanized in extremis due to mammary tumor (official cause of death) had no record of mammary tumors in the histopath evaluation.

Lorcaserin Dose, mg/kg	0	10	30	100
Number of death due to mammary tumors in female rats				
Number of animals per group	65	65	65	75
Death due to adenocarcinoma and or fibrado	13	25	29	50
Death due to fibroadenoma	2	6	14	10
Combined	**15**	**31**	**43**	**68**

Graphical representation of deaths due to mammary tumors in female rats and number of days animals survived before death are represented below.





Lorcaserin resulted in significant BW reduction in male at 100 mg/kg (10% at WK 51 to 28% at WK 99) but with little effect in females. The sensitivity of male rats to lorcaserin is consistent with other rat studies. The decrease in food intake was variable in both sexes but slightly lower in males. Since the decrease in BW and food intake is an expected pharmacological effect of lorcaserin, the significant decrease in BW was not regarded as sign of toxicity.

Oral administration of 10, 30 and 100 mg/kg of lorcaserin resulted in significant lorcaserin related tumors in the 2-year rat carcinogenicity study. The prominent tumors identified in the study were mammary (fibroadenoma/ adenocarcinoma) and brain tumors (astrocytoma) in rats. Other notable tumors in male rats included hepatocellular adenoma/carcinoma, skin fibroma (subcutis) and squamous cell carcinoma, schwannoma (all sites) and follicular cell adenoma in the thyroid gland.

Neoplastic tumors in male rats treated with lorcaserin [a]
(n= 65/sex/C, LD, MD and n=75/sex/HD)

Tumors in male rats		Lorcaserin dose, mg/kg				Trend Analysis
		0	10	30	100	
Brain	astrocytoma	1	0	4 NS	8[b] p=0.0019	< 0.0001
Liver	hepatocellular carcinoma	1	3	2	4	NS
	hepatocellular adenoma	1	1	2	6 p=0.0302	p=0.0033
	combined	**2**	**4**	**4** NS	**10** p=0.0048	p=0.0012
Mammary	adenocarcinoma	0	0	2	2 NS	p=0.0464
	fibroadenoma	0	1	4 NS	6 NS	p =0.0001
	combined	**0**	**1**	**6** p=0.0131	**8** p=0.0009	p=0.0003
Skin, subcutis	benign fibroma	3	7 NS	11 p=0.0175	17 p<0.0001	p <0.0001
Skin	squamous carcinoma	0	0	4 NS	5 p=0.014	p=0.0030
Schwannoma, all sites		0	0	2 NS	9 p<0.0037	p< 0.0001
Thyroid	follicular cell adenoma	0	5 p=0.028	4 NS	8 p=0.0011	p=0.0035

[a] The statistical analysis and p values in the table were provided by the FDA statistician, Dr. Mathew Jackson.
[b] One of the astrocytomas in the HD males was reclassified as infarct due to lymphocytic leukemia in an amendment to the NDA
NS = not significant (p > 0.05)

Neoplastic tumors in female rats treated with lorcaserin
(n= 65/sex/C, LD, MD and n=75/sex/HD)

Tumors in female rats		Lorcaserin dose, mg/kg				Trend Analysis
		0	10	30	100	
Brain	astrocytoma	0	2	0	1	NS
Mammary	adenocarcinoma	28	34 NS	35 NS	60 p<0.0001	p < 0.0001
	fibroadenoma	20	47 p<0.0001	53 p<0.0001	45 p<0.0001	p < 0.0001
	combined	**40**	**56** p=0.0004	**61** p<0.0001	**70** p<0.0001	p<0.0001

[a] The statistical analysis and p values in the table were provided by the FDA statistician, Dr. Mathew Jackson.
NS = not significant (p > 0.05)

Mammary tumors

Lorcaserin dose-dependently increased both mammary adenocarcinoma (females) and fibroadenoma (female and male rats, trend analysis). The incidence of adenocarcinoma was significantly increased in female rats at 100 mg/kg (80%, HD) relative to the concurrent control. The incidence of adenocarcinoma in females at 10 (52%, LD) and 30 mg/kg (54%, MD) was above the concurrent control (43%) and (b) (4) historical control values (8.3 to 37%, x=24%). The incidence of fibroadenoma alone was significantly increased at all doses of lorcaserin (LD: 52%, MD: 53% and HD: 60%) relative to the control (31%) with safety margin less than 7x the clinical dose of 10 mg BID based on AUC. The (b) (4) historical control for fibroadenoma in females ranged from 22 to 54% with mean value of 36%. The combined incidence of adenocarcinoma and fibroadenoma was statistically significant ($p<0.0001$) at all lorcaserin doses (C:61%, LD:86% MD:94% and HD:94%). The combined incidence of fibroadenoma and adenocarcinoma was significantly increased with all doses of lorcaserin in female rats. Both adenocarcinoma and fibroadenomas were the predominate causes of deaths in lorcaserin treated female rats. Although the incidence of adenocarcinoma in the interim TK female rats was not included in the analysis, there were more incidences of adenocarcinoma in the lorcaserin treated than control TK female rats.

Lorcaserin Dose, mg/kg	0	10	30	100
Mammary tumors in TK female SD Rats (n = 5-14/group)				
Adenocarcinoma	**0**/5	**7**/14	**6**/14	**7**/10
Fibroadenoma	3/5	5/14	8/14	5/10

Interestingly, two HD females (4202 and 4212) that had nodules in the auxiliary area with the official cause of death due to consequence of mammary tumor, had no evidence of mammary tumor in the histopath results. It appears that the nodules were lost during data collection.

In male rats, the incidence of mammary fibroadenoma was significantly increased at only at100 mg/kg (8%) but was above the control (0%) and (b) (4) historical controls data (0 to 2%) in the MD males (3%). The combined incidence of fibroadenoma and adenocarcinoma was significantly increased in both MD and HD male rats. A peculiar finding in male rats was the high incidence of feminization defined as partial or complete replacement of typical lobulo-alveolar appearance of the mammary gland with ductuloalveolar appearance was high in all treated males (LD: 64%, MD: 69% and HD: 63%) as well as controls (48%). The significance and possible cause of this is not clear.

Mid way through the rat study, the sponsor submitted a 15-day safety report regarding higher than normal incidence of mammary tumors in lorcaserin treated female rats. This lead to bimonthly updates from that time forward. With each report, the pathologist identified a higher incidence of adenocarcinoma in groups treated with lorcaserin (Main and TK) compared to the control group. At week 96, when nearly all HD and the majority of MD female rats were evaluated histologically, there was an apparent dose-related increase in incidence of adenocarcinoma in female rats. The Division considered putting the on-going phase 3 clinical studies on hold in 2008. But since the

rat study was incomplete and the number of tumors could balance out as more animals necropsied and the ongoing mouse study was negative, the plausible prolactin-based hypothesis for the tumorigenic mode of action appeared logical, the Division decided to continue the ongoing phase 3 clinical trials and asked for mechanistic studies exploring the role of prolactin. In the final tally the incidences of adenocarcinoma (WK 104) in the MD and HD females were revised lower than earlier reports (WK 96). It appears that the decrease in the number of adenocarcinoma after week 96 were due to reclassification of adenocarcinoma to fibroadenoma which was itself also down graded in the later updates.

Changes in diagnosis of adenocarcinoma and fibroadenoma over time (from Wk 55 until the final NDA submission)

Mammary Adenocarcinoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
Week 55 update	0/1	2 / 4	5 / 7	13 / 15
Week 68 update	2 / 5	6 / 6	16 / 18	45 / 46
Week 88 update	16 / 28	27 / 38	36 / 45	72 / 74
Week 96 update	20 / 39	34 / 50	43 / 57	72 / 75
Week 104 update	30 / 65	35 / 65	35 / 65	63 / 75
Final update	29 / 65	35 / 65	36 / 65	62 / 75
Final NDA	28 / 65	34 / 65	35 / 65	60 / 75

Mammary Fibroadenoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg	30 mg/kg	100 mg/kg
Week 55 update	0 /1	1 / 4	3 / 7	2 / 15
Week 68 update	1 / 10	1 / 11	5 / 18	20 / 46
Week 88 update	4 / 28	16 / 38	24 / 45	35 / 74
Week 96 update	10 / 39	27 / 50	36 / 57	36 / 75
Week 104 update	20 / 65	47 / 65	60 / 65	53 / 75
Final update	20 / 65	48 / 65	56 / 65	51 / 75
Final NDA	20 / 65	47 / 65	53 / 65	45 / 75

The reclassification of the mammary tumors from adenocarcinoma to fibroadenoma by the CRO pathologist suggests that a) there are significant histological similarities between fibroadenoma and adenocarcinoma that are not easily distinguishable, b) a reclassification rule was applied biased toward fibroadenoma, c) tumors were initially classified in error.

Prolactin has been known to be the intermediary hormone in the development of mammary tumors in rodents. Several drugs including CNS active antipsychotic anti-dopaminergic compounds cause mammary tumors in rats by indirectly altering pituitary dopamine in rodents. Although these compounds also increase serum prolactin in humans, a relationship between hyperprolactinemia and mammary tumors in humans has not been established.

To address the hypothesis that the lorcaserin-related increase in mammary tumors in rats was due to lorcaserin-induced increase in serum prolactin, the sponsor evaluated serum prolactin and the number of prolactin positive staining cells in the pituitary and

mammary tissue in the TK rats in the carci study. Serum analysis found prolactin levels to be similar among groups in female SD rats (~115 ng/ml). The levels in treated males was reduced by 50 % relative to control males. The numbers of pituitary prolactin positive staining cells were similar among males while MD and HD females had slightly higher incidence than control females. The incidence of mammary prolactin positive cells in the HD was lower than the corresponding control.

Additional single dose (males) and multiple dose mechanistic studies in intact and ovariectomized female rats with or without hormone supplement were conducted. The single and multiple doses of lorcaserin (10 to 100 mg/kg) consistently failed to show a significant rise in serum prolactin levels in female rats at any time period (2 to 24 hrs post dose) whether intact or ovariectomized. In contrast, animals treated with positive control, haloperidol (dopamine antagonist) saw a robust and significant rise in serum prolactin levels in intact and ovariectomized rats, consistent with prolactin's role as a central hormone for haloperidol-induced mammary tumors. Contrary to lorcaserin, dexfenfluramine, a non-selective 5HT agonist, increased serum prolactin presumably by increasing brain serotonin levels. However, dexfenfluramine does not increase mammary tumors in rats (albeit a different strain), suggesting that perhaps a robust chronic increase in prolactin is needed for rats to develop mammary tumors as is the case for haloperidol. The lack of lorcaserin on prolactin was further supported by the absence of any change in pituitary and mammary immunohistochemistry staining in the 28-day study in female SD rats.

There is some evidence from the single dose study that lorcaserin may have a small acute effect on prolactin in male but not female rats, even though there was a 50% decrease in prolactin in males after 54 weeks of dosing. The acute rise in prolactin in the single dose male rat study lead to the hypothesis that reproductive hormones in females were masking detection of an increase in prolactin with lorcaserin. To achieve a controlled level of reproductive hormones, females were ovariectomized then replenished with specified doses of estradiol+progesterone. Under these conditions, lorcaserin increased prolactin levels a marginal degree over the robust increase observed with the hormones. The relevance of the finding is questionable because the degree of increase in prolactin was marginal, and occurred under experimental conditions that bear little resemblance to those encountered by the rats tested in the carcinogenicity study. Interestingly, the estradiol level (~ 50 pg/ml) in the ovariectomized rats before hormone replenishment for some reason was equivalent or higher than normal estradiol levels in intact animals (2 to 50 pg/ml), raising concern regarding the validity of these non-GLP studies carried out at the sponsor's own labs, which appears inconsistent with the expectation of reduced estrogen with ovariectomy.

Overall, the effect of lorcaserin on serum prolactin in rats is consistent with the clinical observation that a small increase in prolactin may occur for a short time following a dose of lorcaserin but is not sustained under chronic conditions. The acute effect of lorcaserin is consistent with the published literature showing that repeated dosing with a serotonin 5HT2A/C agonist can quickly lead to rapid tolerance in rats (Aulakh CS et al 1994) and humans (Greenberg J et al, 1996). Together these studies suggest that a lorcaserin related increase in prolactin, if any, is likely to be short lived with minimal consequences. It is the reviewer's opinion that the sponsor failed to show a meaningful

role for prolactin in the development of mammary tumors with lorcaserin in rats. With no role ascribed to prolactin, human risk becomes difficult to predict. The sponsor has to show a link between prolactin and lorcaserin if they want to explain mammary tumors via this mode of action. Since lorcaserin's effect may be independent of prolactin (e.g., a direct effect on serotonin receptors in mammary tissue), the sponsor is advised to explore other modes of action to explain the drug-related increase in mammary tumors and their clinical relevance.

Brain Astrocytoma

Lorcaserin also significantly increased brain astrocytoma in male rats in a dose-dependent manner (trend p<0.003). The incidence of astrocytoma was significant in HD (10.67%, 55x the clinical dose of 10 mg BID based on AUC) and numerically higher in the MD male rats (6.15%) than concurrent (1%) and (b) (4) historical control data (0-5%). The increase at the MD and HD is considered related to lorcaserin. The total number of astrocytoma was unusually high in the lorcaserin treated rats overall (19 incidences) than the control rats (1 incidence).

Brain astrocytoma in 2-year carcinogenicity study in SD rats		Lorcaserin dose, mg/kg			
		0	**10**	**30**	**100**
Main study, astrocytoma	M	1/65	0/65	4/65	8/75
	F	0/65	2/65	0/65	1/75
TK study, astrocytoma	M	0/6	0/14	0/11	1/14
	F	0/5	0/14	1/14	2/10
Combined		**1**	**2**	**5**	**12**

In an attempt to identify the lineage of the brain astrocytoma in male rats, 19 identified brain tumors in the carci study were processed by immunohistochemistry staining (ED1, GFAP and MHCII). Out of 19 tumors, only 13 of the new slides had astrocytoma. Seven of the tumors were missed in the new slides. This finding alone suggests that these small tumors can be easily missed and perhaps more sections of brain tissue should be prepared if the slides are re-examined. All the 13 slides stained positive for ED1 and none for GFAP and only one was positive for MHCII suggesting a macrophage/histiocyte lineage (ED1). There are published reports suggesting that astrocytomas in rats are from macrophage linage vs. glial lineage in humans. The issue of lineage is unresolved, although this has been known for over 20 years and they are still classified as astrocytoma. Brain levels of lorcaserin can be as high as 35x the plasma levels in rats (13 - 35x) and monkeys (10x), which raises overall concern. With no clinical data, use of monkey brain exposure as a surrogate for humans is reasonable but since the brain exposure in monkeys can vary from 10 to 23 fold, the safety margin is not much improved. Wide variability in brain partitioning among and within species makes calculation of safety margins based on monkey brain exposure unreliable. Lorcaserin significantly increased the incidence of astrocytoma in HD male rats (55x the clinical dose, based on plasma AUC), and numerically in the MD males (greater than background). A safety assessment based on brain levels between animals and humans is the most appropriate, but with no human brain exposure data available and variability in brain exposure among species, a more conservative approach to safety assessment

should be considered. If the brain levels in humans are similar to monkeys, the safety margin is about 17x the MRHD but if the brain exposure in humans is similar to rats, the safety margin would be about 5x the MRHD, and is thus a clinical concern.

Exposure multiple based on estimated brain concentrations of lorcaserin in humans		
Brain : Plasma Ratio	10 mg/kg (**No** astrocytoma)	30 mg/kg (astrocytoma)
Assuming 10x →	**14 x**	50x
Assuming 25x →	**5 x**	17x

Skin fibroma and Squamous cell carcinoma

There was a statistically significant positive dose-dependent trend for both skin fibroma and squamous cell carcinoma in males but not in females. In the pairwise comparison the incidence of skin fibroma was statistically increased in MD (16.9%) and HD (22.7%), the incidence in the LD males (10.8%) was above the concurrent control (4.6%) and the (b) (4) historical control data (0 to 5%). The number of squamous cell carcinoma in MD (4/65, 6.15%) and HD (5/75, 6.67%) males were above the control and (b) (4) historical control data (0 to 5%) but significant only in the HD males. The skin in these animals was visibly ulcerated and increased with dose. The skin effect may represent an off-target activation of receptors by lorcaserin (i.e. $5HT_{2A,}$). It is unclear why they were more common in males. Whether shortened duration of exposure in female rats had a role is not clear. Skin tumors can be easily monitored and treated, so the clinical risk compared to a brain tumor is lower, but nevertheless of concern given the clinical indication being considered.

Malignant schwannomas

Lorcaserin also resulted in higher incidence of malignant schwannomas (all sites combined) in male rats at 30 (2/65) and 100 (9/75, $p<0.004$) mg/kg. There was no schwannomas in the control or LD males (NOAEL = 10mg/kg, or 4.8x the clinical dose of 10 mg BID). Schwannomas across all locations (kidney, eyes thoracic and abdominal cavity, bone, skin subcutis) were characterized as small round neoplastic cells with unclear border. In at least 3 of the HD male rats their metastasis were seen in the lungs and thymus. Overall, the incidence of combined schwannomas in the HD males ($p=0.06$) was above the (b) (4) historical control suggesting that schwannomas were lorcaserin-related. The acceptability of a 5x safety margin must be weighed against the clinical benefits afforded by lorcaserin.

Liver tumors

Lorcaserin dose-dependently increased the incidence of hepatocellular adenoma and carcinoma in male rats but the increase was significant only in the HD males in the pair wise comparisons. There was no drug-related increase in hepatic tumors in females. The incidence of both adenoma and carcinoma in HD (adenoma 8% and carcinoma 5.3%) which were greater than the (b) (4) historical data for adenoma (0-5.7%) and carcinoma (0 to 1.7%) were likely drug metabolism related. The increase in hepatic tumors was likely to metabolic adaptation to high drug load in liver leading significant induction of liver metabolizing enzymes, as evidenced by the greater degree of

hepatocellular hypertrophy in HD males. Females at the high dose had a lesser degree of hepatocellular hypertrophy and displayed basophilic foci of cellular alterations (preneoplastic). The disproportionate effect on the liver in males may reflect greater induction of drug-metabolizing enzymes, as reflected by the 1.5 fold decrease in drug exposure in males. With no significant increase in pair wise comparison and high exposure multiples (> 55x the clinical dose of 10 BID on AUC basis), the potential risk to humans is deemed minimal.

Thyroid Tumors
The trend for incidence of thyroid follicular cell adenoma was significant in lorcaserin treated males (0/65, 5/65, 4/65 and 8/75 for C, LD, MD and HD male, respectively). No significant thyroid tumors were noted in females. The profile of thyroid and liver tumors appears similar, as a possible adaptation to increased T3 turnover and high liver drug load.

To summarize carcinogenicity studies, lorcaserin significantly increased the incidence of mammary tumors (fibroadenoma and/or adenocarcinoma) at all doses in females and MD and HD males and brain tumors (astrocytoma) in HD males in the 2-year rat carcinogenicity study. There was no safety margin for mammary fibroadenoma in females (< 7x the MRHD). Both fibroadenoma and adenocarcinoma were fatal. Since the mechanistic studies failed to persuasively demonstrate prolactin as the intermediary hormone as is the case for antipsychotic drugs, the mechanism remains unresolved and clinically relevant. With regards to astrocytoma in males, a safety margin to the NOAEL was identified (5x to 17x the MRHD) based on plasma exposure. A safety margin based on comparative brain levels of lorcaserin is most appropriate because lorcaserin significantly accumulates in the brain (drug pharmacology target). Because brain levels of lorcaserin in human subjects is not known and there is a significant variability in brain exposure among species, the estimated safety margin of 5x to 17x is somewhat unreliable and may be greater or smaller depending on the degree of drug partitioning in the human brain. Lorcaserin also dose-dependently increased liver adenoma, benign skin fibroma, benign thyroid adenoma and malignant schwannoma in male rats. The NOAELs for these tumors provides a safety margin of 5x to 17x. Although lorcaserin did not result in neoplasm in mice, the AUC exposure at the high dose (50 mg/kg, 4 to 7x the MRHD) was less than the exposure at the lowest dose of lorcaserin in rat study, therefore absence of neoplastic tumors in mice might be due to low lorcaserin exposure.

Reproductive Studies
The reproductive effect of lorcaserin was evaluated in rats and rabbits. Lorcaserin doses of 5, 15 and 50 mg/kg were given to male (before and after mating) and female rats (before and after mating DG 7) for fertility assessment. Lorcaserin slightly reduced BW gain (~7%) in males at 50 mg/kg but was unremarkable in female rats. Lorcaserin doses up to 50 mg/kg had no effect on fertility parameters in male or female rats. The NOAEL for embryonic development and fertility was 50 mg/kg.
In the Seg II rat study, lorcaserin doses of 10 and 50 mg/kg (DG7 to DG17) resulted in slight but significant decrease in maternal BW. The decrease in BW correlated with a decrease in food intake in dams. There was no statistically significant change in fetal external, visceral or skeletal malformations. Minor fetal variations were considered

incidental. The maternal NOAEL was selected as 10 mg/kg (8x the MRHD) in rats due to weight loss at 50 mg/kg, which was also selected as fetal NOAEL (48x the MRHD).

The fetal developmental study in New Zealand white lorcaserin doses of 20, 60 and 200 mg/kg were administered to pregnant rabbits from DG 7 through DG 19. One HD and one LD dam aborted on Day 23 and 26, respectively while one MD female delivered prematurely on GD 28. The incidence of spontaneous abortion in LD and HD was within the historical control (0 to 6.9%). Lorcaserin significant decreased BW and food intake of dams at 200 mg/kg. Gross necropsy findings were limited in one LD, MD and HD dam. These animals had either empty implantation sites or early resorption in the case of MD and LD females. Overall, there were no statistically significant differences in C-section parameters, total fetal external, visceral or skeletal malformations or developmental variations between lorcaserin treated animals and control. However, there was incidence several variations i.e. heart and greater vessel anomaly in 2 HD fetuses were greater than historical background. Based on significant decrease in BW, the NOAEL for maternal toxicity was 60 mg/kg (0.6x the MRHD). Even though fetal variations in the HD were not significant, the reviewer selected 60 mg/kg (0.6x the MRHD) as the NOAEL for fetal toxicity due to slightly higher incidence fetal variations such as heart and greater vessel anomaly at high dose.
The pre- and post-natal development studying rats were performed with 5, 15 and 50 mg/kg of lorcaserin. There were no drug-related deaths; however, lorcaserin reduced BW gain of dams in a dose-dependent manner during gestation and lactation which lead to lower pup (F1) weight at all doses but reaching statistical significant at 50 mg/kg. The percentage of live pups was reduced and the number of pups found dead was increased by lorcaserin dose of 50 mg/kg resulting in reduced viability index (87.3% vs. 98% in control). The gestation index was similar while lactation index. The slightly lower postweaning BW of the F1 generation recovered as the terminal BW was similar to control. There were no notable differences in F1 behavioral tests. Pups generation from mating of F1 generation had no significant gross alterations. The NOAEL dose of 5 mg/kg was selected for dams (weight loss). The reproductive NOAEL in dams was 15 mg/kg due to reduction in lactation index, increased stillborn pups at higher lo dose.

In summary, lorcaserin was not teratogenic in rat and rabbit reproductive studies. Lorcaserin appeared to reach fetal plasma in rats at concentrations equivalent to 1/3 of the maternal exposure. Surprisingly, the relative bioavailability of lorcaserin in rabbits was very poor, less than that in mice and significantly less than those in rats and monkeys. Therefore, it wasn't surprising when no measurable drug levels were detected in fetal plasma due to poor systemic maternal exposure in rabbits. Lorcaserin had no notable effect on fertility and mating in female and male rat. Lorcaserin dose-dependently reduced BW in pregnant rats and rabbits. The maternal and fetal NOAEL in rats was 10 and 50 mg/kg (1.3x and 48x the MRHD), respectively. The maternal and fetal NOAEL in rabbits was 60 mg/kg (0.6x the MRHD). In the pre- and post-natal developmental study in rats, lower BW gain at $\geq$ 5 mg/kg resulted in lower initial pup weight at 50 mg/kg. By the study termination, the BW of the affected was recovered matching those in the controls. The maternal NOAEL in dams was 5 mg/kg (4x the MRHD) while reproductive NOAEL was 15 mg/kg (12x the MRHD) in F1 generation rats.

Exposure margins

Species	Daily Dose, (mg/kg)	lorcaserin AUC_{0-24} (µg.h/ml)	NOAEL, (mg/kg) M/F	Exposure margins based on AUC (Animal/Human)	
				male	Female
13-Week mouse Study	25	M:3.4 F:1.0		3.3	1
	50	M:7.6 F: 2.3	50/50	7.4	2.2
	250	M:34.8 F:9.2		34.1	9
	350	M:25 F:27		24.5	26.4
13-Week rat study	1	M:0.143 F:0.33	5/1	<1	<1
	5	M:0.75 F:1.71		<1	2
	50	M:16.6 F:32.5		**16**	**32**
	100	M:33.6 F:55.8		**33**	**55**
6-Month rat study	1	M:0.20 F:0.31		0.2	0.3
	5	M:1.19 F:2.87	5/5	1.2	2.8
	50	M:22.0 F:34.4		22	34
12-Month cynomolgus monkey study	2	M: 1.0 F: 0.6	2 / 2	1	0.6
	10	M: 7.9 F: 4.5		7.7	4.4
	50	M:43.6 F:31.4		43	30.8
	125	M: 50.9 F: 51		50	50
104-Week Mouse Carci Study	5	M:0.55 F:0.32		0.5	0.3
	25	M:3.9 F: 1.6		3.8	1.5
	50	M:7.5 F:3.7	50/50	7.3	3.6
104-Week Rat Study	10	M:4.78 F:6.7	5 /<7	4.7	6.6
	30	M:16.9 F:24.1		16.6	24
	100 [b]	M:55.9 F:83.8		**55**	**82**
Fertility and early embryonic development in rats	5	M:2.68 F: 4 [a]		2.6	4
	15	M:9.91 F:12 [a]	15/50	9.7	12
	50	M: 29.3 F:48.7 [a]		28.7	48
Oral Embryo-fetal development in rats	2	F:1.34			1.3
	10	F:7.99	10		7.8
	50	F:48.7			47.7
Oral Embryo-fetal development in rabbits	20	F: 0.155			0.15
	60	F: 0.443	60		0.43
	200	F:19.3			18.9
Pre- and postnatal development in rats	5	F:4 [a]	<5		4
	15	F:12 [a]			12
	50	F:48.7 [a]			48
Clinical Dose: lorcaserin, 10 mg BID		**1.02**			

[a] The AUC value is derived from other existing similar studies.
[b] The lorcaserin AUC in females in the 2-year rat study was about 50% higher than the AUC in female rats in the 13-week toxicology and 28-day prolactin mechanistic study (AUC 53 µg.hr/ml).

12 Appendix/Attachments

Appendix A

Meeting Minutes from FDA Executive Carcinogenicity Assessment Committee

Executive CAC
Date of Meeting: August 10, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHP, Alternate Member
Todd Bourcier, Ph.D., Team Leader
Fred Alavi, Ph.D., Presenting Reviewer

NDA 22-529
Drug Name: Lorcaserin HCl
Sponsor: Arena Pharmaceuticals

Background:

Lorcaserin is a first-in-class serotonin 5HT2C receptor agonist. The sponsor is seeking an indication for the treatment of obesity.

Mouse Carcinogenicity Study
Carcinogenic assessment in CD1 mice was initiated at doses of 25, 50, and 100mg/kg, in accordance with the Committee's dosing recommendations. High mortality within two weeks of dosing initiation prompted a reduction in doses to 5, 25, and 50mg/kg, and the addition of 10 mice/sex to the control and 50mg/kg groups on day 19. The survival rate across the dose groups was similar to control for the remainder of the study. Drug exposure at the 5, 25, and 50mg/kg dose groups provided multiples of 0.5x, 4x, and 7x in males and 0.3x, 1x, and 4x in females relative to the clinical dose of 10mg bid.

Rat Carcinogenicity Study
Carcinogenic assessment in Sprague Dawley rats was initiated at doses of 10, 30, and 100mg/kg, in accordance with the Committee's dosing recommendations. Survival declined significantly at all doses in females due to the emergence of drug-related mammary tumors. Survival also declined significantly in high dose males, due to the emergence of drug-related tumors in the brain, skin, mammary tissue, and nerve sheaths (schwannoma). Drug exposure at the 10, 30, and 100mg/kg dose groups provided multiples of 5x, 17x, and 55x in males and 7x, 24x, and 82x in females relative to the clinical dose of 10mg bid.

Because excess mortality was due to drug-induced tumors rather than dose-limiting toxicity, the high dose of 100mg/kg is not considered to have exceeded the MTD.

Mechanistic studies were presented showing, at most, a small and non-sustained increase in serum prolactin in rats administered lorcaserin. Immunohistochemical staining of pituitary and mammary tissue failed to establish a correlation between prolactin and mammary tumors. Conversely, the anti-dopaminergic compound haloperidol readily

increased prolactin in these studies, and is associated with rodent mammary tumors via this mechanism.

Immunohistochemical staining of astrocytoma in thirteen sections showed a lack of staining with GFAP, and occasional staining with MHCII and an anti-CD68 marker, suggesting that the cellular lineage of the astrocytomas was not astrocytic but rather monocytic. The literature reports an absence of GFAP staining in rat astrocytoma, but this lack of staining is not necessarily evidence of a non-astrocytic origin of the tumor (Nagatani M et al; Toxicol Path, 2009). Regardless of cell lineage, the mechanism of tumor induction was not assessed and the relevance to human risk cannot be dismissed.

The incidence of mammary adenocarcinoma and fibroadenoma was reported on a quarterly basis in response to the Division's request starting at week 55. The Division expressed concern that the number of adenocarcinoma in the mid- and high-dose groups decreased from week 96 to the final study report, whereas the incidence in the control and low dose groups either increased (control) or stayed the same (low dose) over the same time period. Additionally, the Division identified 2 cases of high dose females suspected of having a mammary tumor that were not counted as such in the study report.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed that the study was acceptable, as mortality was encountered at doses higher than 50mg/kg.
- The Committee concluded that the study was negative for any statistically significant drug-related tumor findings.

Rat:

- The Committee expressed some concern about the conduct and evaluation of the study. Specifically, concern was expressed about a large number of diagnostic changes of mammary tumor type in the evaluation for the mid and high dose group.
- The Committee noted that because high-dose animals died due to drug-induced tumors, the MTD was not exceeded in this study.
- The Committee was not persuaded by the sponsor's argument that mammary tumors were caused by increased prolactin levels. Specifically, the sponsor's data failed to demonstrate an increase in prolactin in repeat-dose mechanistic studies and in the 2 year carcinogenicity study.

- A mechanism for the induction of astrocytomas was not identified. Drug-induced astrocytomas were observed at exposures equal to 17x the clinical exposure, with a NOAEL that provides a 5x multiple to the clinical dose.

The Committee concluded that the following tumors were drug-related:

Males
Brain: Astrocytoma at HD. Numerical, non-statistically significant increase in astrocytoma at mid-dose also considered drug-related.

Liver: Hepatocellular adenoma and carcinoma combined, at HD.

Mammary: Adenocarcinoma and fibroadenoma combined, at MD & HD.

Skin, subcutis: Fibroma at MD & HD

Skin: Squamous Carcinoma at HD. Numerical, non-statistically significant increase in squamous carcinoma at MD also considered drug-related.

Schwannoma (all sites) at HD. Numerical, non-statistically significant increase at the MD also considered drug-related.

Thyroid: Follicular cell adenoma at HD.

Females
Mammary: Adenocarcinoma + fibroadenoma at LD, MD, HD

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DMEP
/Todd Bourcier, DMEP
/Fred Alavi, DMEP
/Pat Madara, DMEP
/ASeifried, OND IO

Appendix B

Receptor Profile of Lorcaserin, Lorcaserin Enantiomer and Metabolites for a Collection of Human GPCRs, Ion Channels and Neurotransmitter Transporters

Receptor	Lorcaserin % Inhibition[a]	Enantiomer % Inhibition[b]	M1 % Inhibition[c]	M2 % Inhibition[d]	M5 % Inhibition[e]
Adenosine A_1	-11	13	-6	6	-5
Adenosine A_{2A}	7	1	-11	21	14
Adenosine A_3	-1	1	4	13	14
α_1 Adrenergic (nonselective) (rat)	18	16	27	22	9
α_2 Adrenergic (nonselective) (rat)	30	41	13	65	9
β_1 Adrenergic	21	52	-8	56	7
β_2 Adrenergic	19	22	-3	47	10
Angiotensin AT_1	-12	3	11	-18	-13
Angiotensin AT_2	1	13	1	1	3
Benzodiazepine (central) (rat)	0	6	-2	6	11
Benzodiazepine (peripheral) (rat)	-3	-1	6	-1	1
Bombesin (nonselective) (rat)	-16	2	-10	6	1
Bradykinin B_2	-3	-15	11	1	-4
CGRP	-10	-8	-9	-4	-2
Cannabinoid CB_1	3	8	-9	5	-2
Cannabinoid CB_2	-8	ND	-3	-6	-8
Cholecystokinin CCK_A	-2	-9	-11	29	18
Cholecystokinin CCK_B	3	-1	6	-2	3

Receptor	Lorcaserin % Inhibition[a]	Enantiomer % Inhibition[b]	M1 % Inhibition[c]	M2 % Inhibition[d]	M5 % Inhibition[e]
Dopamine D_1	-2	14	-1	-3	-7
Dopamine D_{2S}	-1	0	9	2	1
Dopamine D_3	7	23	2	21	-2
Dopamine $D_{4.4}$	-1	-4	-5	4	4
Dopamine D_5	-3	5	-3	8	-1
Endothelin ET_A	-8	3	-23	-2	2
Endothelin ET_B	-14	-8	-7	1	9
GABA (nonselective) (rat)	9	-3	-15	9	2
Galanin GAL_1	5	-6	4	-1	4
Galanin GAL_2	-18	-10	3	-10	-2
PDGF (mouse)	-9	ND	-13	1	-7
CXCR2	8	-14	12	-12	-2
TNF-α	ND	4	6	-21	-1
CCR1	-3	-2	0	-4	-3
Histamine H_1	-4	10	8	9	8
Histamine H_2	6	16	-12	-3	-1
Melanocortin MC_4	-7	1	1	2	4

Receptor Profile of Lorcaserin, Lorcaserin Enantiomer and Metabolites for a Collection of Human GPCRs, Ion Channels and Neurotransmitter Transporters [redacted]

Receptor	Lorcaserin % Inhibition[a]	Enantiomer % Inhibition[b]	M1 % Inhibition[c]	M2 % Inhibition[d]	M5 % Inhibition[e]
Melatonin MT_1	-5	2	1	6	9
Muscarinic M_1	12	1	-27	9	6
Muscarinic M_2	3	9	-1	-4	-7
Muscarinic M_3	3	11	-29	10	5
Muscarinic M_4	4	18	-2	7	2
Muscarinic M_5	0	14	-4	4	-3
Neuronal nACh (rat)	30	ND	4	20	13
NMDA (rat)	-4	ND	17	5	1
Neurokinin NK_1	10	-4	-4	4	2
Neurokinin NK_2	-5	10	4	1	-3
Neurokinin NK_3	7	-3	-6	13	11
Neuropeptide Y	-9	-4	21	-6	-10
Neuropeptide Y_2	-1	-18	-15	-3	-2
Neurotensin NT_1	-2	-1	4	2	0
δ_2 Opioid	4	5	10	10	0
μ Opioid	26	5	0	28	7
κ Opioid (rat)	6	24	0	18	19
Nociceptin ORL1	1	9	-2	17	10

Receptor	Lorcaserin % Inhibition[a]	Enantiomer % Inhibition[b]	M1 % Inhibition[c]	M2 % Inhibition[d]	M5 % Inhibition[e]
PPARγ	-9	8	ND	ND	ND
PAC_1 (PACAP)	-15	-3	-12	-18	6
PCP (rat)	8	3	-22	-14	-6
Prostanoid EP_2	ND	7	ND	ND	ND
Prostanoid EP_4	-3	ND	ND	-3	0
Prostanoid TP	0	11	-2	30	32
Prostanoid IP	-5	0	ND	-2	-3
P2X (rat)	9	-2	-5	-3	0
P2Y (rat)	1	-5	-4	5	11
Serotonin $5\text{-}HT_{1A}$	**85**	**92**	22	**72**	22
Serotonin $5\text{-}HT_{1B}$ (rat)	**69**	**92**	13	49	4
Serotonin $5\text{-}HT_{2A}$	29	**50**	-3	22	-6
Serotonin $5\text{-}HT_{2B}$	**78**	**78**	ND	**51**	9
Serotonin $5\text{-}HT_{2C}$	**67**	**62**	-7	32	15
Serotonin $5\text{-}HT_3$	7	14	-3	10	8
Serotonin $5\text{-}HT_{5A}$	7	10	-4	17	24
Serotonin $5\text{-}HT_5$	15	47	1	17	1
Serotonin $5\text{-}HT_7$	**61**	**82**	7	40	1

Receptor Profile of Lorcaserin, Lorcaserin Enantiomer and Metabolites for a Collection of Human GPCRs, Ion Channels and Neurotransmitter Transporters

Receptor	Lorcaserin % Inhibition[a]	Enantiomer % Inhibition[b]	M1 % Inhibition[c]	M2 % Inhibition[d]	M5 % Inhibition[e]
Sigma σ (nonselective)	14	23	6	8	14
Somatostatin (nonselective)	12	6	12	3	3
Glucocorticoid	-2	2	ND	-8	2
$VIP_1(VPAC_1)$	-8	3	-25	-3	-2
Vasopressin V_{1a}	3	0	-5	2	-1
L-Type Ca^{++} Channel (rat)	15	19	-18	12	-8
K^+_v Channel (rat)	-4	3	-11	0	2
SK^+_{Ca} Channel (rat)	1	3	6	0	1
Na^+ Channel (rat)	3	13	-17	18	32
Cl^- Channel (GABA-gated) (rat)	3	-3	8	1	-1
Norepinephrine Transporter	0	21	-2	11	8
Dopamine Transporter	7	9	-20	6	5
5-HT Transporter	20	29	-12	3	1

[a] Data from DBR-09-004, Sections 9 & 10. Lorcaserin test concentration = 1 μM
[b] Data from DBR-09-008, Section 7. Lorcaserin enantiomer test concentration = 1 μM
[c] Data from DBR-09-005, Sections 6 & 7. Lorcaserin metabolite M1 test concentration = 10 μM
[d] Data from DBR-09-006, Sections 6 & 7. Lorcaserin metabolite M2 test concentration = 1 uM
[e] Data from DBR-09-007, Sections 6 & 7. Lorcaserin metabolite M5 test concentration = 1 μM
[f] Bold font indicates >50% inhibition of radioligand binding. ND = not determined.
All assays utilized human receptors except were indicated in the table.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRED K ALAVI
10/20/2010
Nonclinical review of lorcaserin NDA 22529
(IND 69,888)

TODD M BOURCIER
10/20/2010
Reviewer recommends non-approval. I concur with Dr Alavi's recommendation.

EXHIBIT D

Summary Review for Regulatory Action

Date	
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	22529
Applicant Name	Arena Pharmaceuticals
Date of Submission	December 22, 2009
PDUFA Goal Date	October 22, 2010
Proprietary Name /Established Name	Lorcaserin/Lorqess
Dosage Forms / Strength	Tablet/10 mg BID
Proposed Indication(s)	Weight Management
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Julie Golden, MD
Statistical Review	Janice Derr, PhD/Xiao Ding, PhD
Pharmacology/Toxicology Review	Fred Alavi, PhD/Todd Bourcier, PhD
CMC Review/OBP Review	Olen Stephens, PhD/John Duan, PhD/Raanan Bloom, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Immo Zdrojewski, PhD/Sally Choe, PhD
DDMAC	Sam Skariah, PharmD
DSI	Kassa Ayalew, MD
CDTL Review	See Deputy Division Director Summary Memorandum
OSE/DMEPA	Lubna Najam, MS, PharmD
DRISK	NA
Thorough QT Consult	Christine Garnett, PhD
Controlled Substance Staff	Katherine Bonson, PhD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

This memorandum summarizes the conclusions and regulatory recommendations of the review disciplines assigned to this application. I am not aware of any significant disagreements within or between the review disciplines regarding final regulatory recommendations. A sizable portion of this memorandum deals with nonclinical carcinogenicity data – specifically mammary and brain tumors in rats – and issues of clinical efficacy and safety – in particular evaluations for valvular heart disease.

2. Background

Lorcaserin is a first-in-class, relatively selective oral agonist of the 5HT2c receptor, which as of this writing, has not been approved by any regulatory body in the world. The sponsor is seeking approval of lorcaserin 10 mg BID for the treatment of obesity in obese (BMI $\geq$ 30 kg/m^2) or overweight (BMI 25 – 29.9 kg/m^2) individuals with at least one weight-related comorbidity. Activation of 5HT2c receptors, which densely populate areas of the brain controlling appetite, has been shown in animal models to reduce caloric intake and decrease body weight. There is sufficient justification to study the weight-loss efficacy and safety of a 5HT2c receptor agonist in humans.

Activation of the 5HT2b receptor is believed to account for the association between dexfenfluramine and fenfluramine with left-sided valvular heart disease (VHD). These two weight-loss drugs were removed from the United States market following identification of this adverse effect in 1997. A detailed discussion of cardiac valve evaluation during the phase 3 lorcaserin clinical trials is provided in the reviews of Drs. Julie Golden and Xiao Ding and in the Clinical Safety section of this memorandum.

As discussed in detail in the reviews by Drs. Alavi and Bourcier and in the Nonclinical Pharmacology/Toxicology section of this memorandum, the Division was notified by the sponsor in late spring of 2007 that some rats in the then ongoing 2-year carcinogenicity had died and upon necropsy were found to have malignant tumors of the mammary gland and brain. These findings led to a series of interactions between the sponsor and the Division and the Agency's Executive Carcinogenicity Committee, as outlined below.

3. CMC

The CMC reviewer states that there are no pending deficiencies to resolve and recommends that the application be approved. I agree that there are no outstanding CMC issues at this time. Dr. Bloom from the Office of Pharmaceutical Science recommends a finding of no significant impact (FONSI).

4. Nonclinical Pharmacology/Toxicology

Nonclinical Carcinogenicity

Drs. Alavi and Bourcier recommend against approval of lorcaserin due to its characterization as a non-genotoxic carcinogen. Following review of the two-year rat carcinogenicity study of lorcaserin at low-dose (LD), mid-dose (MD), and high-dose (HD), the Agency's Executive Carcinogenicity Assessment Committee concluded that the following tumors were lorcaserin-related: Male: hepatocellular adenoma and carcinoma combined (HD), mammary adenocarcinoma and fibroadenoma combined (MD and HD), skin/subcutis squamous carcinoma and fibroma (MD and HD), schwannoma (MD and HD) and thyroid adenoma (HD); Female: mammary adenocarcinoma and fibroadenoma combined (LD, MD, and HD). Of particular concern are the mammary and brain tumors.

As shown in the table on pages 5-6 of Dr. Alavi's review, in female rats, the incidence rates of mammary adenocarcinoma as reported in the NDA were 43%, 52%, 54%, and 80% in the control, LD, MD, and HD groups, respectively. The incidence rates of mammary fibroadenoma in female rats were 31%, 72%, 82%, and 60% in the control, LD, MD, and HD groups, respectively. The test of trend was statistically significant for adenocarcinoma, fibroadenoma, and adenocarcinoma combined with fibroadenoma. Compared with the control group, the incidence of adenocarcinoma alone and fibroadenoma alone in the HD lorcaserin groups were statistically significantly greater. When adenocarcinoma and fibroadenoma are combined, the incidence rates in the individual active-treatment groups were statistically significantly greater versus control. The exposure margins were 7X the proposed clinical dose for the LD group, 24X for the MD group, and 82X for the HD group.

The incidence rates of mammary tumors in male rats exposed to lorcaserin was much lower than the rates observed in female rats. The tests of trend were statistically significant for fibroadenoma and for adenocarcinoma combined with fibroadenoma. There were no male rats in the control or LD groups that developed mammary adenocarcinoma; two rats in each of the MD and HD groups developed adenocarcinomas. The exposure margins were 5X the proposed clinical dose for the LD group, 17X for the MD group, and 55X for the HD group.

As pointed out by Drs. Alavi and Bourcier and shown in the table on pages 5-6 of Dr. Alavi's review, it appears that a number of female rats in the MD and HD groups identified as having mammary adenocarcinoma at the Week 96 time point were no longer classified as having adenocarcinoma in the final analysis. The incidence rates of adenocarcinoma decreased by 8%, 16%, 21%, and 16% in the control, LD, MD, and HD groups, respectively, from Week 96 to the final evaluation. Likewise, a number of female rats in the MD and HD groups classified as having mammary fibroadenomas at Week 104 were not classified as having fibroadenomas in the final analysis. In numerous cases, an initial classification of adenocarcinoma was subsequently changed to fibroadenoma. While there may be a logical explanation for these patterns of change, the sponsor has not provided one and they raise concern about the validity of the histological evaluations and diagnostic accuracy of the tumor data. That Dr. Alavi noted inconsistencies in the reporting of mammary tumor-related findings in some female rats adds to this concern.

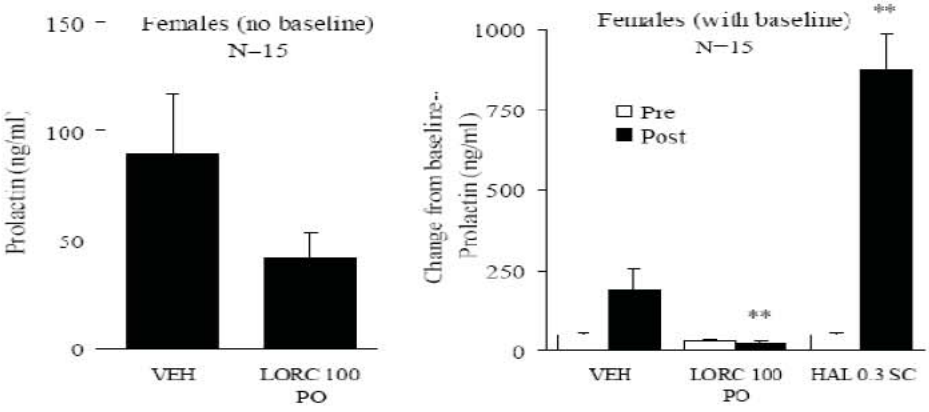
If tumors were reclassified due to difficulty distinguishing benign versus malignant masses, this supports combining adenocarcinoma with fibroadenomas for statistical analysis. As noted above, the incidence rates of mammary adenocarcinoma plus fibroadenoma in female rats were statistically significantly greater in each of the lorcaserin groups versus control.

I would mention that while fibroadenomas may not represent a life-threatening risk to humans, a drug that increased the incidence of these breast tumors would add at least a temporary emotional burden to women following detection of a breast mass of unknown histology. This is admittedly a softer safety concern than adenocarcinoma.

The sponsor claims that the mammary tumor findings are not relevant to humans because they are due to lorcaserin-mediated increases in serum prolactin, a rodent-specific mechanism according to their consultant (b) (4) While drugs such as haloperidol have been shown to increase the risk for mammary tumors in rodents through increases in serum prolactin levels, Drs. Alavi and Bourcier do not believe that the totality of data provided by the sponsor support the hypothesis that lorcaserin increases prolactin levels in rats to an extent commensurate with the increase in the incidence of mammary tumors observed in the 2-year carcinogenicity study.

For example, as discussed in Dr. Alavi's review and shown in the figure below, following administration of a single oral doses of 100 mg/kg lorcaserin and a single subcutaneous dose of 0.3 mg/kg of haloperidol to female rats, compared with vehicle-treated animals, serum prolactin levels 30 minutes post-dosing were significantly lower in the lorcaserin-treated animals and significantly higher in haloperidol-treated animals.

Effects of lorcaserin and haloperidol on serum prolactin levels in female Sprague Dawley rats **p<0.01 compared to vehicle controls



In another study, following 28 days of treatment of female rats with 100 mg/kg lorcaserin or vehicle, serum prolactin levels were 569 ng/ml in the vehicle group and 167 in the lorcaserin group 2-hours post-dose; 409 ng/ml in the vehicle group and 882 ng/ml in the lorcaserin group 6-hours post-dose; and 294 ng/ml in the vehicle group and 205 ng/ml in the lorcaserin group 24-hours post-dose.

Following standard histological sampling and detection methods, one rat was identified with malignant astrocytomas in the control group compared with 2, 5 and 12 mostly male animals in the LD, MD, and HD groups, respectively. The concentration of lorcaserin in plasma is much lower than the concentration in the central nervous system (CNS). The CNS-to-plasma ratio is 35X in rats and 10X in monkeys. Hence, as pointed out by Dr. Alavi, if the CNS-to-plasma ratio of lorcaserin in humans is similar to rats, the safety margin for astrocytomas is only 5X the proposed clinical dose of lorcaserin; if the CNS-to-plasma ratio in humans is similar to monkeys, the safety margin is 14X the proposed clinical dose.

There were no notable tumor findings in the 2-year mouse carcinogenicity study of lorcaserin. However, drug exposure in female mice did not exceed 4X the proposed clinical dose and did not exceed 7X the proposed clinical dose in male mice. Thus, the mouse carcinogenicity data do not provide reassurance regarding the rat carcinogenicity findings.

Before lorcaserin is considered for approval, I agree with Drs. Alavi and Bourcier that all slides of mammary tissue need to be re-evaluated by an independent pathologist or pathologists. Ideally, the evaluations should be conducted blinded to treatment allocation. Particular attention should be paid to the tissue samples initially classified as adenocarcinoma and then re-read as fibroadenoma. The sponsor should also provide an explanation for the changes in the number of mammary tumors in female rats between the Week 96 and the final histological evaluation. In addition, the sponsor may need to explore mechanistic explanations other than prolactin for the mammary tumor findings as they relate to human risk.

Regarding astrocytomas, Dr. Bourcier recommends that additional CNS tissue samples from all experimental rat groups be evaluated to verify the dose-response relationship for astrocytomas. He believes that a more extensive evaluation of brain tissue is warranted because the standard carcinogenicity evaluation of brain tissue is limited and may have missed tumors. I do not disagree with this recommendation. However, given that lorcaserin levels are significantly higher in brain tissue, but not cerebrospinal fluid, than the plasma, it may prove difficult if not impossible to obtain an accurate measure of CNS levels of lorcaserin in humans to determine if an adequate margin of safety exists for this tumor. Our concern would be lessened if the sponsor provided data to support their assertion that the astrocytoma findings in rats are not relevant to humans.

Chronology of Events Related to the Nonclinical Carcinogenicity Assessments

Following the September 16, 2010, advisory committee meeting on lorcaserin, the Agency received numerous public emails raising the question of why the lorcaserin development program was allowed to proceed if FDA scientist were “so concerned” about the breast tumor findings in the 2-year rat carcinogenicity study. A chronology of interactions among the sponsor, the Division, and the Executive Carcinogenicity Committee related to nonclinical carcinogenicity information follows.

For point of reference, one of the pivotal phase 3 clinical trials was initiated in November of 2006, and was completed in February of 2009. A second pivotal phase 3 trial was initiated in January of 2008 and was completed in July of 2009. The third pivotal trial was initiated in

December of 2007 and was completed in mid-2010 (data not included in the NDA submission).

During discussions within the Division on and around June 20, 2007, Dr. Fred Alavi notified the clinical team that interim histological examination of rats that died prematurely during 2-year carcinogenicity study revealed the development of astrocytomas in 2 MD animals and 3 HD animals.

On June 28, 2007, the Division sent an advice letter to the sponsor acknowledging their plans to revise the investigator brochure and patient informed consent forms to include the rat mammary and brain tumor findings.

On August 29, 2007, the Division sent an advice letter to the sponsor requesting revisions to language in the patient informed consent form related to the rat mammary and brain tumor data.

At this time, the sponsor hypothesized that the mammary tumors were due to lorcaserin-induced increases in serum prolactin levels. It is well known that antipsychotics, for example, cause rat mammary tumors through elevations in serum prolactin levels – a mechanism that some believe does not pertain to humans. The sponsor's hypothesis was reasonable, but it needed to be substantiated with data on prolactin levels in animals and humans exposed to lorcaserin.

In September of 2007, the Division requested that Arena provide bi-monthly updates on the status of the ongoing carcinogenicity studies in rats and mice

From September 2007, through March 2008, the Division and the sponsor exchanged numerous communications related to the nonclinical tumor data and the assessment of serum prolactin levels, adverse events related to hyperprolactinemia, and breast cancer risk in subjects taking part in the ongoing clinical trials.

The bi-monthly updates on the ongoing carcinogenicity studies indicated a strengthening of the mammary adenocarcinoma and astrocytoma dose-response relationship with continued dosing of lorcaserin in rats. On April 1, 2008, The Agency's Executive Carcinogenicity Assessment Committee was briefed on the information, and stated that while conclusions must await completion of the studies, the interim data indicated that lorcaserin increases mammary adenocarcinoma at all dose levels in female rats and astrocytoma at the MD and HD levels.

Prior to meeting with the Executive Carcinogenicity Assessment Committee on April 1, 2008, the Division discussed internally whether the lorcaserin IND should be placed on clinical hold due to the nonclinical tumor/cancer data. The sponsor was made aware of our concerns and was asked to meet with us to defend continuation of their clinical development program. The sponsor provided a background package containing information not included in prior updates.

A face-to-face meeting with the sponsor was held on April 9, 2008.

Our decision to allow the clinical program to proceed following our meeting with the sponsor was based on the following: 1) the updated informed consent forms included the nonclinical breast and brain cancer findings; 2) we learned that drug exposure in rats was nearly twice as high as predicted, which increased the safety margin to clinical exposure; 3) preliminary data showed a modest increase in serum prolactin levels after a single dose in male rats, lending support to the hypothesis that prolactin was responsible for the rat mammary findings; 4) we acknowledged that the interim tumor incidence data would change (e.g., might be less worrisome) as full histopathology assessments became available after completion of the study, particularly for astrocytoma; 5) only with continued clinical study was it possible to assess whether long-term dosing with lorcaserin increased serum prolactin levels in humans; 6) only with continuation of clinical dosing would we obtain an accurate assessment of lorcaserin's weight-loss efficacy and safety in diabetics; and 7) given that lorcaserin is non-genotoxic, we believed that cancer risk was low under the conditions of use in the ongoing clinical trials (not the case with chronic or indefinite use).

Receptor Binding Affinity and Activation and Cardiac Valvulopathy

As stated by Dr. Bourcier in his briefing document for the September 16, 2010 advisory committee meeting, "lorcaserin preferentially activates 5HT2C with 8 to 15-fold greater potency compared to 5HT2A, and 45 to 90-fold greater potency compared to 5HT2B. Depending on the studies one considers, off-target activation of 5HT2A and 2B appears unlikely (2002/04 data) or plausible (2009 data) when compared to clinically relevant plasma drug levels based on the *in vitro* estimates of receptor potency. Cross-activation of these receptors may be more likely in the CNS, where the lorcaserin concentration is 10 to 25-fold higher than in plasma of rats and monkeys, but is unknown in human subjects." Data on the relative binding and activation of serotonin receptors by lorcaserin are shown in the below table from excerpted from Dr. Bourcier's briefing document.

Lorcaserin's Relative Receptor Binding and Activation Profile

	5HT2A	5HT2B	5HT2C
Receptor Binding (Ki, nM)	92	147	13
PI Hydrolysis (EC50, nM)	133	811	9
Calcium release (EC50, nM)	52	350	6

These *in-vitro* data provide a modest degree of comfort regarding lorcaserin's potential to active the 5HT2b receptor and promote cardiac valvular abnormalities.

I am also somewhat reassured by the fact that there were no notable imbalances in cardiac valve abnormalities (e.g., hypertrophy) reported in rats treated long-term with lorcaserin versus control.

5. Clinical Pharmacology

The clinical pharmacology reviewer concludes that the data submitted in support of the NDA are acceptable and recommends that the application be approved. I agree with the reviewer that there are no outstanding clinical pharmacology issues.

Based on review of the data from a thorough QT study, the Agency's interdisciplinary review team for QT studies concluded that lorcaserin does not significantly prolong the QT interval. The largest upper bounds of the 2-sided 90% CI for the mean difference between lorcaserin (10 mg and 50 mg) and placebo was below 10 ms.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Dr. Golden is recommending that the lorcaserin application not be approved at this time due to an unfavorable benefit-to-risk profile: marginal weight-loss efficacy, coupled with the inability of the sponsor to rule out an increase of 50% in the risk for valvulopathy, and unclear relevance of the rat tumor findings, particularly of breast and brain tissue, to humans.

Phase 3 Clinical Trials

The long-term efficacy of lorcaserin was examined in two phase 3 clinical trials.

BLOOM was a placebo-controlled two-year trial that randomized approximately 3000 overweight and obese male and female subjects to placebo or lorcaserin 10 mg BID in a 1:1 manner. After one year of treatment, the lorcaserin group was re-randomized 2:1 to lorcaserin

10 mg BID or placebo, stratified by 5% weight loss responder status. The subjects originally randomized to placebo remained on placebo during the second year. The primary endpoints were weight loss following one year of treatment and maintenance of weight loss during a second year of treatment.

BLOSSOM was a placebo-controlled one-year trial that randomized approximately 4000 overweight and obese male and female subjects to placebo, lorcaserin 10 mg QD, or lorcaserin 10 mg BID in a 2:1:2 fashion. The primary endpoint was weight loss following one year of treatment.

As shown in the below table from Dr. Golden's review, the baseline demographic characteristics were well-matched for the three treatment groups. The mean age of the study participants was about 44 years, 82% were women, and 67% were Caucasian and 20% African-American. The average BMI was 36 kg/m^2. Approximately 42% of the subjects had at least one weight-related comorbidity, primarily hypertension and/or dyslipidemia. There were no overweight or obese type 2 diabetic subjects in BLOOM or BLOSSOM.

Baseline Subject Demographics - Pooled Data from BLOOM and BLOSSOM

	Lorcaserin 10 BID N=3195	**Lorcaserin 10 QD N=801**	**Placebo N=3185**
Age, years mean +/- SD	43.8 +/- 11.6	43.8 +/- 11.7	44.0 +/- 11.4
Sex, % female	81.7	81.9	81.0
Race White, % Black, % Hispanic, %	 67.7 18.9 11.1	 67.2 20.0 10.7	 66.2 19.4 12.4
BMI, kg/m² mean +/- SD	36.1 +/- 4.3	35.8 +/- 4.3	36.1 +/- 4.2
Weight, kg mean +/- SD	100.4 +/- 15.7	99.8 +/- 16.6	100.2 +/- 15.9
Any Comorbidity, % *	44.3	40.1	43.7
Hypertension, %	22.6	21.8	22.7
Dyslipidemia, %	30.9	27.2	30.2
CVD, %	0.6	0.5	0.9
Glucose intolerance, %	1.5	1.9	1.0
Sleep apnea, %	4.5	3.4	4.0
* Denominators used for comorbidity percentages were numbers of patients randomized CVD=cardiovascular disease			

In BLOOM, 55% of subjects randomized to lorcaserin and 45% of subjects randomized to placebo completed the first year of the study. Approximately 73% of subjects who entered the second year of the study completed that phase of the trial. In BLOSSOM, 57% of subjects randomized to lorcaserin 10 mg BID, 59% of subjects randomized to lorcaserin 10 mg QD, and 52% of subjects randomized to placebo completed the one-year trial. These drop-out rates are consistent with those from other weight-loss drug trials. The most commonly-reported reason for premature withdrawal from the two lorcaserin phase 3 studies was "patient decision" followed by "lost to follow-up". Adverse events accounted for approximately 6-7% of the drop-outs in the lorcaserin groups and about 5% in the placebo groups.

The primary efficacy analyses were performed on the modified intent-to-treat (MITT) population, defined as all randomized subjects who had a baseline weight measurement, took at least one dose of study drug, and had at least one post-baseline weight measurement. Unless indicated otherwise, the below efficacy data are from the MITT population with the last observation carried forward (LOCF).

In BLOOM, the mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was -3.7% ($p<0.0001$). In BLOSSOM, mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was -3.0% and -1.9% with lorcaserin 10 mg QD ($p<0.0001$ for both groups). In an analysis of data pooled from BLOOM and BLOSSOM, the mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was approximately -3.0% ($p<0.001$).

In BLOOM, the percentages of subjects achieving $\geq$ 5% weight loss following up to one year of treatment were 48% in the lorcaserin 10 mg BID group and 20% in the placebo group ($p<0.001$). In BLOSSOM, the percentages of subjects achieving > 5% weight loss following up to one year of treatment were 47% in the lorcaserin 10 mg BID group, 40% in the lorcaserin 10 mg QD group, and 25% in the placebo group ($p<0.0001$ for both groups vs. placebo). In an analysis of data pooled from BLOOM and BLOSSOM, the percentages of subjects achieving $\geq$ 5% weight loss following up to one year of treatment were 47% in the lorcaserin 10 mg BID group and 23% in the placebo group ($p<0.001$).

As stated in the Agency's 2007 Draft Guidance for Developing Products for Weight Management, in general, a product can be considered effective for weight management if after one year of treatment either of the following occurs:

1. The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant

2. The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Lorcaserin 10 mg BID failed to satisfy the mean efficacy criterion but did, by a slim margin, satisfy the categorical efficacy criterion when data from the BLOOM and BLOSSOM trials were pooled.

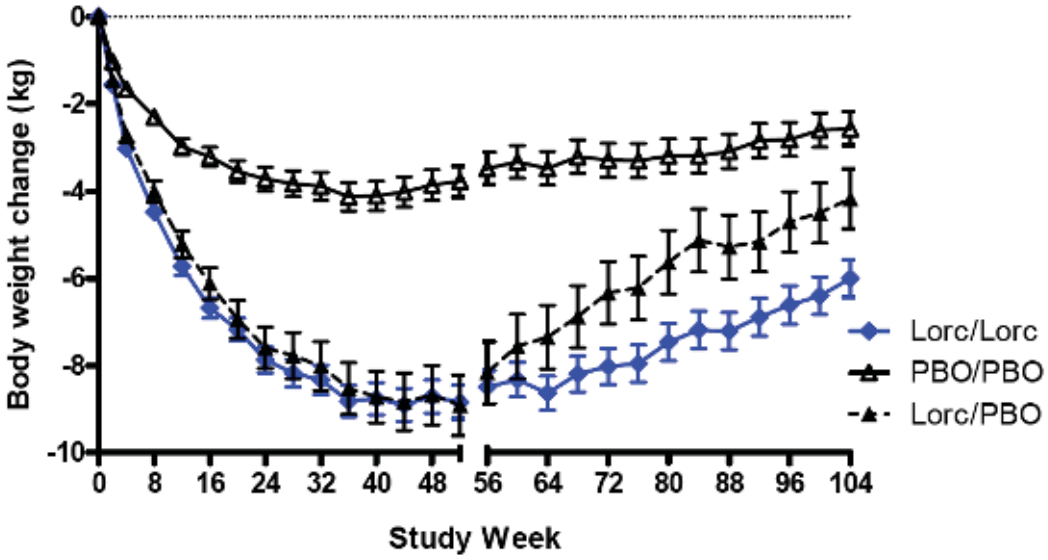
In general, lorcaserin-associated weight loss was associated with improvements in blood pressure, levels of high-density lipoprotein lipid and triglycerides, and fasting glucose and insulin concentrations commensurate with the degree of weight loss.

Other efficacy endpoints of interest include the percentage of subjects achieving $\geq$ 10% weight loss and the durability of lorcaserin-induced weight loss.

In an analysis of data pooled from BLOOM and BLOSSOM, 22% of subjects treated with lorcaserin 10 mg BID versus 9% of subjects treated with placebo lost ≥ 10% of baseline weight following up to one year of treatment.

As shown in the figure below, compared with placebo, treatment with lorcaserin 10 mg BID attenuated weight regain during a second year of treatment. Of note, however, the slope of the line depicting the change in mean body weight in the subjects treated with lorcaserin is more positive during the second year of treatment than the line depicting the mean change in body weight in the placebo group (similar patterns of change were shown for the Completers population). This raises the question of whether body weight in lorcaserin-treated subjects would reach that of placebo-treated subjects with treatment beyond 2 years.

Change in Body Weight from Baseline to Week 104 (Per-Protocol Population)



The BLOSSOM and BLOOM trials did not include subjects with type 2 diabetes. To the best of my knowledge, the efficacy of all weight-loss drugs tends to be less in overweight and obese type 2 diabetics compared with overweight or obese nondiabetics. It will therefore be important to review the data from a recently-completed study of lorcaserin in overweight and obese type 2 diabetics. The sponsor stated that data from the study in diabetics should be available by the end of 2010. The data from type 2 diabetics take on greater significance given that the efficacy of lorcaserin in nondiabetics is marginal.

8. Safety

Valvular Heart Disease

The weight-loss drugs dexfenfluramine and fenfluramine were removed from the United Stated market in 1997 due to reports implicating their involvement in the development of left-sided VHD. Research conducted subsequent to this discovery suggested that dexfenfluramine and fenfluramine's activation of the 5HT2b receptor on valvular tissue was the mechanism

responsible for the VHD. In a 2002 meta-analysis of nine cross-sectional studies, the incidence of FDA-defined VHD (at least mild aortic regurgitation or at least moderate mitral regurgitation) in subjects exposed to fenfluramine or dexfenfluramine for more than 3 months was calculated to be 12% versus 6% in unexposed or control subjects [OR = 2.2 (95% CI 1.7, 2.7].[1] Subjects exposed to fenfluramine or dexfenfluramine for less than 3 months did not appear to have an increased risk for FDA-defined VHD.

Given that lorcaserin targets the serotonergic system, VHD was identified as a leading safety concern requiring extensive evaluation during the drug's clinical development. Although the results of *in-vitro* studies indicate that lorcaserin's binding affinity for and activation of the 5HT2b receptor are lower than those of dexfenfluramine and fenfluramine, the Division requested that the sponsor conduct echocardiographic evaluation of heart valves in all subjects participating in long-term lorcaserin clinical trials.

Arena proposed that the phase 3 clinical development program be powered to rule out a doubling of the risk for FDA-defined VHD. The Division believed that a doubling was too permissive and requested that the program be powered to rule out at least a 50% increase in risk (i.e., upper bound of the 95% CI 1.5 or less). This necessitated increasing the sample size of the phase 3 program from approximately 4000 to 7000 subjects. It was made clear to the sponsor that ruling out at least a 50% increase in the risk for FDA-defined VHD was an arbitrary benchmark and that the adequacy of the valvulopathy data would be determined by not only the data themselves, but lorcaserin's efficacy and overall safety profile as well.

All echocardiograms obtained in the BLOOM and BLOSSOM trials were over-read by 2 blinded central readers. Any discrepant readings between the two primary readers were adjudicated by a third reader. In BLOOM, echocardiograms were obtained at screening and at Weeks 24, 52, 76, and 104/exit. In BLOSSOM, echocardiograms were obtained echocardiograms were obtained at screening and at Weeks 24 and 52/exit. The primary endpoint of the echocardiographic evaluations was the incidence of FDA-defined valvulopathy at Week 52.

The incidence rates and relative risks for FDA-defined VHD at Week 52 are shown below in a table modified from Dr. Golden's review. In BLOOM, the incidence rates for VHD in the safety population were 2.4% for placebo and 2.7% for lorcaserin 10 mg BID [RR 1.13 (95% CI 0.69, 1.85)]. In BLOSSOM, the incidence rates for VHD were 2.0% for placebo and 2.0% for lorcaserin 10 mg BID [RR 1.0 (95% CI 0.57, 1.75)]. In the analysis of pooled data, the RR for FDA-defined VHD was 1.07 (95% CI 0.74, 1.55). The kappa statistic was 0.32 for reading of the mitral valve and 0.38 for reading of the aortic valve. These values indicate that the echocardiographic readings from the two primary readers were in fair agreement.

Given that the upper bound of the 95% confidence interval for the relative risk for FDA-defined VHD with lorcaserin exceeded 1.5, albeit by a small amount, one cannot conclude that the lorcaserin is non-inferior to placebo. When the valvulopathy analysis is restricted to subjects who completed 52 weeks of treatment, the RR for FDA-defined valvulopathy was

---

[1] Sachdev M, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. Am Heart J 2002; 144:1065-73.

0.90 (95% CI 0.59, 1.38). It should be noted, however, that the RR estimates for VHD in BLOSSOM are considerably different for the safety and completers populations. The reason for the discrepancy is unclear, but it was not observed in BLOOM.

The lorcaserin development program provides the largest amount of controlled data on the prevalence of FDA-defined VHD in overweight and obese individuals and I believe the only data on the incidence of VHD in this target population. It bears mentioning that the prevalence of FDA-defined VHD in subjects screened for participation in the BLOSSOM trial was approximately 4.5%, similar to the 6% prevalence rate for FDA-defined VHD reported in control subjects from the 2002 meta-analysis of observational studies by Sachdev, et al.

Incidence of FDA-Defined Valvulopathy at Week 52

	BLOOM		BLOSSOM			POOLED	
	Pbo	Lorc 10 BID	Pbo	Lorc 10 QD	Lorc 10 BID	Pbo	Lorc 10 BID
Week 52							
Safety pop N	1191	1278	1153	622	1208	**2344**	**2486**
Safety pop n (%)	28 (2.4)	34 (2.7)	23 (2.0)	9 (1.4)	24 (2.0)	**51 (2.18)**	**58 (2.33)**
Relative Risk (95% CI)		1.13 (0.69, 1.85)		0.73 (0.34, 1.56)	1.00 (0.57, 1.75)		**1.07 (0.74, 1.55)**
Completers pop N	698	857	790	448	853	1488	1710
Completers pop n (%)	21 (3.0)	29 (3.4)	19 (2.4)	7 (1.6)	13 (1.5)	40 (2.69)	42 (2.46)
Relative Risk (95% CI)		1.12 (0.65, 1.95)			0.63 (0.32, 1.27)		0.90 (0.59, 1.38)

Although the VHD associated with dexfenfluramine and fenfluramine was predominately left-sided, use of other 5HT2b agonists has been associated with abnormalities of the right-sided heart valves. It is therefore of interest to examine the proportion of subjects who experienced any increase from baseline in valvular regurgitation of any cardiac valve at Week 52 (excluding absent to trace) was 33% in the lorcaserin 10 mg BID group and 28% in the placebo group (see following table from Dr. Golden's review).

Proportion of Subjects with an Increase from Baseline in Valvular Regurgitation at Week 52 Excluding Absent to Trace

	Lorcaserin 10 BID	Placebo	Relative Risk (95% CI)	P value
Aortic	1.25%	1.54%	0.81 (0.51, 1.30)	0.384
Mitral	9.99%	8.47%	1.18 (0.99, 1.41)	0.066
Pulmonic	17.48%	15.32%	1.14 (1.00, 1.30)	0.042
Tricuspid	12.25%	10.03%	1.22 (1.04, 1.43)	0.014
Any Valve	32.76%	28.42%	1.15 (1.06, 1.25)	0.001

The increases in the proportion of subjects exposed to lorcaserin 10 mg BID versus placebo that had increases in regurgitation of the pulmonic and tricuspid valves were of nominal statistical significance. The clinical significance of these findings is unknown.

Importantly, there were no cases of moderate or severe aortic regurgitation or severe mitral regurgitation observed in the BLOSSOM or BLOOM trials.

The echocardiographic data from the lorcaserin program provide reasonable assurance that this drug is not associated with the degree of risk for VHD observed with dexfenfluramine or fenfluramine. Taking into account the *in-vitro*, nonclinical, and clinical data, I do not believe that lorcaserin is associated with a prohibitive risk for FDA-defined VHD. However, I do believe serious thought should be given to obtaining additional echocardiographic data to provide a more precise estimate (i.e., tighter confidence interval) of lorcaserin's effect on valvular morphology and function. This could perhaps be done post-approval, assuming that the sponsor adequately addresses all other outstanding safety concerns and deficiencies.

Primary Pulmonary Hypertension

Some anorexigens, including dexfenfluramine and fenfluramine, have been associated with an increased risk for the development of primary pulmonary hypertension (PPH), a rare but usually fatal disease. As Dr. Golden discusses in her review, it is estimated that no more than 1 in 1000 individuals exposed for more than 3 months to fenfluramine or dexfenfluramine developed PPH. The mechanism(s) responsible for fenfluramine and dexfenfluramine-associated PPH are not well defined. Yet, some evidence suggests that activation of the 5HT2a or 5HT2b receptors may play a causative role. Although cardiac catheterization is required to definitively diagnose of PPH, pulmonary artery systolic pressure (PASP) of 27-50 mmHg suggest *possible* PPH and values greater than 50 mmHg suggest *likely* PPH.

As shown in the following table extracted from Dr. Golden's review, there was a slightly higher percentage of lorcaserin- compared with placebo-treated subjects who developed elevated PASP values during BLOOM and BLOSSOM.

Subjects with Elevated PASP Values during BLOOM and BLOSSOM

	Lorc 10 BID	**Pbo**
Week 52	N=1838	N=1632
≥ 35 mmHg	35 (1.9)	24 (1.5)
≥ 40 mmHg	5 (0.3)	3 (0.2)
≥ 45 mmHg	2 (0.1)	1 (0.1)
≥ 50 mmHg	2 (0.1)	0
≥ 55 mmHg	0	0
≥ 60 mmHg	0	0

On pages 95-96 of Dr. Golden's review case narratives are provided for the two lorcaserin-exposed subjects who developed PASPs > 50 mmHg. Based on this information, it is difficult to conclude that lorcaserin was a probable or even possible cause of the increased PASP readings.

No subject treated with lorcaserin was reported to have been diagnosed with PPH. Given the size and duration of the clinical development program, it is safe to assume that lorcaserin is not associated with an increase in the risk of PPH to a degree observed with fenfluramine and dexfenfluramine. But given the rarity of PPH, it would take wide-spread use of lorcaserin before one could determine if the drug is associated with a small or modest increase in risk for PPH. At this point, PPH remains a theoretical risk for lorcaserin.

Other Relevant Safety Considerations

There were two deaths reported during the development program; both in subjects randomized to placebo. The incidence rates for serious adverse events from the phase 3 clinical trials were 2.3% in placebo-treated subjects and 2.7% in subjects randomized to lorcaserin 10 mg BID.

A total of 0.8% of subjects randomized to lorcaserin 10 mg BID and 1.0% of subjects randomized to placebo from BLOOM and BLOSSOM were diagnosed with any type of cancer.

Four subjects (0.1%) randomized to lorcaserin 10 mg BID and four subjects (0.1%) randomized to placebo in BLOOM and BLOSSOM were diagnosed with breast cancer. The lack of an increase in the number of breast cancer cases in lorcaserin-treated subjects does not indicate that the drug is without risk for this cancer. The size and duration of the phase 3 trials and the average age of the study participants were inadequate to assess the question.

There was an imbalance in cognitive-related adverse events in subjects from the lorcaserin 10 mg BID groups (2.4%) compared with subjects from the placebo groups (0.8%). "Memory impairment," "disturbance in attention," and "amnesia" were the terms with the largest imbalances between active drug and placebo. These effects may be mediated through activation of the 5HT2a receptor in the CNS.

There were no notable imbalances between treatment groups in adverse events related to suicidality in the phase 3 clinical trials. Suicidality has been a concern with some centrally-acting weight-loss drugs.

Given lorcaserin's mechanism of action, serotonin syndrome is a potential risk for this compound. As noted on pages 117-118 of Dr. Golden's review, there were 2 cases from the lorcaserin development program that investigators considered to fall within the spectrum of serotonin toxicity. Both subjects were randomized to lorcaserin 10 mg BID. When all potential clinical signs or symptoms of serotonin toxicity – chills, tremor, confusional state, disorientation, and hyperhidrosis – were assessed, 1.7% of subjects from the lorcaserin 10 mg BID groups verus 0.6% of subjects from the placebo groups reported at least one of these signs or symptoms during the phase 3 clinical trials.

Dr. Alavi raises some concern in his review of nonclinical data about adverse renal findings in monkeys, but not rats, treated with lorcaserin. The adverse effects in monkeys included renal tubular regeneration and degeneration at lorcaserin doses $\geq$ 10 mg/kg and 125 mg/kg, respectively. There was no evidence from the phase 3 clinical trials that lorcaserin 10 mg BID increased risk for renal toxicity.

9. Advisory Committee Meeting

An advisory committee meeting was held on September 16, 2010, to discuss the efficacy and safety of lorcaserin. In response to the question of whether the potential benefits of lorcaserin

outweighed the potential risks, the committee voted 9 "no" and 5 "yes". The marginal weight-loss efficacy combined with uncertainty regarding the clinical relevance of the nonclinical tumor data and the "healthy" status of the subjects studies in the phase 3 clinical trials were principal reasons for the "no" votes.

10. Pediatrics

(b) (4)

Since the application is not being approved this review cycle, details of the proposed pediatric plan will be addressed in consultation with PeRC at a later date.

11. Other Relevant Regulatory Issues

Dr. Golden notes in her review that the sponsor has certified that no investigator from the phase 3 pivotal trials has entered into a financial agreement with the sponsor.

Routine inspection of four clinical sites by the Division of Scientific Investigation did not uncover any significant deficiencies or irregularities in reporting of clinical data.

The Controlled Substance Staff believe that lorcaserin has abuse potential and recommend that it be placed in Schedule IV of the Controlled Substance Act.

12. Labeling

Because the application will receive a Complete Response, there were no labeling reviews or negotiations with the sponsor.

13. Decision/Action/Risk Benefit Assessment

The clinical and pharmacology/toxicology reviewers recommend that the lorcaserin application not be approved at this time. I agree that the currently-available data do not support a favorable benefit-risk profile for lorcaserin. I support issuing a Complete Response on the PDUFA goal date of October 22, 2010.

The mean placebo-subtracted change in body weight in subjects treated with lorcaserin 10 mg BID for up to one year was approximately -3.0%. The proportion of subjects who lost $\geq$ 5% of baseline body weight was 47% in the lorcaserin 10 mg BID group and 23% in the placebo group. It is safe to assume that lorcaserin's efficacy in overweight and obese type 2 diabetics will be less than that demonstrated in the overweight and obese nondiabetics. Before re-considering approval of lorcaserin, the sponsor needs to submit the final study report for the recently-completed study in type 2 diabetics.

Although the Agency's draft obesity drug guidance states that efficacy will be assessed following one year of treatment, the sponsor voluntarily conducted a two-year trial. Data from

this trial raise concern that lorcaserin's efficacy wanes considerably with treatment beyond one year.

Against this marginal and perhaps transient efficacy, one must weigh the following potential risks:

1). Nonclinical tumorigenicity: In a two-year rat carcinogenicity study lorcaserin was associated with an increased number of benign and malignant tumors. Of greatest concern are malignant tumors of breast and brain tissue. Given irregularities in the diagnosing and reporting of breast adenocarcinomas and fibroadenomas during and following completion of the rat carcinogenicity study, I support pharmacology/toxicology's recommendation that *all* of the rat breast tissue slides be re-adjudicated by an independent pathologist(s). It is vital that we are confident in the histological diagnoses of all of the rat breast tumors, given that the target population for weight-loss drugs tends to be overweight and obese middle-aged women, individuals at heightened risk for breast cancer due to their body weight.

Regarding astrocytomas, I do not disagree with the recommendation to have the sponsor conduct a more detailed evaluation of rat brain tissue, but suspect that we will be left with some degree of uncertainty regarding the clinical relevance of the rat findings regardless of the outcome of the additional evaluations. Given that astrocytoma is a relatively uncommon tumor in humans (7-10 cases per 100,000 people), it is possible that a post-approval registry would be an acceptable approach to studying the clinical relevance of the rat data.

2). Valvular heart disease: Based on echocardiographic evaluation of approximately 7000 subjects, the sponsor provided evidence that rules out a 55% or greater increase in the risk for FDA-defined VHD. I believe additional echocardiographic data should be obtained to improve the precision of the risk estimate. However, depending on the sponsor's response to the deficiencies included in the Complete Response letter, it may be appropriate to obtain the additional echocardiographic data as a post-marketing requirement.

3). Cognitive-related adverse events: There was a notable imbalance in cognitive-related adverse event in subjects treated with lorcaserin versus placebo. When viewed in isolation, I do not believe that these adverse events would prevent approval of the drug.

4). Serotonin syndrome: There was a weak signal for serotonin toxicity from the phase 3 clinical data. This is not surprising given lorcaserin's mechanism of action. When viewed in isolation, I do not believe that this potential toxicity would prevent approval of the drug.

5). Primary pulmonary hypertension: There was perhaps a very weak signal for increased pulmonary artery pressure in lorcaserin-treated subjects. Given the rarity of PPH (~ 500 cases per year in the U.S.), the only realistic means to determine if lorcaserin increases the risk for the disease would be by conducting a case-control study post-approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
10/21/2010

COOLEY LLP
WILLIAM E. GRAUER (84806)
(grauerwe@cooley.com)
KOJI F. FUKUMURA (189719)
(kfukumura@cooley.com)
MARY KATHRYN KELLEY (170259)
(mkkelley@cooley.com)
RYAN E. BLAIR (246724)
(rblair@cooley.com)
4401 Eastgate Mall
San Diego, CA 92121
Telephone: (858) 550-6000
Facsimile: (858) 550-6420

Attorneys for Defendants Arena Pharmaceuticals, Inc., Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situation,

Plaintiff,

v.

ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON,

Defendants.

Case No. 10-CV-1959-CAB (BLM)

SECOND SUPPLEMENTAL DECLARATION OF RYAN E. BLAIR IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS SECOND CONSOLIDATED AMENDED CLASS ACTION COMPLAINT

Date: August 2, 2013
Time: 2:30 p.m.
Judge: Hon. Cathy Ann Bencivengo
Ctrm: 4C

[Oral argument requested subject to Court approval]

WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situation, Plaintiffs, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, and WILLIAM SHANAHAN, JR. Defendants.	Case No. 10-CV-1961-CAB (BLM)
WILLIAM PRATT, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1977-CAB (BLM)
CRAIG RUBENSTEIN, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1984-CAB (BLM)

RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2026-CAB (BLM)
THONG VU, Individually and on behalf of all others similarly situated Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2086-CAB (BLM)
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 10-cv-2335-CAB (BLM)

I, Ryan E. Blair, declare as follows:

1. I am an attorney with the law firm of Cooley LLP, counsel for defendants Arena Pharmaceuticals, Inc. ("Arena"), Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson (collectively, "defendants"). I have personal knowledge of the following facts and, if called upon to testify, I could and would testify competently thereto.

2. Attached hereto as Exhibit AZ is a true and correct copy of Arena's press release dated August 9, 2011.

3. Attached hereto as Exhibit BA is a true and correct copy of excerpts of the U.S. Food and Drug Administration's ("FDA") Briefing Document for the FDA Advisory Committee meeting on May 10, 2012 regarding lorcaserin, a copy of which is also available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303198.pdf (last visited June 11, 2013).

4. Attached hereto as Exhibit BB is a true and correct copy of Arena's Form 8-K, filed with the U.S. Securities and Exchange Commission ("SEC") on May 15, 2012.

5. Attached hereto as Exhibit BC is a true and correct copy of Arena's Form 8-K, filed with the SEC on June 28, 2012.

6. Attached hereto as Exhibit BD is a true and correct copy of Arena's Form 8-K, filed with the SEC on April 23, 2009.

7. Attached hereto as Exhibit BE is a chart comparing plaintiff's alleged misstatements in his Consolidated Amended Class Action Complaint (Dkt. No. 43) with the alleged misstatements in his Second Consolidated Amended Class Action Complaint (Dkt. No. 59). Defendants are not seeking judicial notice of Exhibit BE. Rather, they are including this chart for the Court's convenience.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 14 day of June, 2013, at San Diego, California.

Ryan E. Blair

TABLE OF CONTENTS FOR EXHIBITS
to
SECOND SUPPLEMENTAL DECLARATION OF RYAN E. BLAIR IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS THE SECOND CONSOLIDATED AMENDED CLASS ACTION COMPLAINT

Schueneman v. Arena Pharmaceuticals, Inc., et al.
Case No.: 10-CV-1959-CAB (BLM)

Exhibit AZ

Arena and Eisai Announce Results of Re-Adjudication of Rat Mammary Tumors from Lorcaserin Carcinogenicity Study

- Report to be included in Response to Lorcaserin CRL -

SAN DIEGO and WOODCLIFF LAKE, N.J., Aug. 9, 2011 /PRNewswire/ -- Arena Pharmaceuticals, Inc. (NASDAQ: ARNA) and Eisai Inc. announced today results from a Pathology Working Group's (PWG) re-adjudication of female rat mammary tumor diagnoses from a two-year rat carcinogenicity study of lorcaserin. Arena convened the PWG in response to the lorcaserin Complete Response Letter (CRL), which questioned the certainty of the female rat mammary tumor classifications. The PWG reviewed relevant tissues and reported that mammary fibroadenomas (benign tumors) were distinguishable from mammary adenocarcinomas (malignant tumors). The PWG reported shifts in the numbers of both tumor types from the initial report included in the lorcaserin New Drug Application (NDA) and that adenocarcinomas were no longer numerically higher than the control group in the lorcaserin low- and mid-dose groups.

"We believe the PWG's report should further clarify the female rat mammary tumor diagnoses which, in combination with other data, may be helpful in assessing human risk," said William R. Shanahan, M.D., Arena's Senior Vice President and Chief Medical Officer.

The PWG's re-adjudication is one of the activities intended to address the observation of mammary tumors in female rats and is part of the overall plan to submit a response to the lorcaserin CRL. Additional activities intended to address the CRL are ongoing.

Findings from Initial and PWG Reports

The PWG consisted of five pathologists contracted by Arena. Arena consulted the US Food and Drug Administration (FDA) in selecting those pathologists. According to the PWG's re-adjudication, the incidence of adenocarcinomas was numerically lower than the control group in both the lorcaserin low (10 mg/kg/day) and mid (30 mg/kg/day) dose groups and was statistically higher than the control group in the lorcaserin high (100/kg/day) dose group, and the incidence of fibroadenomas was statistically higher than the control group for all three lorcaserin dose groups. The incidences of adenocarcinomas and fibroadenomas from the initial report and the PWG report are summarized below.

Percent of Female Rats with Mammary Adenocarcinoma or Fibroadenoma				
Dose	Control	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
N	65	65	65	70
Mammary Adenocarcinoma (Malignant)				
Initial Report	43.1%	52.3%	53.8%	80.0%
PWG Report	40.0%	37.3%	36.9%	68.6%
Mammary Fibroadenoma (Benign)				
Initial Report	30.8%	72.3%	81.5%	80.0%
PWG Report	36.9%	83.1%	84.6%	88.6%

In addition, the PWG reported that the incidence of mammary adenomas (benign tumors) was 1.5%, 3.1%, 7.7%, 5.3%, the incidence of mammary carcinosarcomas (malignant tumors) was 0%, 0%, 0%, 1.3%, the incidence of lung metastases of mammary gland origin was 0%, 1.5%, 7.7%, 6.7%, and the incidence of lung metastases of non-mammary gland origin was 0%, 4.6%, 6.2%, 2.7% for the control and lorcaserin low-, mid- and high-dose groups, respectively. No mammary adenomas were diagnosed in the initial report, the incidence of mammary carcinosarcomas did not change from the initial report, and the incidence of lung metastases of both mammary and non-mammary origin were reported together in the initial report as 0%, 6.2%, 13.8% and 8.0% for the control and lorcaserin low-, mid- and high dose groups, respectively.

It is important to note that the FDA may have a different interpretation of the re-adjudication and subsequent conclusions of the

PWG. There may be other factors in addition to incidence that may contribute to the FDA's assessment of human risk for the finding of mammary tumors in female rats. The information reported in this press release summarizes a report containing voluminous and detailed data that will be reviewed by the FDA. The FDA may analyze or weigh the importance of data from the report differently than the PWG or Arena.

About Lorcaserin

Lorcaserin is an investigational drug candidate intended for weight management, including weight loss and maintenance of weight loss, in patients who are obese (BMI ≥ 30) or patients who are overweight (BMI ≥27) and have at least one weight-related co-morbid condition. Lorcaserin is a new chemical entity that is believed to act as a selective serotonin 2C receptor agonist. The serotonin 2C receptor is expressed in the brain, including the hypothalamus, an area believed to be involved in the control of appetite and metabolism. Arena has patents that cover lorcaserin in the United States and other jurisdictions that in most cases are capable of continuing into 2023 without taking into account any patent term extensions or other exclusivity Arena might obtain.

Arena submitted a NDA for lorcaserin to the FDA in December 2009, and the FDA issued a CRL in October 2010. Arena's wholly owned subsidiary, Arena Pharmaceuticals GmbH, has granted Eisai Inc. exclusive rights to market and distribute lorcaserin in the United States subject to FDA approval of the NDA for lorcaserin.

About Arena Pharmaceuticals

Arena is a clinical-stage biopharmaceutical company focused on discovering, developing and commercializing oral drugs that target G protein-coupled receptors, an important class of validated drug targets, in four major therapeutic areas: cardiovascular, central nervous system, inflammatory and metabolic diseases.

Arena Pharmaceuticals® and Arena® are registered service marks of the company.

About Eisai Inc.

Eisai Inc. was established in 1995 and is ranked among the top-25 US pharmaceutical companies (based on retail sales). The company began marketing its first product in the United States in 1997 and has rapidly grown to become a fully integrated pharmaceutical business. Eisai's areas of commercial focus include neurology, gastrointestinal disorders and oncology/critical care. The company serves as the US pharmaceutical operation of Eisai Co., Ltd., a research-based *human health care (hhc)* company that discovers, develops and markets products throughout the world.

Eisai has a global product creation organization that includes US-based R&D facilities in Massachusetts, New Jersey, North Carolina and Pennsylvania as well as manufacturing facilities in Maryland and North Carolina. The company's areas of R&D focus include neuroscience; oncology; vascular, inflammatory and immunological reaction; and antibody-based programs. For more information about Eisai, please visit www.eisai.com/us.

Forward-Looking Statements

Certain statements in this press release are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements about the advancement, therapeutic indication and use, safety, efficacy, tolerability, mechanism of action and potential of lorcaserin; the significance of the PWG's re-adjudication and report, including in assessing human risk and clarifying, and addressing, the female rat mammary tumor diagnoses; the FDA's assessment of human risk, analysis and weighting of data and interpretation of the PWG's re-adjudication, report and findings; the response to the CRL for the lorcaserin NDA, including related plans and activities; the Eisai collaboration and potential activities thereunder; lorcaserin's patent coverage, and Arena's focus, goals, strategy, research and development programs, and ability to develop compounds and commercialize drugs. For such statements, Arena claims the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from Arena's expectations. Factors that could cause actual results to differ materially from the forward-looking statements include, but are not limited to, the following: the FDA may not accept the PWG's re-adjudication, report or findings, may interpret and analyze the data differently and may reach different conclusions; the timing of regulatory review and approval is uncertain; the risk that data and other information related to Arena's research and development programs may not meet safety or efficacy requirements or otherwise be sufficient for regulatory approval; Arena's response to the CRL for the lorcaserin NDA or submission of a Marketing Authorization Application for regulatory approval of lorcaserin may not be submitted when anticipated, if at all; the FDA may request other information prior to or after Arena submits such response or approval of the lorcaserin NDA; unexpected or unfavorable new data; risks related to commercializing new products; Arena's ability to obtain and defend its patents; the timing, success and cost of Arena's research and development programs; results of clinical trials and other studies are subject to different interpretations and may not be predictive of future results; clinical trials and other studies may not proceed at the time or in the manner expected or at all; Arena's ability to obtain adequate funds; risks related to relying on collaborative agreements; the timing and receipt of payments and fees, if any, from collaborators; and satisfactory resolution of pending and any future litigation or other disagreements with others. Additional factors that could cause actual results to differ materially from those

stated or implied by Arena's forward-looking statements are disclosed in Arena's filings with the Securities and Exchange Commission. These forward-looking statements represent Arena's judgment as of the time of this release. Arena disclaims any intent or obligation to update these forward-looking statements, other than as may be required under applicable law.

Contacts: Arena Pharmaceuticals, Inc.

Investor Inquiries:	Media Inquiries: Russo Partners
Cindy McGee	David Schull
cmcgee@arenapharm.com	david.schull@russopartnersllc.com
858.453.7200, ext. 1479	858.717.2310

Contacts: Eisai Inc.

Investor Inquiries:	Media Inquiries:
Alex Scott	Lynn Kenney
alex_scott@eisai.com	lynn_kenney@eisai.com
201.746.2177	201.746.2294
www.arenapharm.com	www.eisai.com

SOURCE Arena Pharmaceuticals, Inc.

News Provided by Acquire Media

EXH. AZ
P. 461

Exhibit BA

FDA Briefing Document

NDA 22529

Lorcaserin Hydrochloride Tablets, 10 mg

Sponsor: Arena Pharmaceuticals

Endocrinologic and Metabolic Drugs Advisory Committee Meeting – May 10, 2012

DISCLAIMER

This briefing document contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The background package may not include all issues relevant to the final regulatory recommendation; instead, its intent is to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Section:

Discussion Points for Advisory Committee

1. Discuss whether the sponsor has provided an adequate response regarding diagnostic uncertainty for mammary tumors – i.e., adenocarcinomas versus fibroadenomas - in rats treated with lorcaserin.

2. Discuss whether the sponsor has provided an adequate response regarding the potential clinical risk associated with lorcaserin-induced mammary adenocarcinoma in rats (e.g., a sufficient safety margin).

3. Discuss whether the sponsor has provided sufficient evidence to conclude that elevation in plasma prolactin is the primary mode of action for the mammary tumors observed in rats.

4. Discuss whether the sponsor has provided an adequate response regarding the potential clinical risk associated with lorcaserin-induced astrocytoma in rats (e.g., a sufficient safety margin).

5. Taking into account the new in-vitro 5HT2 receptor potency data, discuss whether the phase 3 echocardiography data are sufficient to rule out a clinically meaningful increase in the risk for valvular heart disease in patients treated with lorcaserin.

6. Taking into account the March 28 and 29, 2012 advisory committee meeting on cardiovascular risk assessment of obesity drugs, discuss the available data to assess for excess risk for major adverse cardiovascular events in patients treated with lorcaserin.

7. Do the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals?

   If 'Yes', please provide your rationale and comment on the need for and approach to patient monitoring and risk management.

   If 'No', please provide your rationale and comment on what additional preclinical or clinical information should be required to potentially support approval.

Advisory Committee Nonclinical Briefing Document

Application: Lorcaserin hydrochloride, NDA 22-529
Drug Class: 5HT2c Receptor Agonist
Clinical Indication: Obesity
Reviewer: Fred Alavi, Ph.D. and Todd Boucher, Ph.D.
Division of Metabolism and Endocrinology Products

Re: Carcinogenicity Assessment of Lorcaserin in Rodents

Table of Contents

Executive Summary

Investigational drugs intended for chronic clinical use are evaluated for their potential to be carcinogenic in two species of rodents that are administered the drug for two years, roughly approximating a lifetime exposure. Lorcaserin was identified as a non-genotoxic carcinogen in the two-year bioassay in Sprague-Dawley rats. The incidence of multiple tumor types increased in response to lorcaserin, including mammary neoplasms in males and females, and neoplasms of the brain, peripheral nerves, skin, subcutis, and liver and thyroid gland of males. The Endocrine Advisory Committee convened in September 2010 in part to discuss the impact of these findings on the overall clinical risk/benefit for lorcaserin. Among the tumor types discussed, the occurrence of mammary and brain neoplasms were of most concern regarding human risk assessment because no safety margin was identified for the former, and the safety margin was uncertain for the latter. Also, the imbalanced reclassification of mammary neoplasms reduced confidence in the final incidence data for benign and malignant tumor types. The Agency did not agree that the Sponsor provided adequate information regarding lorcaserin's tumorigenic mode of action, which is critical for evaluating human risk when safety margins are absent or are uncertain.

The Complete Response Letter issued by the Agency in October 2010 directed the sponsor to resolve the diagnostic uncertainty in the classification of mammary masses in female rats and re-address the exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma. Also, the sponsor was directed to either establish a tumorigenic mode of action for lorcaserin-induced increases in astrocytoma or clarify the safety margin to the tumorigenic dose of lorcaserin.

The sponsor convened a pathology working group (PWG) to readjudicate all mammary and lung masses from female rats. Several changes were made to the dataset, and the re-adjudicated tumor incidence data is considered definitive based on the high degree of diagnostic consensus reached by the PWG in the blinded slide evaluation. Lorcaserin increased the incidence, tumor onset and multiplicity, and lethality of mammary adenocarcinoma with a reassuring safety margin of 24-fold to the clinical dose. Lorcaserin also increased the incidence, tumor onset and multiplicity, and lethality of benign fibroadenoma at all doses without a safety margin (≤ 7-fold) to the clinical dose. Lorcaserin minimally effected plasma and tissue prolactin and differentiation of mammary lobular structures in female rats in mechanistic studies up to three months duration, but the changes that were observed are consistent with hormonal action on mammary tissue. No pattern of change was observed for estrogen, progesterone, or luteinizing hormone, and the Agency is not aware of a threshold of prolactin beyond which mammary tumors emerge. Given the high sensitivity of SD rats to prolactin and the absence of changes in other hormones, it is plausible that minimal increases in prolactin induced by lorcaserin contributed to the emergence of fibroadenoma in female rats.

The sponsor chose to clarify the safety margin for lorcaserin-induced astrocytoma in rats rather than establish a tumorigenic mode of action. Clinical data was submitted indicating that partitioning of lorcaserin to the CNS in human subjects is substantially lower than predicted by nonclinical studies in rats and non-human primates. A safety margin of 70-fold for astrocytoma in rats, based on estimated brain levels of lorcaserin, presents a negligible clinical risk and obviates the need for mode-of-action data.

EXH. BA
P. 467

Background

Carcinogenic Assessment of Investigational Pharmaceutical Compounds
Investigational drugs intended for chronic (≥ 6 months) use in human subjects are evaluated for their potential to be carcinogenic. Because genotoxic compounds are closely associated with carcinogenicity, the potential genotoxicity of pharmaceutical compounds and associated metabolites is also assessed in a standard battery of studies. Carcinogenesis is formally evaluated in two species of rodents that receive the drug for two years, roughly approximating lifetime exposure to drug. The two-year 'bioassay' is designed to detect drug-induced tumors that arise from genotoxic as well as non-genotoxic mechanisms of action.

Lorcaserin Genotoxicity Assessment
Lorcaserin and its major sulfated metabolite (APD244208) showed no evidence of genotoxic effects in a standard battery of bacterial and mammalian systems. Non-genotoxic mechanisms are therefore thought to underlie lorcaserin-induced tumors observed in the rat carcinogenicity study (described below). Examples of non-genotoxic mechanisms of neoplasia include direct or indirect promotion of cell growth or survival and persistent perturbation of hormone status.

Toxicological Findings in Short-Term Studies Pertinent to Assessment of Carcinogenicity
Toxicity of lorcaserin was tested in standard 3- and 6-month studies in Sprague Dawley rats. Doses were tolerated up to 100 mg/kg in the 3 month study, and doses up to 50mg/kg were evaluated in the 6-month study. The final report for both studies stated that the principle test article-related effect was hepatocellular centrilobular hypertrophy (minimal to moderate) and red cell turnover with splenic extramedullary hematopoeisis. Reproductive organ weight and histology of other organs, including the mammary, skin, and nervous system tissues, were reported as being within the range commonly seen in rats of this strain and age.

Summary of Carcinogenicity Studies Submitted in Original NDA

Mouse Carcinogenicity study
The carcinogenicity study in mice was completed with doses of 5, 25 and 50 mg/kg. These doses were tolerated and survival in lorcaserin-dosed groups was similar to the control group at the end of the 2 year study period. Review of the results by the Agency and the FDA's Executive Carcinogenesis Assessment Committee is consistent with the Sponsor's conclusion that no drug-related tumors were observed in mice (**Appendix A**). Exposure to lorcaserin at the No-Observed Adverse Effect (NOAEL) of 50mg/kg is 4- to 7-times higher than exposure at the clinical dose of 10mg BID, based on AUC.

Rat Carcinogenicity Study
The carcinogenicity of lorcaserin was assessed at 10, 30 and 100 mg/kg of lorcaserin in seven-week old male and female Sprague-Dawley (SD) rats. Lorcaserin was prepared in water and administered daily by gavage to rats. Note that the doses and exposure to lorcaserin in rats (**Table 1**) was substantially greater than that achieved in mice (≤ 7x clinical exposure).

Table 1: Lorcaserin doses and multiples of clinical exposure achieved in 2yr rat study

	Dose, mg/kg	Rats/sex/group	Male	Females
104-week Rat Carcinogenicity Study	0 (C)	65	-	-
	10 (LD)	65	5x	7x
	30 (MD)	65	17x	24x
	100 (HD)	75	55x	82x

Exposure multiples calculated as plasma AUC exposure in rats divided by average AUC exposure of the clinical dose of lorcaserin, 30mg BID, 3.02 ug*h/ml AUC

In May 2007, the sponsor submitted a safety report informing the Agency of increased mortality of female rats due to mammary adenocarcinoma and fibroadenoma at all doses of lorcaserin by week 55 of the ongoing study. Additionally, the sponsor described a higher incidence of astrocytoma in a few mid- and high-dose males and females, but none in the control or low dose groups. In response, the Agency requested that the sponsor provide bi-monthly updates on survival and tumor incidence, along with data to support the sponsor's suggestion that prolactin dysregulation may be causative of the mammary neoplasms in rats. These bi-monthly updates were reviewed and the findings were periodically consulted with the FDA's Executive Carcinogenicity Assessment Committee (eCAC), and considered consequential for the ongoing phase 3 clinical studies. By week 96 of the rat study, the number of deaths and the incidence of malignant and benign mammary tumors were reportedly increased at all doses of lorcaserin (**Table 2a**). The Agency requested that the sponsor meet with the Agency in April 2008 to discuss the tumor findings in rats and the potential safety implications for the ongoing clinical studies. At that meeting, the sponsor reported that the incidence of malignant adenocarcinoma in the mid- and high-dose females at week 104 was in fact notably lower than reported at the week 96 update (**Table 2a**), and that the incidence of benign fibroadenoma was notably higher than previously reported (**Table 2b**). This pattern of tumor reclassification was imbalanced and favored lorcaserin by reducing the malignancies at the low and mid-doses. Reasons for the apparent diagnostic uncertainty between the primary and peer-reviewing pathologists were not documented and therefore not available. Continuation of clinical studies was considered appropriate because: 1) the rat study was not yet complete and tumor incidence could change further, 2) the reclassified interim tumor data suggested that malignancies were confined to the highest dose of lorcaserin, 3) preliminary data in male rats suggested that lorcaserin may modestly increase prolactin, and prolactin would be monitored in the ongoing clinical trials. Investigator brochure and patient informed consent documents were updated to include the tumor findings in rats.

NDA Resubmission and Responses to Complete Response Letter

This section summarizes the Agency's review of the new data provided in the sponsor's NDA resubmission that included responses to the CRL items discussed above.

CRL Item #1: ***Resolve diagnostic uncertainty in the classification of mammary masses in female rats***

Under this item, the sponsor was tasked with accounting for the change in mammary tumor diagnoses from the interim updates to the final study report and with having all mammary and lung tissues (for metastases) re-adjudicated by an independent pathologist(s). The sponsor informed the Agency that the contracting lab that conducted the rat study had not kept records of diagnostic changes for rats in the course of submitting the bimonthly updates, despite the fact that such updates were being used by the Agency in making regulatory decisions. This information is therefore unattainable. While such information may have shed light on the reasons for the prior diagnostic changes, the Agency agrees that re-adjudication of slides by independent pathologists would provide the definitive tumor incidence data necessary for re-assessing risk.

In consultation with the Agency, the sponsor convened a five member pathology working group (PWG) to re-adjudicate all mammary and lung tissues from female animals of all dose groups from the 2yr study. In addition, all subcutaneous tumors were submitted for re-adjudication. Mammary slides were blinded for animal ID and prior diagnosis. After each pathologist had diagnosed each slide, the PWG was convened to produce a consensus diagnosis for each slide and animal. The animal ID and prior diagnoses were then unblinded to document the diagnostic changes made by the PWG from the original study report. The PWG issued separate blinded and unblinded reports discussing the results. Members of the PWG are identified in **Appendix D**.

The PWG reached a high degree of consensus in accurately diagnosing mammary adenocarcinoma and fibroadenoma in the blinded assessment (**Table 5**). There was complete agreement on diagnosing metastatic mammary adenocarcinoma in lung tissue. The diagnostic certainty reported by the PWG in distinguishing benign from malignant mammary tumors contrasts sharply with the diagnostic uncertainty apparent in the original study report. Therefore, the Agency considers the results of the PWG as the definitive dataset for mammary tumor incidence in female rats for this study.

Table 5
Degree of Consensus for Neoplastic Lesions among PWG Group Members

Diagnosis	Number of consensus by 3/5 on PWG	Number of consensus by 4/5 on PWG	Number of consensus by 5/5 on PWG	% Unanimous Consensus
Adenocarcinoma	3	12	156	92.9%
Adenoma	2	2	15	78.9%
Fibroadenoma	7	14	715	97.1%
Fibroma	3	1	9	69.2%
Mammary Adenocarcinoma (metastatic)	0	0	21	100%
Carcinoma (metastatic, not mammary origin)	0	3	11	78.6%

The PWG reduced the incidence of adenocarcinoma particularly in the lorcaserin-dosed groups, while increasing the incidence of fibroadenoma more consistently across all groups including the control group. The number of adenocarcinoma in the vehicle, LD, MD and HD groups were reduced by 1, 13, 11 and 9, respectively. Fibroadenoma was diagnosed more frequently by the PWG and the incidence increased by 4, 7, 2 and 6 in the control, LD, MD and HD groups, respectively (**Table 6**).

Table 6
Re-adjudicated incidence of mammary tumors compared to incidences reported in the original study report.

Re-Adjudicated Mammary Tumors in Female SD Rats		Lorcaserin dose, mg/kg			
		0	**10**	**30**	**100**
	Number of female rats/group	**65**	**65**	**65**	**75**
Adenocarcinoma	Original study	28	34	35	60
	PWG	**26**	**21**	**24**	**51***
Fibroadenoma	Original study	20	47	53	45
	PWG	**24**	**54***	**55***	**51***
Adenoma	Original study	0	0	0	0
	PWG	**1**	**2**	**5**	**4**
Lung metastases from primary mammary adenocarcinoma	Original study	0	2	7	6
	PWG	**0**	**1**	**5**	**5**

*statistical significance by trend and pair-wise comparison
Historical range for female rats from study site for last 5yrs.
Adenocarcinoma: 8.3 – 37%, mean 24%
Fibroadenoma: 22 – 54%, mean 36%

EXH. BA
P. 471

The diagnostic certainty expressed by the PWG members allows adenocarcinoma and fibroadenoma to now be evaluated separately with confidence. Statistical analysis of re-adjudicated incidence data demonstrated that adenocarcinoma increased with statistical significance at 100mg/kg lorcaserin. The numerical increase at the low and mid-doses of lorcaserin seen in the prior data is now absent, with the incidence of adenocarcinoma in these groups now similar to the concurrent and historical controls. A No-Observed-Adverse-Effect-Level (NOAEL) for adenocarcinoma is confidently identified at 30mg/kg lorcaserin. This NOAEL provides a safety margin of 24-fold to the clinical dose of 10mg BID, based on AUC exposure.

The re-adjudicated incidence data demonstrated that benign mammary fibroadenoma increased at all doses with statistical significance, with no safety margin identified (safety margin is less than 7-fold the clinical dose).

CRL Item #2: ***Clarify the exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma***

Under this item, the Sponsor was tasked with demonstrating that the apparent increase in the aggressiveness of adenocarcinoma at all doses of lorcaserin was reasonably irrelevant to human risk assessment. This item was based on several observations in the low- and mid-dose lorcaserin groups, particularly the numerical increase in adenocarcinoma, the higher incidence of lung metastases originating from mammary tissue, and the apparent decrease in tumor latency and increase in tumor multiplicity that could not be clearly ascribed to benign or malignant tumor types.

As discussed under CRL Item #1, the PWG reduced the number of adenocarcinoma in the low- and mid-dose groups such that the numerical increase reported in the original NDA was no longer present. As stated, the Agency accepts the PWG findings as definitive based on the degree of consensus reached among the five PWG members.

In consultation with the PWG, the Sponsor provided new analyses pertinent to metastases, onset, and multiplicity of adenocarcinoma in female rats.

Metastases

In the original report, mammary adenocarcinoma metastasized to the lung in groups administered lorcaserin but not in control, with an incidence of 0, 2, 7, and 6 for the control, low, mid, and high doses, respectively. The PWG lowered the incidence of lung metastases that originated from mammary adenocarcinoma to 0, 1, 5, and 5 for the control, mid, and high doses (**Table 7**).

Consistent with an increased incidence at all doses of lorcaserin, the reduced time to tumor onset, increased tumor multiplicity, and increased lethality of fibroadenoma clearly indicates a treatment-related effect of lorcaserin without a safety margin to the clinical dose.

Tumorigenic Mode of Action Data

Summary

Readjudication by the PWG allowed identification of a 24-fold safety margin for mammary adenocarcinoma relative to the clinical dose of 10mg bid lorcaserin. In general, the Agency interprets a 24-fold safety margin to a non-genotoxic carcinogen in rodents as indicative of negligible risk to human subjects. Therefore, identifying a tumorigenic mode of action is not necessary to re-assess risk when a sufficient safety margin has been confidently established, as is now the case with lorcaserin.

Benign fibroadenoma, however, increased at all doses of lorcaserin and no safety margin to the clinical dose was identified. The clinical risk presented by benign fibroadenoma in SD rats is appreciably less than for malignant adenocarcinoma, whether or not a tumorigenic mode of action has been identified. Nevertheless, in an effort to further characterize the clinical risk presented by fibroadenoma in female rats, the Sponsor submitted a series of studies that addressed the potential role of prolactin as the tumorigenic mode of action for lorcaserin.

Sprague Dawley rats spontaneously develop mammary and pituitary tumors with age, and pituitary-derived prolactin is known to be the primary hormone that drives mammary development in rodents. Anti-dopaminergic drugs (anti-psychotics and anti-emetics) result in persistent hyperprolactinemia in rodents that eventually lead to benign and malignant mammary neoplasms in 2yr bioassays. The SD rat is considered very sensitive to prolactin-induced mammary tumorigenesis, but this pathway is not considered a rodent-specific response. The clinical relevance of prolactin-induced mammary neoplasia in rodents remains unsettled, but the current literature points to an association of high prolactin, including that induced by dopamine antagonists, with human breast cancers in women[1].

Lorcaserin minimally effected plasma and tissue prolactin levels and resulted in minimal differentiation of mammary lobular structures and increased secretory product in studies up to three months duration in female rats. By comparison, the dopamine antagonist perphenazine resulted in unequivocal and robust increases in plasma and tissue prolactin and resulted in clear differentiation of mammary lobular structures and secretory product in the same studies. In the Agency's opinion, experimental efforts to block the effect of prolactin yielded equivocal results as a consequence of the small prolactin signal generated by lorcaserin and by the dose/duration limitations encountered in the studies. No clear pattern of change was noted in the level of other hormones including estrogen, progesterone, and luteinizing hormone. Despite the minimal prolactin signal generated by lorcaserin, the equally minimal histological changes in the mammary tissue are consistent with the hormonal effect of prolactin on these tissues. To the Agency's knowledge, there is no threshold of exposure to prolactin identified in the literature beyond which results in mammary neoplasms after chronic exposure in SD rats. Given the high sensitivity of SD rats to prolactin and the absence of changes in other hormones, it is plausible that the minimal increase in exposure to prolactin induced by lorcaserin contributes to the emergence of fibroadenoma in female rats.

[1] Tworoger & Hankinson (2008) J Mammo Gland Biol Neoplas. 13(1):41-53. Harvey PW et al (2008) J Psychopharmacol. 22:20-25. Wang et al (2002) Arch Gen Psychiatry. 59(12). 1147-1154

Exhibit BB

ARENA PHARMACEUTICALS INC

FORM 8-K
(Current report filing)

Filed 05/15/12 for the Period Ending 05/15/12

Address	6166 NANCY RIDGE DR SAN DIEGO, CA 92121
Telephone	8584537200
CIK	0001080709
Symbol	ARNA
SIC Code	2834 - Pharmaceutical Preparations
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	12/31

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): May 15, 2012

Arena Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware	000-31161	23-2908305
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

6166 Nancy Ridge Drive
San Diego, CA 92121
(Address of principal executive offices, including zip code)

Registrant's telephone number, including area code: 858.453.7200

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

EXH. BB
P. 475

In this report, "Arena Pharmaceuticals," "Arena," "Company," "we," "us" and "our" refer to Arena Pharmaceuticals, Inc., unless the context otherwise provides.

Item 8.01 Other Events.

We are filing the following information with the Securities and Exchange Commission for the purpose of updating certain aspects of our publicly disclosed description of our business and risk factors, as set forth below.

BUSINESS

We are a clinical-stage biopharmaceutical company focused on discovering, developing and commercializing oral drugs that target G protein-coupled receptors, or GPCRs, an important class of validated drug targets, in four major therapeutic areas: cardiovascular, central nervous system, inflammatory and metabolic diseases. We have submitted regulatory applications for US and EU approval of our most advanced drug candidate, lorcaserin, which is intended for weight management. We intend to selectively advance certain of our research and development programs, and also to seek collaborators or other licensing opportunities for our programs.

In December 2011, we resubmitted to the US Food and Drug Administration, or FDA, a New Drug Application, or NDA, for lorcaserin. The FDA accepted the resubmission for filing and review and assigned a new Prescription Drug User Fee Act, or PDUFA, target date of June 27, 2012. Previously, in October 2010, the FDA issued a Complete Response Letter, or CRL, with respect to the original lorcaserin NDA we submitted in December 2009. In the CRL, the FDA stated that it had determined that it could not approve the application in its then present form.

On May 10, 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the lorcaserin NDA. The advisory committee voted 18 to 4, with one abstention, that the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals.

We are also seeking regulatory approval for lorcaserin in the European Union. On March 2, 2012, we filed a marketing authorization application, or MAA, for lorcaserin through the centralized procedure with the European Medicines Agency, or EMA. The EMA accepted the filing, which initiates the EMA's review process.

Our wholly owned subsidiary, Arena Pharmaceuticals GmbH, or Arena GmbH, has provided Eisai Inc., or Eisai, exclusive rights to commercialize lorcaserin in most of North and South America, including the United States, Canada, Mexico and Brazil, subject to applicable regulatory approval. We have retained commercial rights to lorcaserin outside of North and South America, including in the European Union and Asia.

Our prioritized earlier stage programs include APD811, an internally discovered, orally available agonist of the prostacyclin receptor intended for the treatment of pulmonary arterial hypertension. APD811 completed a single-dose, Phase 1 clinical trial in 2011, and we plan to initiate a multiple dose, dose titration, Phase 1 clinical trial of APD811 this year. We also plan to file in 2012 an Investigational New Drug, or IND, application with the FDA for APD334 (an internally discovered, orally available agonist of the S1P1 receptor intended for the treatment of a number of conditions related to autoimmune diseases, including multiple sclerosis) and to continue development of our programs on APD371 (an internally discovered, orally available agonist of the cannabinoid receptor 2 intended for the treatment of pain) and GPR119 agonists (intended for the treatment of type 2 diabetes).

Along with lorcaserin and our prioritized earlier-stage programs, we have additional internally discovered oral drug candidates as well as active research programs intended to discover drug candidates. With respect to the additional drug candidates, we are not planning to conduct significant development activities, including any clinical trials, at this time. We may consider resuming their development in the future with one or more collaborators or independently, depending on the cost of further development, financial resources and their potential.

The headquarters of our operations outside of the United States is in Switzerland at Arena GmbH. Activities conducted at this location include manufacturing, quality control, quality assurance, development of manufacturing processes, qualifying suppliers and otherwise managing the global supply chain, regulatory compliance, distribution of finished products, and European strategic planning and development.

We have commercial rights for all of our programs and drug candidates, with the exception of Eisai's right to commercialize lorcaserin in most of North and South America. We have not received regulatory approval to market or sell any drugs to generate commercial revenues from selling any drugs, other than in connection with manufacturing drugs for Siegfried Ltd. in our Swiss drug product manufacturing facility.

RISK FACTORS

Investment in our stock involves a high degree of risk. You should consider carefully the risks described below, together with the other information in this Current Report and in our other public filings before making investment decisions regarding our stock. If any of the following events actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. Moreover, the risks described below are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business, operating results, prospects or financial condition.

Risks Relating to Our Business

We may not receive FDA approval for lorcaserin despite the recent vote of the FDA advisory committee.

In December 2011, we resubmitted the lorcaserin NDA, and the FDA subsequently accepted the NDA for filing. On May 10, 2012, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the resubmitted NDA, and the committee voted 18 to 4, with one abstention, that the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals. The FDA is not bound by the recommendations of its advisory committees, but is expected to consider their guidance during the review of the NDA. The PDUFA target date for lorcaserin is June 27, 2012. There is no assurance that we will receive approval for lorcaserin on the PDUFA target date or ever. The FDA may decline not to approve lorcaserin, may issue another CRL, may extend the PDUFA target date or may take various other actions. If lorcaserin is not approved for commercial sale or if its development or approval is delayed for any reason, our full investment in lorcaserin may be at risk, the market price of our common stock could decline significantly, we may not be able to generate sufficient revenues to continue our operations at the current level or become profitable, our reputation in the industry and in the investment community would likely be significantly damaged, additional funding may not be available to us or may not be available on terms we or others believe are favorable, our ability to enter into additional collaborative agreements would likely decrease significantly, we may face costs associated with stopping development of lorcaserin, and our business and financial condition could be materially adversely affected.

Risks Relating to Our Securities

We have reserved for future issuance substantially all of our authorized but unissued shares of common stock, which may impair our ability to conduct future financing and other transactions.

Our certificate of incorporation currently authorizes us to issue up to 242,500,000 shares of common stock and 7,500,000 shares of preferred stock. As of May 10, 2012, we had a total of 184,500,778 shares of common stock outstanding. Of the remaining shares of common stock that were authorized but unissued, a substantial portion are reserved for future issuance pursuant to options outstanding under our equity incentive plans, shares issuable under our 2009 Long-Term Incentive Plan, shares issuable under our 2009 Employee Stock Purchase Plan, shares issuable under our Deferred Compensation Plan, and shares issuable under warrants to purchase shares of our common stock with an expiration date of June 17, 2015, a seven-year warrant issued in June 2006 to purchase shares of our common stock and a seven-year warrant issued in August 2008 to purchase shares of our common stock. As a result, our ability to issue shares of common stock other than pursuant to existing arrangements will be limited until such time, if ever, that we are able to further amend our certificate of incorporation to increase our authorized shares of common stock or shares currently reserved for issuance otherwise become available (for example, due to the termination of the underlying agreement to issue the shares).

In lieu of issuing common stock or securities convertible into or exercisable for shares of our common stock in any future equity financing transactions, we may need to issue some or all of our authorized but unissued shares of preferred stock, which would likely have superior rights, preferences and privileges to those of our common stock, or we may need to issue debt that is not convertible into shares of our common stock, which may require us to grant security interests in our assets and property or impose covenants upon us that restrict our business. If we are unable to issue additional shares of common stock or securities convertible into or exercisable for shares of our common stock, our ability to enter into strategic transactions, such as acquisitions of companies or technologies, may also be limited.

We are proposing to our stockholders at our June 2012 annual stockholders' meeting to further amend our certificate of incorporation to increase the total number of our authorized shares from 350.0 million to 375.0 million and to increase the number of authorized shares of common stock from 262.5 million to 367.5 million. This proposal requires approval by the holders of a majority of our outstanding shares of common stock then entitled to vote, and we cannot assure you that such a proposal will be approved. If we are unable to complete financing, strategic or other transactions due to our inability to issue additional shares of common stock or securities convertible into or exercisable for shares of our common stock, our financial condition and business prospects may be materially harmed.

Forward-Looking Statements

Certain statements in this Form 8-K are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include statements about the advancement, therapeutic indication and use, safety, efficacy, mechanism of action and potential of lorcaserin; the regulatory review of lorcaserin regulatory filings; the potential approval and commercialization of lorcaserin; the collaboration with Eisai and activities thereunder; our plans to further amend our certificate of incorporation to increase our number of authorized shares; and our focus, goals, strategy, research and development programs, and ability to develop compounds and commercialize drugs. For such statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from our expectations. Factors that could cause actual results to differ materially from the forward looking statements include, but are not limited to, the following: the timing of regulatory review is uncertain and our applications for regulatory approval of lorcaserin may not be reviewed when or as anticipated; the timing, results, influence and other impact of FDA advisory committee meetings relating to lorcaserin and other drug candidates; the FDA may not complete its review of the lorcaserin NDA resubmission by the PDUFA date, nonclinical and clinical data is voluminous and detailed, and regulatory agencies may interpret or weigh the importance of data differently and reach different conclusions than we or others, request additional information, have additional recommendations or change their guidance or requirements before or after approval; data and other information related to lorcaserin and our other research and development programs may not meet safety, efficacy or other regulatory requirements or otherwise be sufficient for regulatory review or approval; even if any of our drug candidates is approved for marketing, such approval may be subject to limitations on the indicated uses, restricted distribution methods and other limitations; risks related to commercializing new products; unexpected or unfavorable new data, our ability to obtain and defend our patents; the timing, success and cost of our research and development programs; results of clinical trials and other studies are subject to different interpretations and may not be predictive of future results; clinical trials and other studies may not proceed at the time or in the manner expected or at all; risks associated with obtaining stockholder approval; having adequate funds; risks related to relying on collaborative agreements; the timing and receipt of payments and fees, if any, from collaborators; and satisfactory resolution of litigation or other disagreements with others. Additional factors that could cause actual results to differ materially from those stated or implied by our forward-looking statements are disclosed in our filings with the Securities and Exchange Commission. These forward-looking statements represent our judgment as of the time of the filing of this Form 8-K. We disclaim any intent or obligation to update these forward looking statements, other than as may be required under applicable law.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ARENA PHARMACEUTICALS, INC.

Dated: May 15, 2012

By: /s/ Steven W. Spector
Steven W. Spector
Executive Vice President, General Counsel and Secretary

Exhibit BC

ARENA PHARMACEUTICALS INC

FORM 8-K
(Current report filing)

Filed 06/28/12 for the Period Ending 06/27/12

Address	6166 NANCY RIDGE DR SAN DIEGO, CA 92121
Telephone	8584537200
CIK	0001080709
Symbol	ARNA
SIC Code	2834 - Pharmaceutical Preparations
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	12/31

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): June 27, 2012

Arena Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware	000-31161	23-2908305
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

6166 Nancy Ridge Drive, San Diego, California 92121
(Address of principal executive offices) (Zip Code)

858.453.7200
(Registrant's telephone number, including area code)

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

In this report, "Arena Pharmaceuticals," "Arena," "Company," "we," "us" and "our" refer to Arena Pharmaceuticals, Inc., unless the context otherwise provides. BELVIQ® is a registered trademark of Arena Pharmaceuticals GmbH.

Item 8.01 Other Events.

On June 27, 2012, we and Eisai Inc., or Eisai, announced that the U.S. Food and Drug Administration, or FDA, approved Arena's internally discovered and developed drug, BELVIQ (lorcaserin hydrochloride). Below is information on the following: (i) certain expected payments and financial terms relating to the previously announced Amended and Restated Marketing and Supply Agreement between Eisai and our wholly owned subsidiary, Arena Pharmaceuticals GmbH; (ii) the FDA approval of BELVIQ; and (iii) the lorcaserin marketing authorization application, or MAA, submission with the European Medicines Agency, or EMA.

Update on Amended and Restated Marketing and Supply Agreement with Eisai

Following the FDA approval of BELVIQ, we will receive the following milestone payments from Eisai under the Amended and Restated Marketing and Supply Agreement:

- $20 million, which is due within 30 days of the FDA approval. This payment was triggered because the FDA approved prescribing information includes the efficacy and safety data from our BLOOM-DM trial in patients with type 2 diabetes.
- $5 million following the scheduling designation for BELVIQ by the Drug Enforcement Administration of the US Department of Justice, or DEA.
- $60 million following DEA scheduling designation and delivery of launch supply.

Other financial terms, including additional milestones, the purchase prices and purchase price adjustments are described in the current report on Form 8-K we filed with the Securities and Exchange Commission on May 16, 2012. The first purchase price adjustment of $25 million, plus a milestone payment of $30 million, are due if annual net sales reach $250 million.

FDA Approval of BELVIQ

The FDA approved BELVIQ (pronounced BEL-VEEK) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index, or BMI, of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes). The indication includes the following limitations of use: (i) the safety and efficacy of coadministration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established, and (ii) the effect of BELVIQ on cardiovascular morbidity and mortality has not been established.

Three double-blind, randomized, placebo controlled trials demonstrated that BELVIQ along with diet and exercise was more effective than diet and exercise alone at helping patients lose 5% or more of their body weight after one year and managing the weight loss for up to two years.

In clinical trials, the most common adverse reactions for patients without diabetes treated with BELVIQ were headache, dizziness, fatigue, nausea, dry mouth, and constipation. In patients with diabetes, the most common adverse reactions were hypoglycemia, headache, back pain, cough, and fatigue.

The FDA has recommended that BELVIQ be classified by the DEA as a scheduled drug. The DEA will review the FDA's recommendation and determine the final scheduling designation. Once the DEA has provided the final scheduling designation, Eisai will announce when BELVIQ will be available to patients and physicians in the United States.

We will manufacture and supply the finished commercial product from our facility in Switzerland, and Eisai will market and distribute BELVIQ in the United States.

As part of the approval of BELVIQ, we and Eisai committed to conduct post-marketing studies to assess the safety and efficacy of BELVIQ for weight management in obese pediatric patients, as well as to evaluate the effect of long-term treatment with BELVIQ on the incidence of major adverse cardiovascular events in overweight and obese subjects with cardiovascular disease or multiple cardiovascular risk factors. The cardiovascular outcomes trial will include echocardiographic assessments.

Important Safety Information

- **Pregnancy:** BELVIQ should not be taken during pregnancy or by women who are planning to become pregnant.
- **Nursing:** BELVIQ should not be taken while breastfeeding.
- **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions**: BELVIQ and certain medicines for depression, migraine, the common cold, and mood, anxiety, psychotic or thought disorders or other medical problems may affect each other causing serious or life threatening side effects. Patients should tell their doctor if they are taking medicines to treat any of these conditions such as: triptans, tricyclics, lithium, selective serotonin uptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), or antipsychotics; linezolid, an antibiotic; tramadol, dextromethorphan, an over-the-counter medicine used to treat the common cold or cough; over-the-counter supplements such as tryptophan or St. John's Wort. BELVIQ and these medicines should be discontinued immediately and symptomatic treatment measures should be initiated if patients taking BELVIQ and these other medicines experience any of the following: mental changes such as agitation, hallucinations, confusion, or other changes in mental status, coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes); restlessness; racing or fast heartbeat, high or low blood pressure; sweating or fever; nausea, vomiting, or diarrhea; or muscle rigidity (stiff muscles).
- **Valvular Heart Disease:** Certain weight loss drugs have been associated with problems with the valves in the heart. Patients taking BELVIQ who have trouble breathing,

swelling of the anus, legs, ankles, or feet, dizziness, fatigue, or weakness that will not go away, or fast or irregular heartbeat should call their doctor right away. Before taking BELVIQ, patients should tell their doctor if they have or had heart problems including congestive heart failure, or heart valve problems. Patients should not take BELVIQ in combination with drugs that have been associated with valvular heart disease (such as cabergoline). Patients who develop signs and symptoms of valvular heart disease while taking BELVIQ should be evaluated and discontinuation of BELVIQ should be considered by their doctor.

- **Changes in Attention or Memory:** Problems with thinking, sleepiness, confusion, and fatigue have been reported in patients taking BELVIQ.
- Patients taking BELVIQ should not drive a car or operate heavy machinery until they know how BELVIQ affects them.
- **Mental Problems:** Taking BELVIQ at higher than the recommended dose may cause psychiatric problems such as: hallucinations, feeling high or in a very good mood (euphoria), feelings of standing next to yourself or out of your body (dissociation). The recommended dose of 10 mg twice daily should not be exceeded. Patients should be monitored for the development or worsening of depression, suicidal thoughts or behaviors, and/or any changes in mood. BELVIQ should be discontinued if patients develop suicidal thoughts or behaviors.
- **Low Blood Sugar (Hypoglycemia):** Weight loss can cause low blood sugar in people with type 2 diabetes mellitus who are on medicines to treat it such as metformin, insulin, or sulfonylureas. Blood sugar levels should be monitored for patients who take BELVIQ. Changes to medicines may be needed if low blood sugar develops.
- **Painful Erections (Priapism):** If patients taking BELVIQ experience an erection lasting more than 4 hours, whether it is painful or not, they should stop using BELVIQ and call their doctor or go to the nearest emergency room right away. BELVIQ should be taken with caution by men who have conditions that might predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with a deformed penis. Patients should tell their doctor if they take medicines used to treat erectile dysfunction.
- **Slow Heartbeat:** BELVIQ may cause a slow heartbeat. Patients taking BELVIQ should tell their doctor if they have a history of a slow heartbeat or heart block.
- **Decreases in Blood Cell Count:** BELVIQ may cause decreases in red or white blood cell count. A doctor may do tests to check a patient's blood cell count during treatment with BELVIQ.
- **Increase in Prolactin:** BELVIQ may increase the amount of a hormone the body makes, called prolactin. Patients taking BELVIQ should tell their doctor if their breasts begin to make milk or have a milky discharge or if their breasts begin to increase in size.
- **Increased Pressure in the Arteries of the Lung (Pulmonary Hypertension):** Certain weight loss drugs have been associated with the rare but life threatening side effect of increased pressure in the arteries of the lung. It is unknown if BELVIQ increases the risk for this condition.
- **Most Common Adverse Reactions in Non-Diabetic Patients:** Headache, dizziness, fatigue, nausea, dry mouth, and constipation.
- **Most Common Adverse Reactions in Diabetic Patients:** Hypoglycemia, headache, back pain, cough, and fatigue.
- Response to BELVIQ should be evaluated at 12 weeks of treatment to determine if therapy should be discontinued.

<u>**Lorcaserin MAA submission with the EMA**</u>

We previously filed an MAA for lorcaserin with the EMA, which was accepted in March 2012. In accordance with the MAA review process, we have received from our rapporteur and co-rapporteur a draft assessment report which provides an initial review of our application and sets forth proposed questions and requests for additional information. We expect to receive the definitive list of questions in the form of a final 120 day assessment report around the end of July 2012. The final list of questions and requests for additional information in this 120 day assessment report will need to be addressed before lorcaserin can be recommended for approval for commercialization in the European Union. Under the applicable rules, the 120 day assessment report should be responded to within three months, and we expect to respond within such time period.

Forward-Looking Statements

Certain statements in this Form 8-K are forward-looking statements that involve a number of risks and uncertainties. Such forward looking statements include statements about the safety, efficacy, mechanism of action, DEA scheduling, commercialization and use of BELVIQ; rights and obligations under the amended and restated marketing and supply agreement with Eisai; future studies of BELVIQ; and the timing and other aspects of the MAA review process. For such statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from our expectations. Factors that could cause actual results to differ materially from the forward-looking statements include, but are not limited to, the following: the timing and outcome of DEA, EMA and other regulatory review is uncertain; approval of lorcaserin in the United States or other territories does not assure that our MAA filing will be approved by the EMA; limitations on the indicated uses, restricted distribution methods and other limitations on BELVIQ or, if approved, any of our other drug candidates; risks related to commercializing drugs, including regulatory, manufacturing and supply issues and the pace of market acceptance; cash and revenues generated from BELVIQ, including timing and impact of competition; government and commercial reimbursement and pricing decisions; risks related to relying on collaborative agreements; the timing and receipt of payments and fees, if any, from collaborators; unexpected or unfavorable new data; nonclinical and clinical data is voluminous and detailed, and regulatory agencies may interpret or weigh the importance of data differently and reach different conclusions than we or others, request additional information, have additional recommendations or change their guidance or requirements before or after approval; data and other information related to any of our research and development programs may not meet safety, efficacy or other regulatory requirements or otherwise be sufficient for regulatory review, approval or continued marketing; our ability to obtain and defend our patents; the timing, success and cost of our research and development programs; results of clinical trials and other studies are subject to different interpretations and may not be predictive of future results; clinical trials and other studies may not proceed at the time or in the manner expected or at all; having adequate funds; and satisfactory resolution of litigation or other disagreements with others. Additional factors that could cause actual results to

differ materially from those stated or implied by our forward-looking statements are disclosed in our filings with the Securities and Exchange Commission. These forward looking statements represent our judgment as of the time of the filing of this Form 8-K. We disclaim any intent or obligation to update these forward-looking statements, other than as may be required under applicable law.

EXH. BC
P. 486

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: June 27, 2012

Arena Pharmaceuticals, Inc.

By: /s/ Steven W. Spector
Steven W. Spector
Executive Vice President, General Counsel and Secretary

Exhibit BD

ARENA PHARMACEUTICALS INC

FORM 8-K
(Current report filing)

Filed 04/23/09 for the Period Ending 04/23/09

Address	6166 NANCY RIDGE DR SAN DIEGO, CA 92121
Telephone	8584537200
CIK	0001080709
Symbol	ARNA
SIC Code	2834 - Pharmaceutical Preparations
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	12/31

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 8-K

Current Report Pursuant to Section 13 or 15(d) of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 23, 2009

Arena Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	000-31161	23-2908305
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

6166 Nancy Ridge Drive, San Diego California	92121
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: 858.453.7200

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

In this report, "Arena Pharmaceuticals," "Arena," "we," "us" and "our" refer to Arena Pharmaceuticals, Inc., and its wholly owned subsidiaries, unless the context otherwise provides.

Item 2.05 Costs Associated with Exit or Disposal Activities.

On April 23, 2009, we committed to a reduction in our U.S. workforce of approximately 31%, or a total of approximately 130 employees. This reduction is expected to be completed by June 22, 2009. Given the challenging economic environment, we believe it is necessary to reduce our cash usage and provide Arena with additional financial flexibility to support our expected filing of a New Drug Application, or NDA, for lorcaserin, our drug candidate for weight management that is being investigated in a Phase 3 clinical trial program, by the end of 2009.

As a result of this workforce reduction, we expect to incur cash charges, primarily in the second quarter of 2009, of approximately $3.0 million in connection with one-time employee termination costs, including severance and other benefits. We believe that this workforce reduction will result in annual operating cost savings of approximately $25.0 million. We expect to provide additional details on the financial impact of these changes when we report our first quarter 2009 financial results.

We intend to continue to focus on our clinical development program for lorcaserin and on select earlier-stage research and development projects.

Forward-Looking Statements

Certain statements in this Form 8-K are forward-looking statements that involve a number of risks and uncertainties. Such forward looking statements include statements about the planned reduction of our workforce, including the expected size, timing, related charges and savings, and other expected impact of such reduction; the expected filing of an NDA for lorcaserin; future research and development focus and plans; and other statements about our strategy, internal programs, and ability to develop compounds and commercialize drugs. For such statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from our expectations. Factors that could cause actual results to differ materially from the forward looking statements include, but are not limited to, the risk that the charges related to this reduction may be greater than anticipated, the risk that we may not realize the savings expected from this reduction, our ability to obtain additional funds, the timing, success and cost of our lorcaserin program and our other research and development programs, the risk that results of clinical trials or preclinical studies may not be predictive of future results, clinical trials and studies may not proceed at the time or in the manner we expect or at all, our ability to partner lorcaserin or other of our compounds or programs, the timing and ability of us to receive regulatory approval for our drug candidates, our ability to obtain and defend our patents, and the timing and receipt of payments and fees, if any, from our collaborators. Additional factors that could cause actual results to differ materially from those stated or implied by our forward-looking statements are disclosed in our other filings with the Securities and Exchange Commission. These forward-looking statements represent our judgment as of the time of the filing of this 8-K. We disclaim any intent or obligation to update these forward-looking statements, other than as may be required under applicable law.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: April 23, 2009

Arena Pharmaceuticals, Inc.

By: /s/ Jack Lief
Jack Lief
President and Chief Executive Officer

COOLEY LLP
WILLIAM E. GRAUER (84806) (grauerwc@cooley.com)
KOJI F. FUKUMURA (189719) (kfukumura@cooley.com)
MARY KATHRYN KELLEY (170259) (mkkelley@cooley.com)
RYAN E. BLAIR (246724) (rblair@cooley.com)
4401 Eastgate Mall
San Diego, CA 92121
Telephone: (858) 550-6000
Facsimile: (858) 550-6420

Attorneys for Defendants Arena Pharmaceuticals, Inc., Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situation, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON, Defendants.	Case No. 10-CV-1959-CAB (BLM) **SUPPLEMENTAL DECLARATION OF RYAN E. BLAIR IN SUPPORT OF MOTION TO DISMISS CONSOLIDATED AMENDED CLASS ACTION COMPLAINT** Hearing Date: April 13, 2012 Hearing Time: 1:30 p.m. Courtroom: 2, 4th Floor Judge: Hon. Cathy Ann Bencivengo **[Per Chambers, no oral argument unless requested by the Court]**
WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situation, Plaintiffs, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, and WILLIAM SHANAHAN, JR. Defendants.	Case No. 10-CV-1961-BTM (BLM)

WILLIAM PRATT, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1977-BTM (BLM)
CRAIG RUBENSTEIN, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1984-BTM (BLM)
RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2026 BTM (BLM)

THONG VU, Individually and on behalf of all others similarly situated Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2086-BTM (BLM)
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON, Defendants.	Case No. 10-cv-2335-BTM (BLM)

I, Ryan E. Blair, declare as follows:

1. I am an attorney with the law firm of Cooley LLP, counsel for defendants Arena Pharmaceuticals, Inc. ("Arena"), Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson. I have personal knowledge of the following facts and, if called upon to testify, I could and would testify competently thereto.

2. Attached hereto as Exhibit AX is a true and correct copy of an Order Granting Motion to Dismiss, filed on December 2, 2003, in *Martin v. Maxim Pharmaceuticals, Inc.*, Case No. 00-cv-2507-JM (LSP) (S.D. Cal.).

3. Attached hereto as Exhibit AY is a true and correct copy of excerpts from Arena's Form 424B Prospectus Supplement, filed with the U.S. Securities and Exchange Commission on July 9, 2009.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 15th day of March, 2012 at San Diego, California.

Ryan E. Blair

Exhibit AX

FILED
03 DEC -2 PM 4:23
DISTRICT COURT
CALIFORNIA
DEPUTY

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BLAKE MARTIN, on behalf of himself and All Others Similarly Situated, Plaintiffs, vs. MAXIM PHARMACEUTICALS, INC., et al., Defendants.	CASE NO. 00cv~~2484~~ 2507 ORDER GRANTING MOTION TO DISMISS

Defendants Maxim Pharmaceuticals, Inc. ("Maxim"), Larry G. Stambaugh, Dale A. Sander, and Kurt Gehlsen move to dismiss the third amended [corrected] consolidated federal securities law complaint ("TAC") filed by Plaintiffs, consisting of a class of Maxim shareholders who purchased Maxim common stock between November 17, 1999 and December 13, 2000 (the "Class Period"). Plaintiffs oppose the motion. For the reasons set forth below, the motion to dismiss is granted with prejudice and without leave to amend. The Clerk of Court is instructed to close the file.

BACKGROUND

Maxim is a San Diego-based biopharmaceutical company whose product, Maxamine, is at the heart of the present dispute. Maxamine is a drug designed to treat patients suffering from late-stage metastatic melanoma. Metastatic melanoma is almost always fatal, and no effective treatment exists. In June 1997, the Food and Drug Administration ("FDA") approved Maxim's protocols for the Phase III clinical study and Maxim commenced a multi-center, Phase III clinical trial of Maxamine for the primary purpose of evaluating its safety and efficacy in the treatment of late-stage, metastatic

melanoma. Patients were randomly assigned to one of two treatment arms: one receiving high-dose Interleukin-2 ("IL-2") and the other receiving IL-2 and Maxamine. The primary efficacy endpoint was survival measured as the time between the date of randomization and the date of death. (TAC ¶¶ 75).

At the heart of Plaintiffs' claims are allegations that the FDA repeatedly informed Maxim of its concerns regarding the clinical trials, the protocol for conducting the trials, and the statistical analysis plan adopted to analyze the clinical trials. The FDA "recommended" that two clinical trials be conducted unless one clinical trial was strongly confirmatory the two-arms of the study were well-balanced, and there were a minimum of Protocol violations. "Maxim should stratify the patient population between the control and treatment arms by known prognostic factors, such as the presence of liver metastases and prior chemotherapy treatment to ensure an equivalence of prognostic factors in the two treatment arms." (TAC ¶5(b). Maxim would not likely obtain "FDA approval if the only evidence of efficacy was in a subgroup population as the subgroups were not prospectively defined in the Original Protocol or statistically powered to demonstrate statistical significance." (TAC ¶5(c)). Defendants also allegedly failed to heed the FDA's recommendation that Maxim conduct a test to determine the appropriate dosage for the Phase III study which eventually resulted in one-third of the 305 patients enrolled in the study failing to receive two cycles of treatment required to evaluate their response to the drug therapy.

On March 8, 1999 enrollment in the study was closed with 305 patients, located in 56 institutions throughout the United States. Maxim was not directly involved in conducting the trials. Maxim employed a monitoring and data management consultant, Covance Clinical and Periapproval Services, to conduct the trials. (FAC ¶ 77). During the clinical trials, Maxim amended the proposed trial protocol on at least seven occasions. (TAC ¶97). Plaintiffs also allege, based upon interviews with former employees, that Maxim received summaries of the progress of the trials in the form of Case Report Forms ("CRFs") about every four to six weeks. The monitoring of the CRFs allowed Maxim the opportunity to "evaluate the progress of the Study; verify the accuracy and completeness of Case Report Forms; assure that all protocol requirements, applicable FDA regulations and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records." (TAC ¶106).

The allegedly false and misleading statements commenced on November 17, 1999 when Maxim announced in a press release that the "preliminary single-center results demonstrated a significant difference in overall survival times." (TAC ¶58). At some point in time prior to November 17, 1999 Maxim learned, by unblinding the study at one test center, that Maxamine was allegedly not showing a statistically significant survival improvement in the overall patient population, but was showing a possible survival benefit in the liver metastases. This statement was allegedly false and misleading because (1) Defendant knew that an early review of the test data indicated that Maxamine had not proven effective in the intent to treat population and therefore Defendants modified to add the reference to the liver mets subgroup as a primary endpoint; (2) the FDA required at least two studies to prove efficacy; (3) many patients (about one third of the total patients) were unable to complete two cycles of treatment as set forth in the protocol; (4) there were severe imbalances in prognostic factors in that more patients were randomly assigned to the control group with multiple metastases than the treatment group thereby skewing the results in favor of the IL-2 plus Maxamine group; (5) about 40% of the patients had enrollment violations thereby reducing the reliability of the efficacy analysis; and (6) there were other technical protocol violations such as the failure to receive the return of syringes and the failure to ensure that patients kept a diary. (TAC ¶127). Defendants were also motivated to issue this allegedly false and misleading statement because the release of negative news "would cause a decline in Maxim's stock price and make it substantially more difficult for Maxim to sell shares to raise financing required to continue those clinical tests." (TAC ¶128).

On December 28, 1999 Maxim filed its 1999 10-K with the SEC. The form 10-K represented that the launch of Maxamine was planned for 2001, subject to receipt of requisite regulatory approvals. The 1999 10-K also indicated that "MAXAMINE increases the effectiveness of basic immune functions and may be used in combination with, and improve the effectiveness of, many cytokines and other immunotherapeutic agents. . . .In addition, because MAXAMINE has been shown to increase the effectiveness of cytokines, lower doses of cytokines . . can potentially be used in MAXAMINE THERAPY without compromising therapeutic effectiveness, thereby reducing serious side effects associated with the cytokines and permitting treatment at home." (TAC ¶129). This statement was allegedly materially false and misleading for essentially the same reasons as the November 17, 1999

press release. Plaintiffs allege that the statement was false because the FDA informed Maxim on six different occasions from April 7, 1997 through December 4, 1998 that a single study alone likely would not lead to approval (TAC ¶132); the patients were improperly stratified in the study (TAC ¶133); more than 40% of the enrolles did not meet the enrollment criteria (TAC ¶134); and the preliminary results were demonstrated that Maxamine was not effective in treating the overall population. (TAC ¶135).

On January 24, 2000 Maxim filed a Registration Statement with the Securities Exchange Commission ("SEC") for the sale of 2,875,000 shares in a secondary offering. Therein, Maxim stated that in November 1999 the clinicians conducting the Phase III trial at the largest enrolment site (40 patients) submitted an abstract to "an upcoming cancer conference. . . The preliminary single-center results demonstrated a statistically significant increase in overall survival for patients treated with MAXAMINE as compared to the control group." (TAC ¶140). These statements were materially false and misleading for, in essence, the same reasons the above described statements were allegedly false and misleading (i.e., study design flaws, safety issues and protocol violations). Plaintiffs also allege that the statement that the initial test results were "statistically significant" was misleading because it falsely implied that the "studies had been fully analyzed and supported FDA approval based on the standards for statistical significance in the Protocol." (TAC ¶142). On February 23, 2000 Maxim issued 3.2 million shares of common stock at $55 per share.

On February 21, 2000 an analyst publication, Marketletter, reported that Maxim was en route to success with Maxamine. The report also indicated that data from a single site "demonstrated a significant survival benefit among patients receiving the combination therapy." (TAC ¶143). These statements were materially false and misleading for essentially the same reasons that the November 17, 1999 press release was false and misleading. The statement was allegedly false and misleading because of the lack of stratification and other protocol violations, the high toxicity of Maxamine, imbalances in prognostic factors favored the Maxamine plus IL-2 arm, and Maxim modified the study's endpoint from survival of the intent to treat population to survival of the liver subgroup. (TAC ¶144).

On February 24, 2000 Prudential Securities issued a research report, on February 25, 2000

Maxim issued a press release, and on February 28, 2000 J.P. Morgan issued a research report. Each of these public announcements indicated, to the effect, that 40 of the 300 patients showed a statistically significant improvement in overall survival times. (TAC ¶148-153).

On May 2, 2000 Maxim announced the results of the Phase III trial. In pertinent part, Maxim reported that treatment with Maxamine plus IL-2 "improved survival duration over treatment with IL-2 alone for all six patient populations.... These results represent the first well-controlled, multi-center, Phase III trial to demonstrate a significant survival benefit for patients with advanced metastatic melanoma, especially for those patients having liver metastases." (TAC ¶155).

> The results are clear, when patients are treated with the combination of Maxamine and IL-2 under the protocol as designed, the improvement in survival is statistically significant over those patients treated with IL-2 alone," said Dr. Gehlsen. "Moreover, for patients having the worst kind of metastatic disease, melanoma that has spread to their liver, the results are unequivocal. We believe that the results of the trial clearly are compelling and will support our applications for registration of the product.

(TAC ¶155). Plaintiffs allege that the statements in the press release were materially false and misleading for essentially the same reasons that the November 17, 1999 press release was materially false and misleading. Plaintiffs allege that Maxim failed to conduct two clinical studies as the FDA earlier indicated; there was no statistically significant survival difference in the intent to treat population; the test results were neither compelling nor unequivocal; the subgroup of patients with liver metastases was homogeneous; the study protocols were not followed; and many patients experienced toxic reactions to Maxamine. (TAC ¶156).

During the month of May 2000 several articles and research reports issued positive statements regarding the efficacy and likely positive results of Maxim's clinical trials. (TAC ¶160-165). On June 2, 2000 Maxim issued a press release wherein it reiterated that the "improvement in survival was statistically significant in patients having metastasis of their melanoma to the liver." ¶166).

Plaintiffs allege that Defendants continued to issue positive but misleading statements until the true facts regarding Maxamine began to be disclosed on December 12, 2000 by the FDA on its Web site. (TAC ¶ 196). On December 13, 2000 the Advisory Committee voted unanimously to reject Maxim's NDA for Maxamine. In the Second Amended Complaint, Plaintiffs alleged that the Committee noted that the data presented was biased in favor of a treatment benefit and that, with respect to the liver subgroup, the FDA noted that this subgroup was not balanced and "was most likely

a random result that was not attributable to maxamine treatment." (SAC¶127).

On December 12, 2000 the FDA posted the DODP Medical Review on its Website. The Medical Review states that Maxim's survival analysis in the liver mets subgroup as a primary study endpoint was not prospectively defined in the Protocol, yet it was amended four months before the cut-off date of 3/8/2000. (TAC ¶114). The DODP also noted that there were many imbalances in patient characteristics which favored the treatment arm allegedly "resulting from defendants' knowing refusal to pre-stratify the patient population by known prognostic factors (e.g. age, sex, performance status, disease free interval, time since initial diagnosis of metastasis, number and location of disease sites, and prior chemotherapy)." (TAC ¶115). The DODP's Statistical Review also noted:

> The sponsor wishes to claim approval based on a subgroup of non-randomized patients with liver metastasis.

The price of Maxim's common stock fell from $30.06 on December 11, 2000 to close at $13.13 on December 14, 2000. By December 26, 2000 the price of Maxim's common stock reached a low of $5.15. On December 14, 2000 Plaintiffs commenced the present action.

DISCUSSION

Legal Standards

1. Rule 12(b)(6)

When ruling on a motion to dismiss, the court must accept all material allegations of fact as true and must construe those allegations in the light most favorable to the nonmovant. See North Star Int'l v. Arizona Corp. Comm'n, 720 F.2d 578, 581 (9th Cir. 1983). If the complaint fails to state a claim, the court should grant leave to amend unless it appears beyond a doubt the plaintiff would not be entitled to relief under any set of facts proved. See Halet v. Wend Inv. Co., 672 F.2d 1305, 1309 (9th Cir. 1982).

Courts grant 12(b)(6) relief only where a plaintiff's complaint lacks a "cognizable legal theory" or sufficient facts to support a cognizable legal theory. See Balistreri v. Pacifica Police Dept., 901 F.2d 696, 699 (9th Cir. 1990). Courts must construe the complaint in the light most favorable to the plaintiff. See Russell v. Landrieu, 621 F.2d 1037, 1039 (9th Cir. 1980). Accordingly, courts must accept as true all material allegations in the complaint, as well as reasonable inferences to be drawn from them. See NL Industries, Inc. v. Kaplan, 792 F.2d 896, 898 (9th Cir. 1986).

The defense of defect in a plaintiff's claim must appear on the face of the complaint: the court cannot consider material outside the complaint, such as facts presented in briefs, affidavits, or discovery materials. See McCalden v. California Library Assoc., 955 F.2d 1214, 1219 (9th Cir. 1992). However, the moving party may refer to and attach to its papers, and the court may consider, documents to which the plaintiff refers to in the complaint which are not attached to the complaint. See Branch v. Tunnel, 14 F.3d 449, 454 (9th Cir. 1994). The court may also consider any matter that is subject to judicial notice, such as public records. See MGIC Indem Corp. v. Weisman, 803 F.2d 500, 504 (9th Cir. 1986).

2. The PSLRA

In an effort to curtail the filing of perceived abusive lawsuits, see S. Rep. No. 98, 104th Cong., 1st Sess. at 5-9 (1995), Congress enacted the PSLRA to establish a uniform pleading standard:

> **(b) Requirements for securities fraud actions**
>
> **(1) Misleading statements and omissions**
>
> In any private action arising under this chapter in which the plaintiff alleges that the defendant–
>
> (A) made an untrue statement of a material fact; or
>
> (B) omitted to state a material fact necessary in order to make the statements made, in the light of the circumstances in which they were made, not misleading;
>
> the complaint shall specify each statement alleged to have been misleading, the reason or reasons why the statement is misleading, and, if an allegation regarding the statement or omission is made on information and belief, the complaint shall state with particularity all facts on which that belief is formed.
>
> **(2) Required state of mind**
>
> In any private action arising under this chapter in which the plaintiff may recover money damages only on proof that the defendant acted with a particular state of mind, the complaint shall, with respect to each act or omission alleged to violate this chapter, state with particularity facts giving rise to a strong inference that the defendant acted with the required state of mind.

15 U.S.C. §78u-4(b). To allege scienter, Plaintiffs must allege "strong circumstantial evidence of deliberately reckless or conscious misconduct," which is more than "mere recklessness." In re Silicon Graphics Inc. Sec. Litig., 183 F.3d 970, 984 (9th Cir. 1999). However, if the challenged act is a

forward-looking statement, the required state of mind is "actual knowledge . . . that the statement was false or misleading." 15 U.S.C. §78u-5(c)(1). The failure to plead scienter with particularity requires dismissal of the complaint. Id.

The Rule 10b-5 Claims

To state a Section 10(b) or Rule 10b-5 claim, Plaintiffs must allege five elements: (1) a *misrepresentation or material omission; (2) materiality; (3) scienter; (4) reliance; and (5) causation.* See The Ambassador Hotel Co., Ltd. v. Wei-Chuan Investment, 189 F.3d 1017, 1025 (9th Cir. 1999). The focus of the following discussion is on the element of scienter.

Defendants challenge whether Plaintiffs have adequately pled scienter, the "mental state embracing intent to deceive, manipulate, or defraud." Ernst & Ernst v. Hochfelder, 425 U.S. 185, 193 n. 12 (1976). Scienter may be established by showing intentional, knowing or deliberately reckless conduct. See Hollinger v. Titan Capital Corp, 914 F.2d 1564, 1569 (9th Cir. 1990 (en banc). "[R]ecklessness only satisfies scienter under § 10(b) to the extent it reflects some degree of intentional or knowing misconduct." In re Silicon Graphics, 183 F.3d at 977. In order to aver scienter, Plaintiffs "must state specific facts indicating no less than a degree of recklessness that strongly suggests actual intent." Id. at 979. Under the PSLRA, a § 10(b) claim must "state with particularity facts giving rise to a strong inference that the defendant acted with the required state of mind." 15 U.S.C. §78u-4(b)(2). The ultimate inquiry is whether Plaintiffs' allegations, taken as a whole, give rise to a strong inference of scienter. See Ronconi v. Larkin, 253 F.3d 423, 429 (9th Cir. 2001).

As they did in previous complaints, Plaintiffs seek to satisfy the scienter element by showing Defendants' actual knowledge of inconsistent facts and by alleging a motive and opportunity to commit fraud. Before discussing the elements of Plaintiffs' Rule 10-b5 claims, the court will briefly review the NDA process in order to provide some context to Plaintiffs' claims.

The New Drug Application Process

Since 1938, the regulation and control of new drugs has been subject to the approval of the NDA. The NDA process is the vehicle through which drug sponsors formally propose that the FDA approve new pharmaceuticals for sale and marketing in the United States.

> The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drugs quality are adequate to preserve the drug's identity, strength, quality and purity.

U.S. Food and Drug Administration, Center for Drug Evaluation and Research, New Drug Application (NDA) Process, at http:// www.fda.gov/cder/regulatory/applications/NDA.htm.

To market a new drug, the FDA requires the manufacturer to test the new drug in three phases of clinical trials.

> In Phase I, about 20-100 health volunteers receive the new drug to measure drug safety. Phase I tests only safety, researches at this stage do not gather information about safety. Next, during phase II the drug is administered to a group of several hundred patients with the 'target' disease. Phase II tests for efficacy as well as safety. Finally, in phase III, the drug is tested on 'hundreds and even thousands of patients.' This last phase provides information necessary to confirm the risks and benefits associated with the new drug. After completing phase III trials, the manufacturer may submit the research results to the FDA for approval in the form of a New Drug Application.

Dana Ziker, Reviving Informed Consent: Using Risk Perception in Clinical Trials, 2003 Duke L. & Tech. Rev.15 (2003).

Once Phase III is completed, the sponsor submits its formal application to the FDA, and the FDA conducts a thorough investigation into the results of the NDA. The NDA must include results and analysis in six categories: medical, biopharmaceutical, pharmacology, statistical, chemistry, and microbiology. See Christopher Mills, Mainstreaming the Alternative When Complementary and Alternative Medicines Become Westernized, 13 Alb. L.J. Sci. & Tech. 775, 778-79 (2003). The rules require the pharmacological industry to expend large sums of capital to complete clinical trials of new drugs which hold the potential to preserve and enhance human health and life.

The NDA process is a difficult and arduous one. Fewer than one in ten new drugs successfully pass through the NDA process. See Peter Barton Hutt Richard A. Merrill, Food and Drug Law 516 (2d ed. 1991); 2003 Duke L. & Tech Rev. 15. Maxamine, like most new drugs, failed to pass through the NDA gauntlet.

Actual Knowledge

Although a closer call then the earlier complaints, the TAC's scienter allegations still fall short of complying with the PSLRA's scienter pleading requirements. As noted by Plaintiffs, the ultimate

inquiry is whether the "allegations collectively add up to a strong inference of the required state of mind." Fla. State Bd. Of Admin. v. Green Tree Fin. Corp., 270 F.3d 645, 660 (8th Cir. 2001). In seeking to establish scienter, Plaintiffs allege that Defendants had "actual knowledge that (i) the patients in the two arms of the study were not well matched in terms of demographic characteristics, (ii) improvement in survival of the 305 patient intent-to-treat population was not statistically significant over those patients treated with IL-2 alone, (iii) there had been numerous Protocol violations; (iv) Maxamine was demonstrated to be toxic, and (v) the test results in the liver mets subgroup were not unequivocal or compelling, and would not support Maxim's applications for registration of Maxamine." (Opposition at p.11:1-7). Armed with these actual knowledge allegations, Plaintiffs seek to establish scienter by comparing and contrasting Defendants' "actual knowledge" with the publicly disseminated statements.

The May 2, 2000 Press Release: "The patients in the two arms of the study were well matched in terms of demographic characteristics and prognostic factors."

Plaintiffs explain that this statement was false because there was a clear imbalance of healthier patients between the treatment group and the control group of both the ITT population and the liver mets subgroup. The TAC alleges that the study was imbalanced to favor the treatment group. For example, the treatment group contained almost twice as many patients with one site of disease and therefor favored the treatment group. Plaintiffs also cite a statements by ODAC committee members that "these imbalances preclude[] the reliable assessment of the efficacy of the histamine/IL-2 combination." (ODAC Hearing Tr. At 245, 254). At the ODAC hearing, Defendant Gehlsen also stated with respect to the prognostic factors, "[n]ow, also regrettably, there was no prestratification for liver metastases, and there was no prestratification for any other prognostic factor. In hindsight, I will take that one to my grave." (RJN Exh. K-270).

As noted in earlier orders, the difficulty with Plaintiffs' argument is that scienter is not satisfied by pleading that a defendant acted incompetently or that he should have known in hindsight that a better designed clinical trial would not have misled investors. Further, the FDA's concerns, criticisms, and recommendations regarding the study design do not satisfy the scienter element:

> Nor . . . does it matter that one or more FDA staffers may have questioned [the company] or its affiliates about the study design during the review process. Mere questioning by the FDA imposed no duty upon Defendants either to trim back their

> opinions as to the efficacy of the drug or to report to the public the FDA staffers's questions as they arose. Continuous dialogue between the FDA and the proponent of a new drug is the essence of the product license application.

In re Medimmune Sec. Litig., 873 F.Supp. 953, 966 (D. Md. 1995).

Further, the statement was both, in a sense, accurate and inaccurate. With respect to the ITT population, the statement was accurate in that the FDA noted that "there were no significant imbalances in the number of patients between the two treatment arms in the ITT population." (Supp. RJN, Exh. YY at 7). With respect to the liver mets subgroup, the statement was inaccurate because, as noted by Plaintiffs, there were "13 patients with single liver mets in the treatment group and only 7 in the control group and that there was a higher percentage of patients with multiple metastases (91%) in the liver mets control group than in the treatment group (77%)." (Opposition at p.13:18-20). The court concludes that Plaintiffs' allegations that Maxim acted with the requisite recklessness or intent to defraud is absent from these allegations.

> **"The results are clear, when patients are treated with the combination of Maxamine and IL-2 under the protocol as designed the improvement in survival is statistically significant over those patents treated with IL-2 alone. . . . [T]he results are unequivocal. We believe that the results of the trial clearly are compelling and will support our applications for registration of the product."**

Plaintiffs seek an inference of scienter on the ground that "Defendants had been informed by the FDA in a meeting on May 5, 1998 that the test results in the ITT population to be statistically significant in a single Phase III study, the median survival in the treatment group had to be at least 50% greater than the median survival in the control group." (Opposition 15.18). One difficulty with drawing a strong inference of scienter from the public statements and what Maxim was allegedly told two years earlier by the FDA is that the NDA process is inherently a fluid one. As noted in the Medical Officer Preliminary Review of Maxamine, submitted on July 18, 2000, Maxim was informed by the DODP that a "50% increase in media survival in the arm of histamine/IL-2 over IL-2 alone might be compelling." (RJN Exh. N at 9). It is simply not sufficient to identify inconsistent events, facts, or data and then to attribute the difference between these and the desired end result to fraud.

Furthermore, the statement respecting the "compelling" results of the clinical trial referred to the liver mets subpopulation. (RJN Exh. D at 565-67). The Medical Officer Preliminary Review also noted that the "FDA's analysis of the survival using the applicant's dataset confirmed the applicant's

analysis," yet it requested additional information concerning the last visit dates of "living patients." (RJN Exh. D at 482). Plaintiffs also contend that Maxim modified the primary endpoint in late 1999 to account for patients with melanoma that had metastasized to the liver. However, as early as April 1997, Maxim discussed with the FDA its intention to separately examine patients with liver mets. (RJN Exh. N at 443-44). Moreover, a difference of opinion based upon statistical analysis does not amount to fraud so long as defendants had some reasonable basis for believing in the correctness of their interpretation of the data. See DeMarco v. Depotech Corp., 149 F.Supp.2d 1212, 1225 (S.D. Cal. 2001).

In light of the totality of the allegations and submissions of the parties, Plaintiffs' scienter allegations fail to give rise to a strong inference of Defendants' conscious misbehavior or recklessness. The allegations fall short of the mark.

> **"Preliminary results also demonstrated that treatment with Maxamine and IL-2 was safe and well-tolerated and had substantially less toxicity than standard therapy with high-dose IL-2. The tolerability of the Maxamine/IL-2 treatment allowed these advanced-stage malignant melanoma patients to treat themselves at home."**

In support of scienter, Plaintiffs rely on the following data to indicate that Maxamine was not well-tolerated: 14% of patients required dose reduction; 54-60% of patients had Grade 3 to 4 toxicity and 33 patients died within 30 days of the last study medication. Without explanation, Plaintiffs conclude that these facts demonstrate scienter because they undermine the veracity of the statement.

To provide some context to this claim, the court observes metastatic melanoma is nearly always fatal and there is no effective treatment for this disease. (TAC ¶39). Medial survival for patients with Stage IV melanoma is 6 to 10 months. (TAC ¶38). Treatment with IL-2 does not measurably improve survival times and "what they do accomplish is at a very high expense in terms of quality of life," through adverse reactions. (TAC ¶39). Given the dismal survival prognosis for patients with metastatic melanoma and their quality of life, even if Maximine proved effective, the court questions whether such relative terms as "well- tolerated" and "less toxicity" carry much weight.

In sum, viewing the allegations collectively as this court must, see Broudo v. Dura Pharmaceuticals, Inc., 339F.3d 933, 939 (9th Cir. 2003), and as noted by the court in its previous order, the scienter allegations, illuminated by hindsight, set forth an incompetence on the part of

Defendants to draft, plan, conduct, analyze, and report a meaningful Phase III clinical trial. Missing from the complaint is the overriding sense of intentional "mischievousness," deceit, or recklessness and not just incompetence or negligence. The TAC fails to articulate the extreme departure from the ordinary standard of care that is the hallmark of a securities complaint based on recklessness or to allege sufficient facts giving rise to a strong intent to defraud. See In re Silicon Graphics, 183 F.3d at 977. Absent allegations giving rise to a strong inference of scienter, Plaintiffs fail to set forth a necessary element to a Rule 10b-5 claim and dismissal of these claims are therefore warranted.[1]

Motive and Opportunity

Plaintiffs also seek to establish scienter by alleging that Maxim needed to raise capital to fund clinical trials and that certain individual defendants sold shares of Maxim stock during the Class Period. These allegations are insufficient to establish scienter. The following is essentially the same discussion as set forth in the previous order.

Plaintiffs allege that Maxim had a strong motive to violate the securities laws because they needed to complete a secondary offering and to acquire Cytovia, Inc. In February 2000, prior to completion of the Phase III clinical trials, Maxim received $176 million in proceeds from a secondary offering and in June 2000, it acquired Cytovia. Plaintiffs allege that Defendants had a motive to complete the secondary offering at a time when Maxim's stock price was still relatively high before the results of the clinical trials were made public and that it could acquire Cytovia with inflated shares of Maxim stock thus limiting the dilution of Maxim's stock. These allegations reflect common corporate activities that, absent additional allegations, fail to give rise to a strong inference of scienter. See In re PetsMart, Inc. Sec. Litig., 61 F.Supp.2d 982, 999 (D. Ariz. 1999) (allegation that executives hoped to "acquire third parties using the Company's stock as currency" is insufficient to establish scienter).

Plaintiffs further allege that a strong inference of scienter can be inferred from the fact that Maxim possessed only $12 million in cash at year end on December 31, 1999, that it spent

[1] Plaintiffs also allege that scienter is established, in part, by allegations that Maxim was informed about every four to seeks weeks of the progress of the trials by means of Case Report Forms ("CRFs") received from the field during the clinical trials. (TAC ¶106). The court observes that this allegation fails to allege that the CRFs provided sufficiently detailed information to meaningfully analyze and forecast the end results of the study.

approximately $7 million the previous year, and that it did not want to jeopardize funding from a secondary offering by disclosing its communications with the FDA because "Maxim would be unable to complete further Phase III and other clinical testing." (TAC ¶213). The difficulty with this argument is that it is illogical to infer that Defendants needed money to complete the Phase III trials while, at the same time, knowing that Maxamine was ineffective and unsafe and that it would spend funds on pursuing a futile clinical trial. These allegations are insufficient to establish either intentional or reckless conduct. See In re Allscripts, Inc! Sec. Litig., 2001 WL 743411, *11 (N.D. Ill. June 29, 2001 (vague allegation that company was motivated to inflate stock rice to fund acquisitions is too generalized to satisfy PSLRA's scienter requirement).

As set forth in the previous Order, Plaintiffs also seek to establish scienter by allegations of stock sales by two of the three individual defendants.[2] Plaintiffs allege that defendants Sander and Gehlsen, on March 9, 2000, sold 40,000 shares of Maxim common stock for proceeds of $2.6 million. (TAC ¶214). Scienter cannot be established by simply alleging that defendants Sander and Gehlsen had a personal motive to commit securities fraud by selling stock. "Insider trading is suspicious only when it is 'dramatically out of line with prior trading practices at time calculated to maximize the personal benefit from undisclosed inside information.'" In re Silicon Graphics, 183 F.3d at 986. Moreover, "[c]ontext is important, especially for assessing the weight to attach to the time of the sales." In re Vantive Corp. Sec. Litig., 283 F.3d 1079, 1092 (9th Cir. 2002). Here, Plaintiffs allege that the amount of stock sold is suspicious because Sander and Gehlsen did not sell any stock the previous year. Plaintiffs also allege that the timing of the stock sales, shortly after the secondary offering, is suspicious. These allegations of a single stock sales during the Class Period fail, under the circumstances, to raise a strong inference of scienter.

The record of Sander and Gehlsen's actual stock sales also undermines Plaintiffs' claims of scienter. The record also reveals that defendant Sander sold only approximately 20% of his nearly 80,000 shares and vested options during the Class Period. This amount of stock sales is also not out of line with the 12,000 shares (22% of his then existing common stock holdings) sold by Sander 19

[2] Plaintiffs do not allege that defendant Stambaugh, Maxim's Chairman, President and CEO, sold any shares during the Class Period. The court also observes that Stambaugh is the individual who made the majority of the allegedly false and misleading statements during the Class Period.

months earlier. Defendant Gehlsen has a similar stock trading pattern. During the class period defendant Gehlsen sold 25% of his nearly 100,000 shares and vested options. This amount of stock sales is also not out of line with the 25,000 shares (33% of his then existing holdings) he sold 19 months earlier. Furthermore, in June and July 2000 defendant Gehlsen exercised and held nearly 25,000 vested options at a cost to him of approximately $250,000. In addition, Gehlsen incurred a federal tax liability of about $300,000 at the time he exercised the options. He did not sell these optioned shares of stock. It is unlikely that Gehlsen would sustain $600,000 in direct, cash losses by retaining stock that he knew would precipitously decline in value because Maxamine was neither effective nor safe.

In Ronconi v. Larkin, 253 F.3d 423 (9th Cir. 2001) the Ninth Circuit upheld the dismissal of a complaint that alleged stock sales considerably larger then those at issue in the case at bar. There seven of eleven insider defendants had sold 69% or more of their shares and options, and an eighth defendant had sold 98% of her total shares. The Ninth circuit noted that "[o]ne insider's well timed sales do not support the 'strong inference' required by the [PSLRA] where the rest of the equally knowledgeable insiders act in a way inconsistent with the inference that the favorable characterizations of the company's affairs were known to be false when made." Id. at 436. Here, the stock sales at issue fail to give rise to a credible and strong inference of scienter. Not only did the largest insider stockholder, defendant Stambaugh, make the majority of the allegedly false and misleading statements, but he did not sell any shares during the class period. Under the circumstances alleged, Plaintiffs' allegations fail to give rise to a strong inference of deliberate or conscious recklessness.

In sum, the motion to dismiss is granted on the ground that Plaintiffs have failed to adequately allege a strong inference of scienter.[3] The motion to dismiss is granted with prejudice and without leave to amend because any amendment appears futile. At the time of oral argument, Plaintiffs' counsel indicated, in response to the court's inquiry into the viability of future amendments, that the

///

///

[3] Because the court finds that Plaintiffs fail to adequately allege scienter, the court does not reach the remainder of Defendants' arguments.

TAC contained all material allegations and that Plaintiffs would "stand on the complaint and the record as is." (TR 33:8-9). The Clerk of Court is instructed to close the file.

IT IS SO ORDERED.

DATED: 12/1 2003

JEFFREY T. MILLER
United States District Judge

cc: All parties

Laurence D. King (SBN 206423)
Mario M. Choi (SBN 243409)
KAPLAN FOX & KILSHEIMER LLP
350 Sansome Street, Suite 400
San Francisco, CA 94104
Telephone: 415-772-4700
Facsimile: 415-772-4707
lking@kaplanfox.com
mchoi@kaplanfox.com

Robert N. Kaplan (admitted *pro hac vice*)
Frederic S. Fox
Joel B. Strauss
Jeffrey P. Campisi (admitted *pro hac vice*)
KAPLAN FOX & KILSHEIMER LLP
850 Third Avenue
New York, NY 10022
Telephone: 212-687-1980
Facsimile: 212-687-7714
rkaplan@kaplanfox.com
ffox@kaplanfox.com
jstrauss@kaplanfox.com
jcampisi@kaplanfox.com

Lead Counsel for Lead Plaintiff Carl Schwartz and the Proposed Class

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01959-BTM-BLM **LEAD PLAINTIFF'S MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO DEFENDANTS' MOTION TO DISMISS THE CONSOLIDATED AMENDED CLASS ACTION COMPLAINT** Judge: Hon. Barry T. Moskowitz Courtroom: 15, 5th Floor Hearing Date: March 29, 2012 Hearing Time: 11:00 a.m. [Per Chambers, no oral argument unless requested by the Court]

[Additional Captions on Following Pages]

WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF and WILLIAM SHANAHAN, JR. Defendants.	Case No. 3:10-cv-01961-BTM-BLM
WILLIAM PRATT, Individually and on Behalf of All Others Similarly Situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01977-BTM-BLM
CRAIG RUBENSTEIN, Individually and on Behalf of All Others Similarly Situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-01984-BTM-BLM

RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02026-BTM-BLM
THONG VU, individually and on behalf of all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02086-BTM-BLM
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, vs. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR., and CHRISTY ANDERSON, Defendants.	Case No. 3:10-cv-02335-BTM-BLM

TABLE OF CONTENTS

FDA). Similarly, Defendants argument that their statements about animal studies, including carcinogenicity studies were not misleading "as a matter of law" is meritless. Defs' Mem. at 20. When Defendants made representations that their animal studies "assess the potential risk" to humans (*See* ¶¶99, 110, 123), they failed to disclose risks Defendants had already observed in the Rat Study and the FDA's concerns about the Rat Study's observations. These facts would have altered the total mix of information, as demonstrated by the significant decline in Arena's stock price and negative analyst reaction upon their disclosure.[12]

3. Defendants' Representations Are Not Puffery, Optimistic Corporate Statements and Are Not Protected by the PSLRA's Safe-Harbor.

Defendants argue that their representations contain immaterial statements of "optimistic opinions about lorcaserin's risk/benefit profile" (Defs' Mem. at 21-22) (identifying 5 of 58 statements), or were forward-looking statements protected by the PSLRA's Safe Harbor provision. *Id.* at 22-25. Defendants are wrong. The Complaint alleges that Defendants' representations that lorcaserin was "on track" and had a "remarkable safety profile" concerned present or historical facts that were verifiable at the time Defendants made the representations. *Casella v. Webb*, 883 F.2d 805, 808 (9th Cir. 1989) ("What might be innocuous 'puffery' or mere statement of opinion standing alone may be actionable as an integral part of a representation of material fact when used to emphasize and induce reliance upon such a representation.").

Defendants' representations that lorcaserin's safety profile was "excellent" and "remarkable" are actionable because the Complaint alleges facts that indicate (1) Defendants could not have genuinely believed that these representations were accurate; (2) there was no reasonable basis for Defendants' representations and (3) Defendants were aware of undisclosed facts that undermined the accuracy of their representations. *See Infosonics*, 2007 WL 2301757, at *10 (*citing*

---

[12] Defendants' citations to *In re Alkermes Sec. Litig.*, No. Civ.A. 03-12091-RCL, 2005 WL 2848341 (D. Mass. Oct. 6, 2005), and *Brody v. Transitional Hosps. Corp.*, 280 F.3d 997 (9th Cir. 2002) are misplaced because the courts in *Alkermes* and *Brody* found that the plaintiffs did not allege that defendants statements were misleading. *Alkermes*, 2005 WL 2848341, at *16 (citation omitted); *Brody*, 280 F.3d at 1006. In contrast, the Complaint alleges that Defendants' representations were false and misleading. (¶¶83 (setting forth reasons that Defendants' representations were materially false and misleading)).

In re Apple Computer Sec. Litig., 886 F.2d 1109, 1113 (9th Cir. 1989)). *See supra* n. 4; (¶¶ 55-66, 83-104, 108-116, 120-142, 146-175) (allegations that Defendants knew of the Rat Study's observations and the FDA's concerns about them). Accordingly, even assuming, *arguendo,* these representations are considered opinions, they are actionable.[13]

Defendants' reliance on the PSLRA's Safe Harbor defense and "risk factors" mentioned in Arena's SEC filings are equally unavailing. Defendants argue that their "statements about lorcaserin's FDA approval prospects were inherently forward-looking and fall squarely under the safe harbor." Defs' Mem. at 23. However, the Complaint does not allege that the Defendants made false representations about lorcaserin's approval prospects or its "future performance." Rather the Complaint alleges Defendants made materially false and misleading statements concerning lorcaserin's safety and the results of nonclinical studies which were present or historical facts that were demonstratively false and misleading at the time Defendants made these representations. *Amylin*, 2002 WL 31520051, at *9. These statements are not forward-looking.[14]

Even assuming *arguendo* that any of the Complaint's alleged false and misleading statements were forward-looking, the representations did not include "meaningful cautionary language identifying important factors that could cause actual results to differ materially from those in the forward-looking statement." The Complaint alleges that Defendants' cautionary language was not meaningful because the language "was ineffective to warn research analysts . . . of the undisclosed material facts" alleged in the Complaint. (¶191); *see also Amylin*, 2002 WL 31520051,

---

[13] Thus, cases such as *In re Bristol Myers Squibb Sec. Litig.*, 312 F. Supp. 2d 549, 557 (S.D.N.Y. 2004), *In re Sierra Wireless Sec. Litig.*, 482 F. Supp. 2d 365, 367 (S.D.N.Y. 2007), and *Yourish v. Cal. Amplifier*, 191 F.3d 983, 997 (9th Cir. 1999), which stand for the proposition that statements of opinion are insufficient to form the basis of a misrepresentation or omission, are inapposite where, as here, Defendants knew material facts undermining the accuracy of their representations and therefore did not have a reasonable basis for them.

[14] Defendants' reliance on cases such as *Noble Asset Mgmt. v. Allos Therapeutics, Inc.*, No. CIV A-04-CV-1030-RPM, 2005 WL 4161977 (D. Colo. Oct. 20, 2005), *In re Syntex Corp. Sec. Litig.*, 95 F.3d 922 (9th Cir. 1996), and *In re Discovery Labs. Sec. Litig.*, No. 06-1820, 2006 WL 3227767 (E.D. Pa. Nov. 1, 2006), for the proposition that statements concerning FDA approval prospects are not actionable, is misplaced. As noted above, the Complaint does not allege Defendants made false and misleading statements about lorcaserin's prospects for FDA approval, but rather that Defendants knew of and failed to disclose the observations of the Rat Study and the FDA's concerns about them.

at *9 (finding that defendants did not warn investors about specific issues with the drug or the drug's correlation with a particular health issue). Indeed, after the disclosure of the Rat Study on September 14, 2010, analysts stated, "[t]he biggest surprise is a preclinical cancer signal," the "[c]ancer risk in the briefing document was unforeseen," and that they "were completely blindsided by preclinincal carcinogenicity data from the two year lorcaserin animal study." (¶69); *see also Amylin*, 2002 WL 31520051, at *9 (noting that cautionary language was ineffective to warn analysts that the drug might cause the health problem at issue).[15]

Finally, Defendants' Safe-Harbor defense fails because the Complaint alleges that Defendants' representations were made with actual knowledge. *Amylin*, 2002 WL 31520051, at *9. As discussed more fully below in Subsection C (and noted above in footnote 4), Defendants knew about the Rat Study and the FDA's concerns about its results, but nonetheless represented that lorcaserin was safe. (¶¶ 97, 105, 120, 126, 128).

C. The Complaint Alleges Facts That Raise a Strong Inference of Scienter.

The Supreme Court in *Tellabs, Inc. v. Makor Issues & Rights, Ltd.*, 127 S. Ct. 2499, 2505 (2007) held that in order to plead a strong inference of scienter in a securities fraud action brought under the PSLRA, the facts alleged in a complaint must give rise to an inference of scienter that is cogent and at least as compelling as any opposing inference of nonfraudulent intent suggested by defendants. In *Tellabs*, the Supreme Court defined the "strong inference" standard as follows: "When the allegations are accepted as true and taken collectively, would a reasonable person deem the inference of scienter at least as strong as any opposing inference?" *Id.* at 2511. Scienter is adequately pled where the inference of fraud is *equally* as likely as any non-culpable explanation of defendants' alleged conduct. *Id.* "In other words, a tie now goes to the plaintiff." *Sloman v. Presstek, Inc.*, No. 06 Civ. 377, 2007 WL 2740047, at *7 (D.N.H. Sept. 18, 2007). ***"Opposing***

---

[15] Defendants' reliance on *Harris v. Ivax Corp.*, 182 F.3d 799, 807 (11th Cir. 1999) and *In re Columbia Labs, Inc. Sec. Litig.*, 144 F. Supp. 2d 1362, 1368-69 (S.D. Fla. 2001) is misplaced. These cases are from the Eleventh Circuit and apply a different interpretation of "meaningful cautionary language," which only requires that an investor be "warned of risks of a significance similar to that actually realized." Even under this lower standard, Defendants' "warnings" do not come close to disclosing the Rat Study's cancer observations or the FDA's interest in them.

COOLEY LLP
WILLIAM E. GRAUER (84806) (grauerwe@cooley.com)
KOJI F. FUKUMURA (189719) (kfukumura@cooley.com)
MARY KATHRYN KELLEY (170259) (mkkelley@cooley.com)
RYAN E. BLAIR (246724) (rblair@cooley.com)
4401 Eastgate Mall
San Diego, CA 92121
Telephone: (858) 550-6000
Facsimile: (858) 550-6420

Attorneys for Defendants Arena Pharmaceuticals, Inc., Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

TODD SCHUENEMAN, on behalf of himself and all others similarly situation,

Plaintiff,

v.

ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON,

Defendants.

Case No. 10-CV-1959-BTM (BLM)

DECLARATION OF RYAN E. BLAIR IN SUPPORT OF MOTION TO DISMISS CONSOLIDATED AMENDED CLASS ACTION COMPLAINT

Hearing Date: March 30, 2012
Hearing Time: 11:00 a.m.
Courtroom: 15, 5th Floor
Judge: Hon. Barry T. Moskowitz

[Per Chambers, no oral argument unless requested by the Court]

WILLIAM SUTLIFF and JEAN SUTLIFF, on behalf of themselves and all others similarly situation,

Plaintiffs,

v.

ARENA PHARMACEUTICALS, INC., JACK LIEF, and WILLIAM SHANAHAN, JR.

Defendants.

Case No. 10-CV-1961-BTM (BLM)

WILLIAM PRATT, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1977-BTM (BLM)
CRAIG RUBENSTEIN, Individually and on Behalf of All Others Similarly Situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-1984-BTM (BLM)
RODNEY VELASQUEZ, on behalf of himself and all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2026 BTM (BLM)

THONG VU, Individually and on behalf of all others similarly situated Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, and CHRISTY ANDERSON Defendants.	Case No. 10-CV-2086-BTM (BLM)
ARIC D. JACOBSON, individually and on behalf of all others similarly situated, Plaintiff, v. ARENA PHARMACEUTICALS, INC., JACK LIEF, ROBERT E. HOFFMAN, DOMINIC P. BEHAN, WILLIAM R. SHANAHAN, JR. and CHRISTY ANDERSON, Defendants.	Case No. 10-cv-2335-BTM (BLM)

I, Ryan E. Blair, declare as follows:

1. I am an attorney with the law firm of Cooley LLP, counsel for defendants Arena Pharmaceuticals, Inc. ("Arena"), Jack Lief, Robert E. Hoffman, Dominic P. Behan, William R. Shanahan, Jr., and Christy Anderson. I have personal knowledge of the following facts and, if called upon to testify, I could and would testify competently thereto.

2. Attached hereto as Exhibit A is a true and correct copy of excerpts of Arena's Fiscal Year ("FY") 2008 Form 10-K (without exhibits), filed with the Securities and Exchange Commission ("SEC") on March 16, 2009.

3. Attached hereto as Exhibit B is a true and correct copy of the U.S. Food and Drug Administration's ("FDA") Manual of Policies and Procedures, Center for Drug Evaluation and Research, section 6010.5.

4. Attached hereto as Exhibit C is a true and correct copy of excerpts of Arena's FY2009 Form 10-K (without exhibits), filed with the SEC on March 16, 2010.

5. Attached hereto as Exhibit D is a true and correct copy of Arena's press release dated December 22, 2009.

6. Attached hereto as Exhibit E is a true and correct copy of Arena's press release dated March 17, 2008.

7. Attached hereto as Exhibit F is a true and correct copy of Arena's press release dated March 12, 2009.

8. Attached hereto as Exhibit G is a true and correct copy of Arena's press release dated March 30, 2009.

9. Attached hereto as Exhibit H is a true and correct copy of excerpts of Arena's conference call transcript dated May 11, 2009.

10. Attached hereto as Exhibit I is a true and correct copy of Arena's press release dated September 18, 2009.

11. Attached hereto as Exhibit J is a true and correct copy of excerpts of Arena's conference call transcript dated September 18, 2009.

12. Attached hereto as Exhibit K is a true and correct copy of Arena's press release dated October 12, 2009.

13. Attached hereto as Exhibit L is a true and correct copy of Arena's press release dated November 9, 2009.

14. Attached hereto as Exhibit M is a true and correct copy of excerpts of Arena's conference call transcript dated November 10, 2009.

15. Attached hereto as Exhibit N is a true and correct copy of Arena's press release dated February 24, 2010.

16. Attached hereto as Exhibit O is a true and correct copy of Arena's press release dated February 26, 2010.

17. Attached hereto as Exhibit P is a true and correct copy of excerpts of the FDA's Briefing Document for the FDA Advisory Committee meeting on September 16, 2010 regarding lorcaserin, also available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm225628.htm (last visited December 19, 2011).

18. Attached hereto as Exhibit Q is a true and correct copy of a screenshot of a webpage on the FDA's website containing Arena's and the FDA's Briefing Documents for the FDA Advisory Committee meeting on September 16, 2010 regarding lorcaserin, also available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm225628.htm (last visited December 19, 2011).

19. Attached hereto as Exhibit R is a true and correct copy of excerpts of Arena's Briefing Document for the FDA Advisory Committee meeting on September 16, 2010 regarding lorcaserin, also available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm225628.htm (last visited December 19, 2011).

20. Attached hereto as Exhibit S is a true and correct copy of excerpts of the transcript of the FDA Advisory Committee meeting on September 16, 2010.

21. Attached hereto as Exhibit T is a true and correct copy of the FDA's Guidance for Industry: S1C(R2) Dose Selection for Carcinogenicity Studies.

22. Attached hereto as Exhibit U is a true and correct copy of excerpts of Arena's conference call transcript dated December 22, 2010.

23. Attached hereto as Exhibit V is a true and correct copy of Arena's Form 8-K and accompanying Exhibit 99.1, filed with the SEC on August 9, 2011.

24. Attached hereto as Exhibit W is a true and correct copy of, and excerpts from, drug labels for the FDA-approved drugs Caduet, Geodon, Kuvan, Lexapro, Lunesta, Protonix, Vytorin, and Xopenex HFA, and documents filed with the SEC by Pfizer, Inc., BioMarin Pharmaceuticals, Inc., Forest Laboratories, inc., Sepracor, Inc., American Home Products Corp., Schering-Plough Corp., and Merck & Co., Inc. (the makers of the aforementioned drugs). For the convenience of the Court, this exhibit also includes a chart summarizing relevant portions of the attached documents.

25. Attached hereto as Exhibit X is a true and correct copy of excerpts of Arena's Form DEF14A, filed with the SEC on April 24, 2008, and Arena's Form DEF14A, filed with the SEC on April 27, 2011. For the convenience of the Court, this exhibit also includes a chart summarizing the information contained in the attached documents.

26. Attached hereto as Exhibit Y is a true and correct copy of an order issued by the United States District Court, Northern District of California, in the action styled *Kovtun v. Vivus, Inc.*, Case No. 10-cv-4957-PJH (N.D. Cal. Oct. 13, 2011).

27. Attached hereto as Exhibit Z is a true and correct copy of excerpts of Arena's conference call transcript dated March 30, 2009.

28. Attached hereto as Exhibit AA is a true and correct copy of Arena's press release dated May 11, 2009.

29. Attached hereto as Exhibit AB is a true and correct copy of Arena's press release dated June 6, 2009.

30. Attached hereto as Exhibit AC is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending June 30, 2009 (without exhibits), filed with the SEC on

August 7, 2009.

31. Attached hereto as Exhibit AD is a true and correct copy of Arena's press release dated October 27, 2009.

32. Attached hereto as Exhibit AE is a true and correct copy of Arena's Form 8-K, filed with the SEC on October 30, 2009.

33. Attached hereto as Exhibit AF is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending September 30, 2009 (without exhibits), filed with the SEC on November 9, 2009.

34. Attached hereto as Exhibit AG is a true and correct copy of Arena's press release dated July 14, 2010.

35. Attached hereto as Exhibit AH is a true and correct copy of Arena's Form 8-K, filed with the SEC on January 27, 2011.

36. Attached hereto as Exhibit AI is a true and correct copy of excerpts of Arena's conference call transcript dated August 3, 2009.

37. Attached hereto as Exhibit AJ is a true and correct copy of Arena's press release dated August 3, 2009.

38. Attached hereto as Exhibit AK is a true and correct copy of Arena's press release dated March 12, 2010.

39. Attached hereto as Exhibit AL is a true and correct copy of Arena's press release dated August 6, 2010.

40. Attached hereto as Exhibit AM is a true and correct copy of excerpts of Arena's conference call transcript dated March 12, 2009.

41. Attached hereto as Exhibit AN is a true and correct copy of excerpts of Arena's conference call transcript dated March 12, 2010.

42. Attached hereto as Exhibit AO is a true and correct copy of excerpts of Arena's conference call transcript dated August 3, 2010.

43. Attached hereto as Exhibit AP is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending March 31, 2008 (without exhibits), filed with the SEC on

May 12, 2008.

44. Attached hereto as Exhibit AQ is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending June 30, 2008 (without exhibits), filed with the SEC on August 11, 2008.

45. Attached hereto as Exhibit AR is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending September 30, 2008 (without exhibits), filed with the SEC on November 7, 2008.

46. Attached hereto as Exhibit AS is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending March 31, 2009 (without exhibits), filed with the SEC on May 11, 2009.

47. Attached hereto as Exhibit AT is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending March 31, 2010 (without exhibits), filed with the SEC on May 7, 2010.

48. Attached hereto as Exhibit AU is a true and correct copy of excerpts of Arena's Form 10-Q for the period ending June 30, 2010 (without exhibits), filed with the SEC on August 9, 2010.

49. Attached hereto as Exhibit AV is a true and correct copy of Arena's press release dated June 2, 2010.

50. Attached hereto as Exhibit AW is a true and correct copy of Arena's press release dated December 22, 1010.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct. Executed this 30th day of December, 2011 at San Diego, California.

/s/ Ryan E. Blair
Ryan E. Blair

EXHIBIT P

FDA Briefing Document

NDA 22529

Lorqess (lorcaserin hydrochloride) Tablets, 10 mg

Sponsor: Arena Pharmaceuticals

Advisory Committee – September 16, 2010

Table of Contents

Section:

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 19 August 2010

FROM: Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food & Drug Administration

TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 16 September 2010. Advisory Committee meeting for lorcaserin

Background

Thank you for agreeing to participate in the September 16, 2010, advisory committee meeting. This meeting is being held to discuss the efficacy and safety of lorcaserin. Lorcaserin is a 5HT2c receptor agonist being developed by Arena Pharmaceuticals for the treatment of obesity. The sponsor is seeking approval of lorcaserin 10 mg BID.

The FDA briefing document contains reviews of lorcaserin's pharmacology, preclinical carcinogenic profile, and clinical efficacy and safety. The conclusions from the FDA's Executive Carcinogenicity Assessment Committee's review of the lorcaserin carcinogenicity studies in rodents are also included the briefing document.

The 5HT2c receptor subtype, expressed in the hypothalamus and choroid plexus, plays a role in appetite regulation, activation of the HPA axis, locomotion, anxiety, and in the modulation of dopamine release. The 5HT2b receptor subtype, expressed in the central nervous system and in various peripheral tissues, is involved in motor behavior, cerebrovascular tone and mitogenesis of cardiac valves, among other things. The 5HT2a receptor subtype, expressed in the cortex, hypothalamus, cerebellum, and amygdale and the liver, coronary vasculature, adipocytes, platelets, the kidney, and the gastrointestinal tract, functions in the modulation of neurotransmitters and peptides, adipocyte differentiation, platelet aggregation, and enteric neurotransmission.

In-vitro assays indicate that lorcaserin's binding affinity and activation of the 5HT2c receptor subtype is greater than its affinity and activation of the 5HT2a or 5HT2b subtypes. When assessed by calcium release, the EC50s for lorcaserin are 6 nM, 52 nM, and 350 nM for the 2c, 2a, and 2b receptor subtypes, respectively.

EXH. P
P. 92

In 2007 the Division of Metabolism and Endocrinology Products issued a draft guidance entitled Developing Products for Weight Management. The guidance stipulates that a drug will be considered effective if at least one of the following criteria is satisfied after one year of treatment:

1 Mean efficacy criterion - The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant

or

2 Categorical efficacy criterion - The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Efficacy of Lorcaserin

The efficacy of lorcaserin was evaluated in two phase 3 trials comprising approximately 7200 individuals. The BLOSSOM trial was a one-year, placebo-controlled study that randomized 4008 overweight (BMI 27-29.9 kg/m^2) and obese (BMI $\geq$30 kg/m^2) nondiabetic adult male and female subjects to lorcaserin 10 mg BID, lorcaserin 10 mg QD, or placebo in a 2:1:2 fashion. The BLOOM trial was a two-year, placebo-controlled study that randomized 3182 overweight and obese adult males and females to lorcaserin 10 mg BID or placebo in a 1:1 fashion. At the end of one year of treatment, the lorcaserin group was re-randomized in a 2:1 fashion to lorcaserin 10 mg BID or placebo. Subjects originally randomized to placebo remained on placebo during the second year of the study.

The mean percent change in body weight from baseline to Year 1 was approximately -2.5% in the placebo groups and approximately -5.8% in the lorcaserin 10 mg BID groups ($p<0.001$ vs. placebo). The mean percent change in body weight in the lorcaserin 10 mg QD group was nearly -5% ($p<0.001$ vs placebo). In the categorical analyses, approximately 23% of subjects in the placebo groups lost $\geq$ 5% of baseline body weight during Year 1 compared with 47% and 40% of subjects in the lorcaserin 10 mg BID and lorcaserin 10 mg QD groups, respectively ($p<0.001$ both lorcaserin vs. placebo).

The weight loss observed in the lorcaserin-treated groups was associated with improvements in systolic and diastolic blood pressure, lipoprotein lipid levels, fasting glucose and insulin levels, and levels of hsCRP.

When gauged by the standards of the Division's 2007 draft guidance for Developing Products for Weight Management, the mean weight loss associated with the lorcaserin 10 mg QD and BID dose was about 3% greater than the mean weight loss with placebo. Therefore lorcaserin did not satisfy the guidance's mean efficacy criterion. However, the lorcaserin 10 mg BID dose did, by a slim margin, satisfy the categorical efficacy criterion.

Safety of Lorcaserin

Valvular heart disease, neuro-psychiatric and cognitive-related adverse events, and preclinical tumor development are three noteworthy safety issues discussed in the FDA background documents.

Valvular Heart Disease: The weight-loss drugs fenfluramine and dexfenfluramine were removed from the U.S. market in 1997 due to the occurrence of left-sided valvular heart disease (VHD). Recent research suggests that activation of the 5HT2b receptor is the mechanism responsible for fenfluramine- and dexfenfluramine-associated VHD. Lorcaserin's affinity for the 5HT2c receptor is greater than its affinity for the 5HT2b receptor. To evaluate if lorcaserin increases the risk for VHD, subjects in the phase 3 studies were evaluated with serial echocardiograms. Valvular heart disease was defined as mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency. This is referred to as FDA-defined valvulopathy or FDA-defined VHD.

A mutually-agreed upon non-inferiority margin of 1.5 for the development of VHD was used to determine the sample size for the phase 3 lorcaserin development program. While arbitrary, the Division considered this margin reasonable for the initial evaluation of lorcaserin.

In the BLOOM trial, the incidence of FDA-defined VHD over the course of one year was 2.35% in the placebo group and 2.66% in the lorcaserin 10 mg BID group [RR 1.13 95% CI (0.69, 1.85)]. In the BLOSSOM trial, the incidence of FDA-defined VHD over the course of one year was 1.99% in both the lorcaserin 10 mg BID and placebo groups [RR 1.00 95% CI (0.57, 1.75)]. In an analysis of pooled data, the RR was 1.07 (0.74, 1.55) for FDA-defined valvulopathy in the lorcaserin 10 mg BID group versus the placebo group. These data allow one to rule out a 55% or greater increase in the relative risk for FDA-defined VHD with lorcaserin.

Neuro-psychiatric and Cognitive-Related Adverse Events: In the phase 3 clinical trials, perceptual- or dissociative-related adverse events were reported by 21% of subjects treated with lorcaserin 10 mg BID compared with 12% of subjects treated with placebo. A wide variety of individual adverse event terms including dizziness, fatigue, paresthesias, and abnormal dreams, contributed to the overall imbalance between treatment groups. Although a greater percentage of subjects randomized to the lorcaserin 10 mg BID group (2.7%) versus the placebo group (1.4%) reported adverse events mapped to a broad categorization of depression, when confined to a narrower categorization, there was no imbalance between treatment groups in depression-related adverse events. Memory impairment, disturbance in attention, amnesia and other cognitive-related adverse events were reported infrequently overall; however, three times more subjects treated with lorcaserin 10 mg BID reported these types of events compared with subjects treated with placebo.

Malignancies in Rats: A number of malignant tumor types developed in rats treated with lorcaserin for up to two years. An excess number of malignant mammary tumors

developed in female rats treated with lorcaserin at doses within 7-fold of the proposed clinical dose of 10 mg BID. Male rats developed malignant mammary tumors when treated with lorcaserin at doses 17-fold higher than the proposed clinical dose. Although the sponsor believes that lorcaserin-mediated increases in serum prolactin explain the excess risk for malignant breast tumors, FDA reviewers do not believe that the available data support this hypothesis. In addition to breast tumors, lorcaserin-treated rats had an excess number of malignant astrocytomas, squamous carcinomas of the subcutis, and malignant schwannomas. There were no imbalances in reports of cancer between lorcaserin and placebo-treated subjects in the phase 3 clinical studies.

Draft Points for Discussion and Regulatory Question

As you read the background documents from the FDA and Arena Pharmaceuticals please keep in mind the following draft discussion points and regulatory question.

Taking into account the material provided in the background documents and presented at the advisory committee meeting, please comment on whether you believe that the sponsor has:

1. Provided adequate evidence to establish lorcaserin's efficacy as a weight-loss drug
   a. are there additional studies that you would recommend pre- or post-approval to further evaluate lorcaserin's efficacy?

2. Adequately assessed the potential risk for lorcaserin-induced valvular heart disease.
   a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk?
   b. if approved, please discuss need for monitoring and possible monitoring strategies.

3. Provided adequate evidence to assess the potential risk to human subjects of lorcaserin-related neoplasms in rats of the:

   - mammary tissue
   - brain
   - skin
   - subcutis
   - nerve sheath tissue

   a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk?

b. if approved, please discuss need for monitoring and possible monitoring strategies.

4. Adequately assessed and characterized the potential risk for psychiatric adverse events, such as dissociative disorders and depression/suicidality.
   a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk
   b. if approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

5. Adequately assessed and characterized the potential risk for adverse events related to disorders of attention, memory, and other cognitive disorders.
   a. are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk
   b. if approved, please discuss need for monitoring and possible monitoring strategies.

6. Taking into account the clinical and preclinical information provided in the background documents and the presentations made at this advisory committee meeting, please vote whether you believe that the available data adequately demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals.

If voting 'Yes', please provide your rationale and comment on the need for and approach to post-approval risk management.

If voting 'No', please provide your rationale and comment on what additional clinical or preclinical information would be required to potentially support approval.

Advisory Committee Nonclinical Briefing Document

Application: Lorcaserin hydrochloride, NDA 22-529
Drug Class: 5HT2c Receptor Agonist
Clinical Indication: Obesity
Reviewer: Fred Alavi, Ph.D., Division of Metabolism and Endocrinology Products

Re: Genotoxicity and Carcinogenicity Assessment for Lorcaserin

Table of Contents

Abstract

Lorcaserin was identified as a non-genotoxic carcinogen in a two-year bioassay conducted in Sprague-Dawley rats. The incidence of multiple tumor types increased in response to lorcaserin, including mammary neoplasms in males and females, and neoplasms of the brain, skin, subcutis, peripheral nerves, and liver and thyroid gland of males. The tumor response to lorcaserin is not considered secondary to generalized toxicity, as tumor burden was the primary cause of excess mortality. Weight loss, specifically in high dose males, is not considered evidence of generalized toxicity, as weight loss with other investigational anti-obesity agents have generally prolonged survival and lessened tumor burden in two-year rat bioassays. Lorcaserin did not increase tumors in mice, but this is considered a reflection of lower drug exposure achieved in mice compared to rats.

No safety margin was identified in female rats for mammary tumors, which emerged within 7-fold of the proposed clinical dose of 10mg bid. Lorcaserin-emergent mammary tumors were generally lethal and reduced survival time at all doses in females. Mammary tumors emerged in male rats at 17-fold the clinical dose. Studies addressing the mechanism of tumorigenesis failed to demonstrate a robust or sustained elevation in prolactin, providing weak evidence for prolactin as a key event in lorcaserin-emergent mammary tumors. No alternative mechanism of action was addressed to aid in risk assessment.

Lorcaserin increased the incidence of brain astrocytoma in male rats by an unidentified mechanism of action. The cellular lineage of spontaneous astrocytoma in rats compared to other species is unresolved in the literature, but is of secondary concern to the finding that lorcaserin increased brain tumors in rats by an unknown pathway. Without a plausible tumorigenic mechanism identified, risk assessment is based primarily on the difference in exposure between doses in rats and the clinical dose in humans. Comparing brain levels of lorcaserin is most appropriate given the anatomical location of astrocytoma. Lorcaserin preferentially partitions to the brain in rats, mice, and monkeys, but the brain-to-plasma ratio varies across the species. Brain partitioning in human subjects was not determined. Thus, estimating safety margins based on assumptions of partitioning in human subjects is not entirely reliable. Assuming that the monkey best models human partitioning, the estimated safety margin to a non-tumorigenic dose in rats may range from 11x to 17x, with tumors associated with brain exposures that are 40x to 59x higher than clinical exposure. More conservatively, safety margins based on plasma drug levels, which is known for rats and humans, yields a safety margin to the non-tumorigenic dose in rats of 5x, with brain tumors occurring at doses of lorcaserin 17-fold higher than the clinical dose.

Other tumors including benign fibroma of the skin, squamous carcinoma of the subcutis, and malignant schwannoma occurred in male rats with a safety margin to the non-tumorigenic dose of 5x, with lorcaserin increasing the incidence of these tumors at a dose 17-fold higher than the clinical dose. No studies were conducted to address the mechanism by which lorcaserin induced these tumors. Liver and thyroid neoplasms occurred at a high exposure multiple (55-fold) of the clinical dose, and reasonable evidence was provided supporting a rodent-specific mode of action involving induction of hepatic drug-metabolizing enzymes.

Carcinogenic Assessment of Investigational Pharmaceutical Compounds
Investigational drugs intended for chronic (≥ 6 months) use in human subjects are evaluated for their potential to be carcinogenic. Because genotoxic compounds are closely associated with carcinogenicity, the potential genotoxicity of pharmaceutical compounds and associated metabolites is also assessed in a standard battery of studies. Carcinogenesis is formally evaluated in two species of rodents that receive the drug for two years, roughly approximating lifetime exposure to drug. The two-year 'bioassay' is designed to detect drug-induced tumors that arise from genotoxic as well as non-genotoxic mechanisms of action.

Lorcaserin Genotoxicity Assessment
Lorcaserin and its major sulfated metabolite (APD244208) showed no evidence of genotoxic effects in a standard battery of bacterial and mammalian systems. Non-genotoxic mechanisms are therefore thought to underlie lorcaserin-induced tumors observed in the rat carcinogenicity study (described below). Examples of non-genotoxic mechanisms of neoplasia include direct or indirect promotion of cell growth or survival, and persistent perturbation of hormone status.

Mouse Carcinogenicity study
The carcinogenicity study in mice was initiated with 25, 50 and 100 mg/kg of lorcaserin and a vehicle control. Each dose group consisted of 65 mice/sex/group, and lorcaserin was administered daily by oral gavage. Despite selection of doses thought to be tolerable over a two year dosing period, excessive mortality resulted within the first 16 days of dosing at 100mg/kg. The deaths were clearly related to lorcaserin, but necropsies did not identify a definitive cause of death. With no evidence of tissue damage, and because lorcaserin can accumulate up to 25-times higher in the brain vs. plasma in mice, it is plausible that the deaths had a neural origin. However, only one case of convulsion was reported in a male on Day 1 at 100 mg/kg, with no apparent detrimental consequence.

In consultation with the FDA, the doses of lorcaserin were decreased to 5, 25 and 50 mg/kg starting on Day 19. The lowered doses were tolerated and survival in lorcaserin-dosed groups was similar to the control group for the remainder of the 2 year study (Table 1). The high dose of 50mg/kg in the mouse provided exposure 4- to 7-times higher than the clinical dose of 10mg BID (based on AUC, total drug exposure; Figure 1).

Table 1: Survival of mice at lowered doses of lorcaserin in the 2 year bioassay

2-Year mouse study	Sex	Lorcaserin Dose, mg/kg/d			
		Control (H_2O)	5	25	50
Survival rate, %	M	41%	37%	28%	37%
	F	35%	32%	38%	33%

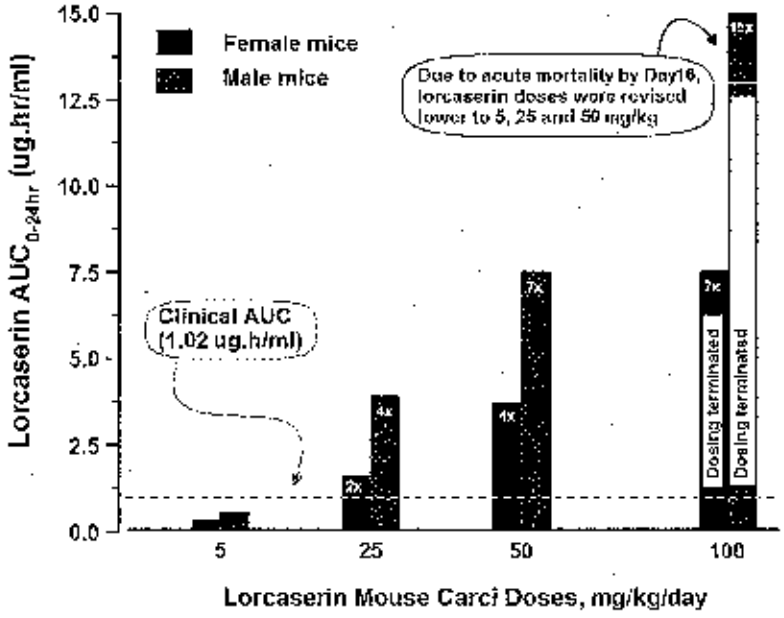
Study Findings in Mice:
Lorcaserin had no substantial effect on body weight or food intake in male or female mice. Lorcaserin effectively reduces food intake and body weight in rodents in shorter term studies, so the lack of effect on body weight after two years of dosing may reflect a loss of pharmacodynamic sensitivity to 5HT2C agonism in appetite regulatory centers.

Review of the study results by the Division and the Executive Carcinogenesis Assessment Committee of FDA is consistent with the Sponsor's conclusion that no drug-related tumors were

observed in mice (see Appendix A). Exposure to lorcaserin at the No-Observed Adverse Effect (NOAEL) of 50mg/kg is 4- to 7-times higher than exposure at the clinical dose of 10mg BID, based on AUC.

The primary safety concern in the mouse study was the apparent and unanticipated steep dose response curve for toxicity not related to tumors. Whereas mice tolerated a 50mg/kg dose for 2 years without apparent adverse effects, a doubling of exposure to 100mg/kg resulted in rapid and unexplained deaths in a number of mice. This was unanticipated because prior studies had shown minimal mortality in the first few days of treatment with higher doses of lorcaserin, including 250 mg/kg in a 13-week study and 350 mg/kg in a 2-week study.

Figure 1: Lorcaserin exposure achieved in mice (bars) compared to the clinical dose of 10mg BID (green horizontal line). The ratio of mouse to human exposure is noted within the bars. Comparisons are based on AUC drug exposure (Area Under the Curve). Dosing was terminated for the 100mg/kg dose group due to excess mortality within the first 16 days of dosing.



Rat Carcinogenicity Study

The two-year carcinogenicity study in Sprague-Dawley rats evaluated lorcaserin at doses of 10, 30 and 100 mg/kg, and included a vehicle control. The high dose groups consisted of 75 rats/sex, with other dose groups consisting of 65/sex (Table 2). The toxicokinetic (TK) groups were used to measure drug exposure and were dosed for 52 weeks. Due to the emergence of mammary tumors in the study, several TK rats were dosed an additional 2 to 4 weeks to allow for serum analysis of prolactin and estradiol and for immunohistochemical staining of prolactin.

Table 2: Group assignments for 2 year rat carcinogenicity study

Group Assignments			
Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
Main Study			
1 Control (C)	0	65	65
2 Low dose (LD)	10	65	65
3 Mid dose (MD)	30	65	65
4 High dose (HD)	100	75	75
Toxicokinetic			
5	0	6	6
6	10	15	15
7	30	15	15
8	100	15	15

Drug exposure in rats substantially exceeded that achieved in mice (Table 3). Drug exposure in male rats achieved a 5x, 17x, and 55x multiple at the LD, MD, and HD compared to the clinical dose. Exposure in female rats was higher, achieving a 7x, 24x, and 82x multiple of the clinical dose.

Table 3: Multiples of clinical exposure to lorcaserin achieved in 2yr rat study

	Dose, mg/kg	Males	Females
104-week Rat Carci Study	10 (LD)	5x	7x
	30 (MD)	17x	24x
	100 (HD)	55x	82x

Exposure multiples calculated as AUC exposure in rats divided by average AUC exposure of the clinical dose of lorcaserin, 10mg BID, 1.02 ug*h/ml AUC

Rat Tumor Findings

A summary of tumors associated with lorcaserin in rats is presented in Table 4. Of particular note, the combined incidence of mammary adenocarcinoma and fibroadenoma increased at all doses in females and in the mid and high dose males. Numerous other tumors were observed in male rats but not in female rats. These include tumors of the brain, peripheral nerves (Schwannoma), skin and subcutis, liver, and thyroid.

Table 4: Incidence of lorcaserin-induced tumors in the 2 year rat carcinogenicity study.
(n= 65/sex for Control, 10, 30mg/kg and n=75/sex for 100mg/kg)

Male rats Incidence of tumors		**Lorcaserin dose, mg/kg/day**			
		Control	**10**	**30**	**100**
Brain	astrocytoma	1	0	4 NS	8[a] SS
Mammary	adenocarcinoma	0	0	2	2 NS
	fibroadenoma	0	1	4 NS	6 NS
	combined	0	1	6 SS	8 SS
Skin, subcutis	benign fibroma	3	7 NS	11 SS	17 SS
Skin	squamous carcinoma	0	0	4 NS	5 SS
Nerve Sheath	Schwannoma, all sites	0	0	2 NS	9 SS
Liver	hepatocellular carcinoma	1	3	2	4
	hepatocellular adenoma	1	1	2	6 SS
	combined	2	4	4 NS	10 SS
Thyroid	follicular cell adenoma	0	5	4 NS	8 SS

Female rats Incidence of tumors		**Lorcaserin dose, mg/kg/day**			
		Control	**10**	**30**	**100**
Brain	astrocytoma	0	2	0	1
Mammary	adenocarcinoma	28	34 NS	35 NS	60 SS
	fibroadenoma	20	47 SS	53 SS	45 SS
	combined	40	56 SS	61 SS	70 SS

[a] One case of astrocytoma in an HD male was reclassified as infarct due to lymphocytic leukemia in an amendment to the NDA

Alavi- 6

EXH. P
P. 102

Statistical analysis provided by the FDA statistician, Dr. Matthew Jackson.
NS = not significant ($p > 0.05$ rare tumor; $p > 0.01$ common tumor)
SS = Statistical significance ($p \leq 0.05$ rare tumor; $p \leq 0.01$ common tumor; pairwise comparison)
Shaded boxes indicate FDA's conclusion of a lorcaserin-related tumor increase, including numerical and 'statistically significant' increases.

Lorcaserin-related tumors other than mammary neoplasms were observed only in male rats. This is not due to a sex difference in exposure; indeed, males had lower overall AUC exposure than females. This is also not interpreted as evidence of a robust tumor response in just one sex. Rather, the lack of other tumor types in females likely reflects the greater and earlier mortality in females compared to males (see Survival, below). For example, half of the high dose females were dead by ~week 67 compared to week 75 for high dose males, and half of the mid-dose females were dead by ~week 80 compared to week 95 for mid-dose males. Had females survived similarly to males, it is reasonable to expect that other tumor types may have emerged.

Survival

Lorcaserin-emergent tumors had a substantial impact on survival in the male and female rats. (Table 5, Figure 2). Surviving females of all dose groups and the high dose (HD) males were necropsied at ~ week 96/99, after consultation with FDA's Executive Carcinogenesis Assessment Committee. Overall, lorcaserin-treated males survived for a longer period than females.

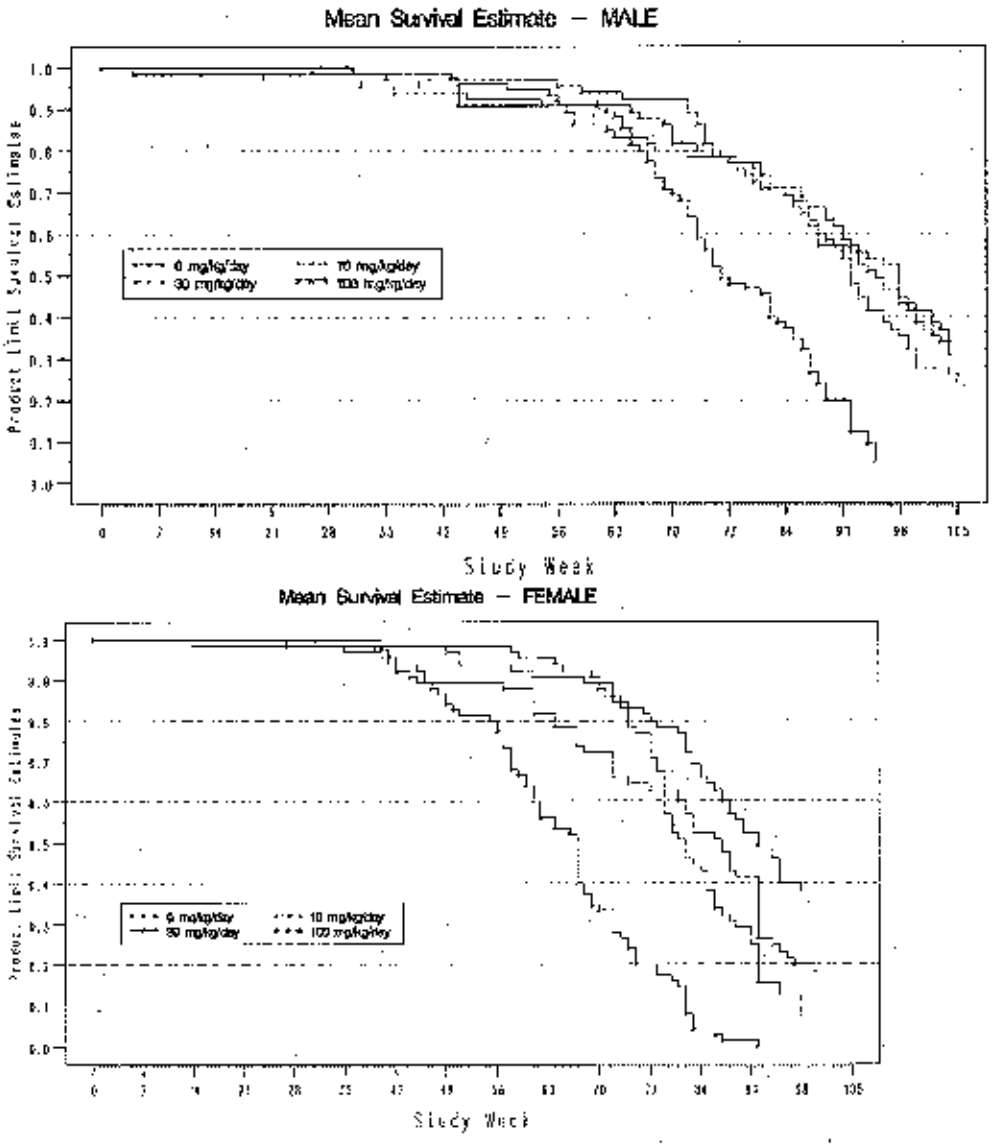
Survival declined significantly at all doses in females due to the emergence of drug-related mammary fibroadenoma and adenocarcinoma. According to the sponsor's study report, survival also declined significantly in HD males, with the excess deaths due to the emergence of drug-related tumors in the brain, skin, mammary tissue, and peripheral nerves (schwannoma).

Excess mortality in carcinogenicity studies is considered evidence that drug exposure has exceeded the maximum tolerated dose (MTD), *but only when* the cause of mortality is related to something other than drug-induced tumors. In those cases, any tumors associated with that dose are not necessarily considered relevant to human risk. However, because the excess mortality observed with lorcaserin was due to drug-induced tumors rather than other toxicity, exposure achieved in the rats did not exceed a maximum tolerated dose, and the relevance of the tumors to human risk cannot be dismissed based on that argument.

Table 5: The number of live rats and survival rate at the end of the 2-year carcinogenicity study

2-Year Rat study	Sex	Lorcaserin Dose, mg/kg/d			
		Control (H_2O)	10	30	100
Number animals alive	M	22/75	16/65	20/65	4/75
	F	23/75	12/65	5/65	0/75
Survival rate, %	M	33.8%	24.6%	30.7%	5.3%
	F	35%	18.4%	7.7%	0%

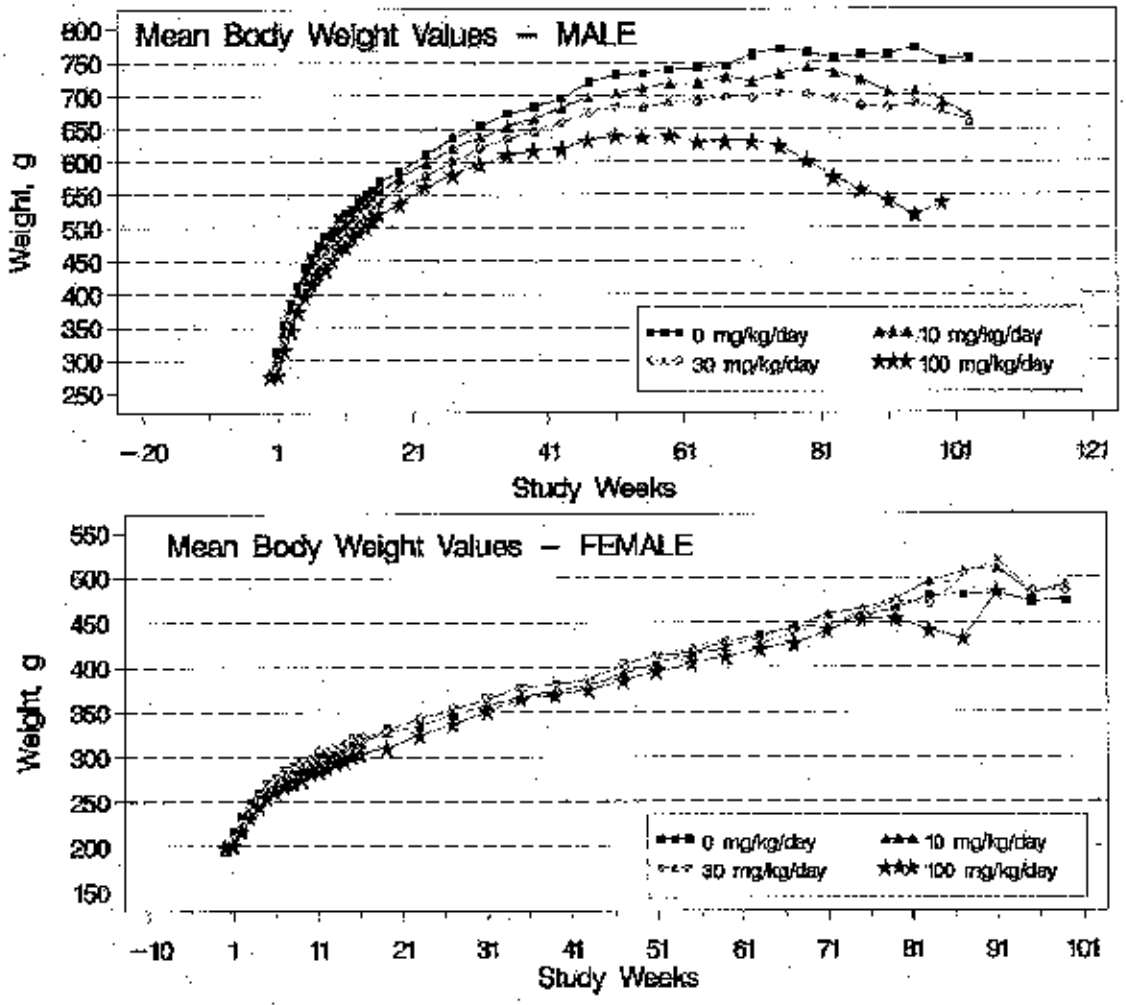
Figure 2: Kaplan-Meir survival estimates in male and female rats treated with 10, 30 and 100 mg/kg of lorcaserin for up to 2 years.



Body Weight changes

Body weight declined in males, most notably at 100 mg/kg, but did not substantially change in females (Figure 3). Decreased food intake was variable in both sexes but slightly lower in males. Equivalent and even greater weight loss observed in carcinogenicity studies conducted with other investigational weight loss drugs is associated with improved 2 year survival and less tumor burden compared to concurrent control groups, not reduced survival and greater tumor burden as seen with lorcaserin. Therefore, weight loss observed in lorcaserin-treated males is not taken as evidence of exceeding a tolerable dose or generalized toxicity, and is not interpreted as a reason for reduced survival or for tumor induction. Rather, the reduced weight in high dose males was likely skewed by the greater tumor burden and earlier mortality in this group.

Figure 3: Mean body weight measurements in the 2 year rat carcinogenicity study.



Mammary tumors

Summary: Lorcaserin significantly increased mammary fibroadenoma alone or combined with adenocarcinoma in females at all doses and at the mid and high doses in males. No safety margin was established in the females (tumors occurred ~7x clinical dose), whereas a safety margin of 5x was identified in males (tumors occurred 17x clinical dose). Lorcaserin-induced mammary tumors, both benign and malignant, were lethal and decreased survival over the 2 year study. The mechanistic studies provide weak support for the hypothesis that lorcaserin-induced mammary tumors are secondary to elevations in prolactin, as occurs with approved anti-dopaminergic agents. No other hypotheses were addressed to identify an alternative mechanism of lorcaserin-induced mammary tumors in rats. Given the lack of a safety margin, an unresolved tumorigenic mechanism of action, and a patient population already at increased risk of breast cancer, the relevance of these finding in rats to human risk cannot be dismissed.

Mammary tumors in rats consisted of fibroadenoma and adenocarcioma. Statistically, the increased incidence of adenocarcinoma was significant only in high dose females. When combined with fibroadenoma, statistical significance is achieved at all doses in females and at mid- and high doses for males (Table 6). A safety margin, defined by a non-tumorigenic dose, was not identified in females because an increased incidence of fibroadenoma was observed at the low dose, or ~7x the clinical dose.

The historical incidence of mammary tumors in male rats is relatively low, so the observation that mammary adenocarcinoma and fibroadenoma combined was significantly increased in mid- and high-dose males is notable (Table 6). The histological data identified a degree of feminization in males, defined as partial or complete replacement of typical lobulo-alveolar appearance of the mammary gland with a ductulo-alveolar appearance in all treated males (LD: 64%, MD: 69% and HD: 63%) as well as controls (48%). Although no mammary tumors were reported for the control group, this degree of feminization may have increased the susceptibility of the male rats to develop mammary tumors in response to lorcaserin.

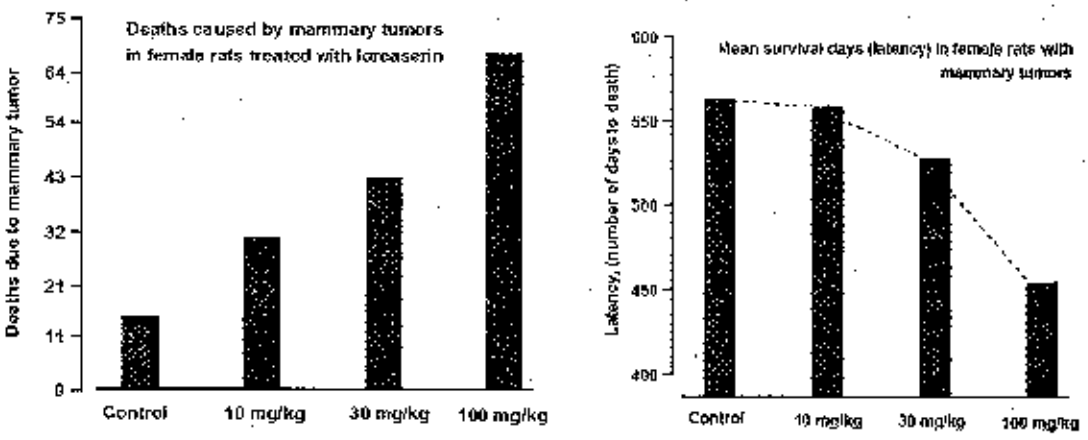
Table 6: Mammary Tumor Incidence in 2 year rat study

Mammary Tumor Incidence # animals effected (% incidence) SS, statistical significance		Lorcaserin dose, mg/kg/day			
		Control n=65	10 n=65	30 n=65	100 n=75
Males	adenocarcinoma	0	0	2 (3%)	2 (2.6%) NS
	fibroadenoma	0	1 (1.5%)	4 (6%) NS	6 (8%) NS
	combined	**0**	**1**	**6** **SS**	**8** **SS**
Females	adenocarcinoma	28 (43%)	34 (52%) NS	35 (54%) NS	60 (80%) SS
	fibroadenoma	20 (31%)	47 (72%) SS	53 (81%) SS	45 (60%) SS
	combined	40	56 SS	61 SS	70 SS

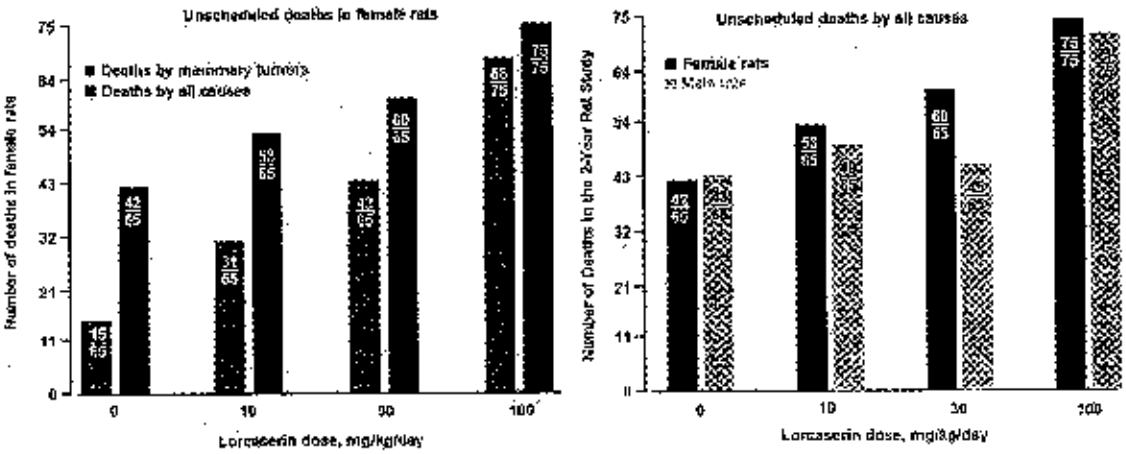
Historical control data for mammary tumor incidence in SD rats for study site (compiled from 11 studies, conducted 2002-2007)			
	Mammary tumor type	Range	Average
Males	Adenocarcinoma	0-2%	0.3%
	Fibroadenoma	0-3.3%	0.9%
Females	Adenocarcinoma	8.3-37%	24%
	Fibroadenoma	22-54%	36%

The FDA's risk assessment is based on the combined incidence of mammary fibroadenoma and adenocarcinoma, and is not substantially swayed by the argument that statistically significant malignant adenocarcinoma was confined to high dose females. As demonstrated in Figure 4, the number of deaths caused by mammary tumors increased in females at all doses, not just the high dose, and mean survival time for females with mammary tumors (latency) decreased with an increase in lorcaserin. As the dose of lorcaserin increased, the more females died of mammary tumors and at an earlier time at all doses. Confining the analysis to the final incidence of mammary tumors without consideration of tumor-related mortality is not justified. Among the deaths attributed to mammary tumors, approximately 1/15, 6/31, 14/43 and 10/68 deaths were attributed to fibroadenoma in the control, LD, MD and HD female rats, respectively, suggesting that fibroadenoma as well as adenocarcinoma were fatal.

Figure 4: Deaths of female rats related to lorcaserin-induced mammary tumors.



Alavi- 11
EXH. P
P. 107



An additional reason that the FDA risk assessment is not substantially weighted toward malignant adenocarcinoma is the uncertainty apparent in the course of diagnosing adenocarcinoma from fibroadenoma in the study (Table 7a,b). The high incidence of mortality and palpable tumors in female rats observed during the course of the study prompted the FDA to request periodic updates from the Sponsor regarding the incidence of observed tumors, particularly mammary and brain tumors. The entire female high dose group and the majority of mid-dose females were evaluated histologically by week 96. In subsequent updates and in the final study report, the incidence of adenocarcinoma in the MD and HD females was lower than that reported at week 96 (Table 7a). The incidence of adenocarcinoma increased in the controls and stayed consistent in the low dose group over the same period. The incidence of fibroadenoma increased in all dose groups from week 96 to the final study report, though the numbers notably varied in the mid- and high dose groups (Table 7b). It appears that some of the decrease in the number of adenocarcinoma after week 96 was accompanied by an increase in fibroadenoma, potentially a consequence of the sponsor/CRO reclassifying the observed tumor types.

Table 7a: Mammary Adenocarcinoma Incidence over time in Female Rats (main study)

Data Update (Week)	Control	10 mg/kg/d	30 mg/kg/d	100 mg/kg/d
Week 55 update	0/1	2 / 4	5 / 7	13 / 15
Week 68 update	2 / 5	6/6	16 / 18	45 / 46
Week 88 update	16 / 28	27 / 38	36 / 45	72 / 74
Week 96 update	30 / 39	34 / 50	43 / 57	72 / 75
Week 104 update	30 / 65	35 / 65	35 / 65	63 / 75
Final update	29 / 65	35 / 65	36 / 65	62 / 75
Final NDA	28 / 65	34 / 65	35 / 65	60 / 75

Table 7b: Mammary Fibroadenoma Incidence over time in Female Rats (main study)				
Data Update (Week)	Control	10 mg/kg/d	30 mg/kg/d	100 mg/kg/d
Week 88 update	4/28	16/38	24/45	35/74
Week 96 update	10 / 39	27 / 50	36 / 52	36 / 75
Week 104 update	20 / 65	47 / 65	60 / 65	53 / 75
Final update	20 / 65	48 / 65	56 / 65	51 / 75
Final NDA	20 / 65	47 / 65	53 / 65	45 / 75

Mechanism of Lorcaserin-related Mammary Tumors in Rats

Summary: The primary hypothesis addressed by the Sponsor was that lorcaserin-induced mammary tumors occurs via a mechanism similar to that demonstrated for compounds with direct or indirect anti-dopaminergic activity, including many approved anti-psychotic medications. Specifically, suppression of dopamine promotes an increase in prolactin levels, which is a known intermediary of mammary tumorigenesis in rodents but of unresolved significance to human breast cancers. Evidence supporting this pathway in the mechanism of lorcaserin-induced mammary tumors is not persuasive. Lorcaserin repeatedly failed to increase serum prolactin or prolactin staining of the pituitary or mammary tissue of intact female rats. A modest increase in serum prolactin after single dose exposure in male rats was not sustained after prolonged exposure. Efforts to reduce perceived variability in the prolactin data by ovariectomizing female rats also did not yield evidence of a lorcaserin-induced increase in prolactin. The experimental condition required to demonstrate even a modest increase with lorcaserin in female rats was ovariectomy plus pharmacologic treatment with ovarian hormones, conditions that bear little resemblance to the 2 year study in which lorcaserin increased mammary tumors. By comparison, haloperidol, an anti-dopaminergic agent associated with rodent mammary tumors, robustly increased serum prolactin regardless of experimental conditions. The serotonergic agent dexfenfluramine modestly increased serum prolactin regardless of experimental condition. Of note, the modest increase in serum prolactin with dexfenfluramine does not result in mammary tumors (Redux NDA 20344). No other hypotheses were addressed to identify an alternative mechanism of lorcaserin-induced mammary tumors in rats, which the FDA considers as yet unresolved.

Prolactin is known to be an intermediary hormone in development of mammary tumors in rodents. Several CNS active drugs (anti-dopaminergic compounds or drugs indirectly affecting dopamine) result in mammary tumors in rodents secondary to increased pituitary output of prolactin. Because serotonin is reported to negatively regulate dopamine release, potentially via activation of 5HT2C receptors, a similar mechanism may exist in lorcaserin-treated rats. To test this hypothesis, the Sponsor conducted several mechanistic studies in males and intact and ovariectomized female rats to demonstrate increased prolactin production or perturbation in hormone status in response to lorcaserin.

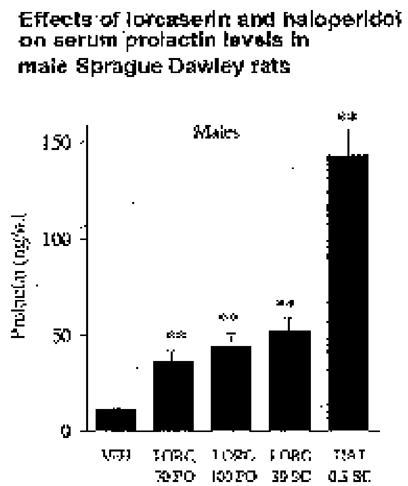
Prolactin responses in male rats

A single dose of lorcaserin increased plasma prolactin in male rats (Figure 5a). Haloperidol is an anti-dopaminergic compound associated with mammary tumors in rodents, which robustly increased prolactin after a single dose in males. However, after one year exposure to lorcaserin,

serum prolactin in treated males was reduced by 50% relative to the control (Figure 5b). Also, prolactin immunoreactivity in the pituitary and mammary tissue showed no change in treated versus control. Thus, the acute but modest increase in prolactin after a single dose of lorcaserin was not observed after repeated doses in males. This was also the case in humans where a single dose of lorcaserin appeared to result in small increases of serum prolactin but not in multiple dose clinical studies (please refer to Dr. Golden's review). This profile is consistent with published data showing that repeated dosing with a 5HT2A/C agonist can quickly lead to rapid tolerance regarding prolactin release in rats[1] and humans[2], suggesting that an increase in prolactin with lorcaserin would be acute with no long lasting change to produce the outcome seen in the carcinogenicity study.

Figure 5: Serum prolactin response in male rats after (A) single dose or (B) 55 weeks of lorcaserin administration. Hal, haloperidol; lorc, lorcaserin (study DBR-08-031, NDA 22529)

(A) Single Dosing



(B) 55 week dosing

MPI Research Study Number 900-063
A 2-Year Carcinogenicity Study of APD356 Given by Oral Gavage to Rats

Summary of Toxicokinetic Neuroendocrine Hormone Values MALE

Endpoint	Interval of Study	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Prolactin ng/ml	Week 55	57.87	32.062	5	28.24[b]	12.479	14	29.90[b]	10.908	10	20.69[a]	16.140	14

[1] Aulakh CS et al. JPET (271) 1994
[2] Benjamin J et al. Psychopharmacology (127) 1996

Alavi- J4
EXH. P
P. 110

Prolactin responses in female rats

Lorcaserin increased mammary tumors in sexually intact female rats in the 2 year bioassay. Several studies failed to demonstrate a persuasive increase in prolactin or estradiol under comparable conditions (i.e., non-ovariectomized, intact female rats). Figure 6 demonstrates that single dose haloperidol increases serum prolactin, but single dose lorcaserin does not. Table 8A demonstrates that serum estradiol and prolactin do not increase in response to lorcaserin after 1, 15, or 28 days of dosing relative to the control group. Table 8B demonstrates that prolactin immunoreactivity in the pituitary and mammary gland is similar to control after 28 days of exposure to lorcaserin. Consistent with the shorter duration studies, 56 weeks of exposure to lorcaserin did not result in increased serum prolactin or estradiol relative to controls, although a slight increase in prolactin immunoreactivity was reported in the pituitary of treated females (Table 9A, B). The positive pituitary finding did not correlate with findings in the mammary tissue, however. According to the sponsor, "*The incidence and the severity of prolactin immunohistochemistry stain* (of mammary tissue) *were similar among control, low dose, and mid-dose animals and were decreased by 40% at the highest dose. There were no correlations between the incidence of mammary gland prolactin stain and the incidence of pituitary gland prolactin stain in females at all dose levels.*" *(page 900-063, study ITX05071, NDA 22529).*

Figure 6: Effect of single dose lorcaserin or haloperidol on serum prolactin in intact female rats (study DBR-08-031, NDA 22529)

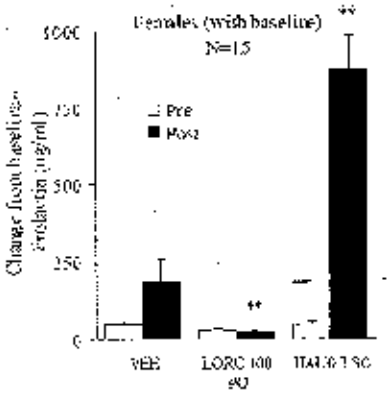


Table 8A: Serum estradiol and prolactin levels in intact female rats in response to lorcaserin after 1, 15, and 28 days administration, (study MPI 900-101, NDA 22529)

Day and time of measurements	Estradiol, pg/ml		Prolactin, ng/ml	
	0 mg/kg	100 mg/kg	0 mg/kg	100 mg/kg
Day 1, at 2hr	<2 to 6	<2 to 6	49	62
Day 1, at 6 hr	<2 to 18	<2 to 33	378	213
Day 1, 12 hr	<2 to 6	<2 to 8	59	95
Day 1, 24 hr	<2 to 15	<2 to 3	87	215
Day 15, 2 hr	<2 to 26	<2 to 13	109	31
Day 15, at 6 hr	<2 to 18	<2 to 24	659	505
Day 15, at 24 hr	<2 to 13	<2	76	109
Day 28, 2 hr	<2 to 15	<2 to 16	569	167
Day 28, at 6hr	<2 to 20	<2 to 13	409	882

Day 28, at 24 hr	<2	<2 to 11	294	205

Table 8B: Prolactin immunoreactivity in mammary and pituitary gland from intact female rats after 28 days lorcaserin administration. (study MPI 900-101, NDA 22529)

MPI Research Study Number 900-101
APD356: Assessment of Serum Prolactin and Estradiol in Female Rats During Daily Dosing for 28 Days

Summary of Microscopic Observations - FEMALE

Tissue / Observation	Severity	0 mg/kg/day	100 mg/kg/day
Number of Animals Examined		20	20
mammary gland (ihc)		(19)	(18)
prolactin stain, increased	- minimal	9	9
within normal limits		10	9
pituitary gland (ihc)		(19)	(20)
prolactin stain, decreased	- mild	0	1
within normal limits		19	19
vagina		(20)	(20)
diestrus		4	2
estrus		5	6
metestrus		6	6
proestrus		5	6

Table 9A: Serum prolactin and estradiol levels in toxicokinetic female rats after 56 weeks administration of lorcaserin. (study 900-063, 2 yr rat carcinogenicity study)

Summary of Toxicokinetic Neuroendocrine Hormone Values -- FEMALE

Endpoint	Interval of Study	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Prolactin ng/mL	Week 56	114.78	79.726	5	129.91	55.678	14	106.12	67.985	13	118.62	62.920	10
Estradiol pg/mL	Week 56	2.0	0.00	5	3.7	3.10	14	2.8	0.60	13	2.0	0.00	10

N - Number of measures used to calculate mean   *Significantly different from control; (p<0.01)
SD - Standard Deviation

Alavi- 16

EXH. P
P. 112

Table 9B: Prolactin immunoreactivity in pituitary gland of toxicokinetic female rats after 56 weeks administration of lorcaserin. (study 900-063, 2 yr rat carcinogenicity study)

MPI Research Study Number 900-063
A 2-Year Carcinogenicity Study of APD356 Given by Oral Gavage to Rats

Summary of Prolactin Positive Stained Cell Counts in the Pituitary Gland - FEMALE

		0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Estrous Stage	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Prolactin Labeling Index (%)	All Stages	60.56	7.566	5	70.42	13.442	14	79.01[a]	14.812	14	79.82[a]	11.286	10

N - Number of measures used to calculate mean
SD - Standard Deviation
[a]Significantly different from control (p<0.05)

Baseline levels of prolactin are higher in females than in males primarily due to the presence of estrogen and progesterone. The sponsor contends that prolactin levels were variable in the intact females and therefore those studies showing lorcaserin's lack of effect on prolactin were 'inconclusive'. That haloperidol robustly increased prolactin in the intact female rats contradicts the sponsor's concern. Nevertheless, to address this perceived shortcoming in the studies, female rats were ovariectomized to reduce levels of sex hormones in an effort to demonstrate a lorcaserin-induced increase in prolactin. Ovariectomy reduced baseline levels of prolactin, but lorcaserin failed to increase serum prolactin or immunoreactivity in the pituitary of ovariectomized females either acutely or after 9 or 20 days of dosing (Table 10). By comparison, the serotonergic agonist dexfenfluramine increased serum prolactin in both intact and ovariectomized females, most likely as a consequence of increasing brain levels of serotonin and suppressing dopamine output. This is of particular interest, because dexfenfluramine *did not* result in mammary tumors in Sprague Dawley rats (NDA 20344), despite the increase in prolactin demonstrated herein.

Table 10: Prolactin release in intact and ovariectomized female rats after administration of lorcaserin (APD356) or dexfenfluramine (D-FEN) for 10 and 21 days (study WIL670002/TX08007). Similar results were obtained in a separate study (WIL670001/TX08001).

Prolactin Analysis						
	Sexually Intact Females			**Ovariectomized Females**		
Group:	**Vehicle**	**APD356**	**D-FEN**	**Vehicle**	**APD356**	**D-FEN**
Prolactin (ng/mL)						
Day 9 Mean:	15.0	6.2	42.1	10.7	3.1	21.5
% Difference		-58.7	180.7		-71.0	100.9
SD	16.42	6.05	41.75	8.73	1.96	15.42
Range	0.4-47.8	1.1-18.1	3.8-105.4	2.2-28.8	0.4-7.0	4.2-38.1
N	10	10	5	10	10	5
Day 20 Mean:	11.7	9.1	98.1*	4.6	4.7	12.6*
% Difference		-22.2	738.5		2.2	173.9
SD	17.03	6.73	143.74	2.79	3.06	11.92
Range	0.8-44.7	0.4-18.3	14.3-354.2	0.4-9.1	0.4-9.8	1.7-27.8
N	10	10	5	10	10	5

* – Significantly different from the control group at 0.05 using Dunnett's test

The lack of lorcaserin's effect on prolactin in intact and ovariectomized female rats prompted the sponsor to further hypothesize that '*controlled levels of ovarian hormones might be required to facilitate the detection of a lorcaserin-stimulated increase in serum prolactin in female rats.*" (Section 2.4.4.8, NDA 22529). That dexfenfluramine readily increased prolactin in intact and ovariectomized females again contradicts the sponsor's reasoning. Nevertheless, to address this issue the sponsor ovariectomized female rats and then implanted pellets to replenish ovarian hormones. The replenishment consisted of 'low' and 'high' doses of an estradiol/progesterone combination. The implanted hormones significantly increased serum prolactin by 10- to 20-fold in ovariectomized females (Figures 7a, b). Lorcaserin had little effect on serum prolactin in ovariectomized females as before, but modestly increased prolactin in the hormone-treated groups (Figure 7a). Expressed as a fold-change to baseline prolactin in ovariectomized rats, the effect of lorcaserin appears particularly minimal (Figure 7b). By comparison, the anti-dopaminergic agent haloperidol robustly increased prolactin regardless of hormone status, with a fold-change similar to that induced by estradiol/progesterone. The conditions required to demonstrate even a minimal increase in serum prolactin with lorcaserin (i.e., ovariectomy + high dose hormones) bears little resemblance to the conditions under which lorcaserin induced mammary tumors in the 2 year bioassay.

Figure 7a: Serum prolactin in response to lorcaserin and haloperidol in ovariectomized females with and without hormonal implantation (study DBR09001). Similar results were obtained in a separate study (DBR08032). Figure 7b depicts the fold change to baseline prolactin in ovariectomized rats without hormone implantation.

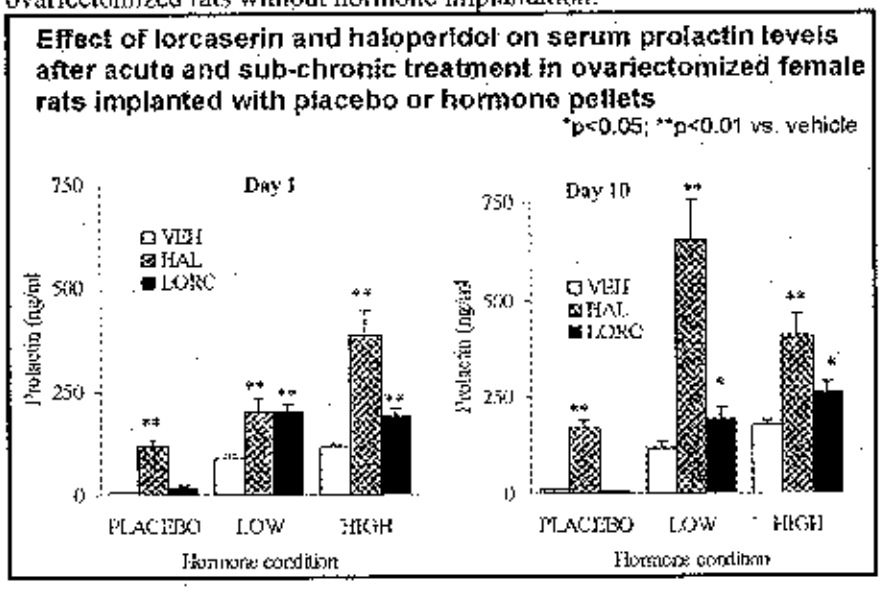


Figure 7b: Fold-change of serum prolactin in ovariectomized female rats administered lorcaserin or haloperidol in the absence or presence of low or high dose hormone pellet implantation. Fold-changes are relative to serum prolactin in ovariectomized rats without hormone implantation on day 1 (5.2ng/ml) and on day 10 (9.8ng/ml). Figure constructed by FDA

EXHIBIT Q

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Advisory Committees

Briefing Information for the September 16, 2010 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee

Persons with disabilities having problems accessing the PDF file(s) below may call (301) 796-3634 for assistance

FDA

Disclaimer

Portions of this document have been determined to be exempt from disclosure under the Freedom of Information Act (the FOIA) (5 U.S.C. § 552).

FDA Briefing Information, LORQESS (Lorcaserin Hydrochloride) Tablets, for the September 16, 2010 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (PDF - 5MB)[1]

Arena Pharmaceuticals, Inc

Disclaimer

The statements contained in this document(s) are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

Arena Briefing Information, LORQESS (Lorcaserin Hydrochloride) Tablets, for the September 16, 2010 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (PDF - 2.3MB)[2]

Errata to the Arena Briefing Information, LORQESS (Lorcaserin Hydrochloride) Tablets, for the September 16, 2010 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (PDF - 57KB)[3]

Links on this page:

1. /downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM225631.pdf
2. /downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM225635.pdf
3. /downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM225636.pdf

EXHIBIT R

LORCASERIN HYDROCHLORIDE (APD356)

NDA 22-529

Briefing Document for FDA Advisory Committee Meeting

Product Name: Lorcaserin hydrochloride (APD356)
Document Number: NDA 22-529
Formulation: Tablets
Indication: Weight Management
Sponsor: Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, CA 92121
Date: 13 August 2010

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

List of In-Text Tables

human renal pathology independently reviewed all monkey kidney slides from the 1-year study in a blinded manner, and reported the findings to be mild and focal, clinically unimportant, without dose relationship, and more likely related to aging, infection, or inflammation than to study drug. Clinical trials showed no evidence of adverse lorcaserin effects on renal function, urinary sediment or urinary protein. To the contrary, a small but greater increase in estimated creatinine clearance was observe in the pooled phase 3 safety data with lorcaserin 10 mg BID that placebo.

4.4.4.3 Genotoxicity

The genotoxic potential of lorcaserin was evaluated in a standard battery of tests consisting of an *in vitro* Ames bacterial reverse mutation assay and a chromosome aberration test in Chinese hamster ovary (CHO) cells up to the limits of toxicity, and an *ex vivo* micronucleus assay in rats at doses up to 250 mg/kg. Results from all three assays were negative, indicating that lorcaserin is not genotoxic.

4.4.4.4 Carcinogenesis

The carcinogenic potential of lorcaserin was evaluated in a 2-year study in mice and a 2-year study in rats.

2-YEAR CARCINOGENICITY STUDY IN MICE

In a mouse carcinogenicity study doses of 5, 25, and 50 mg/kg/day were evaluated. A 100 mg/kg dose was eliminated on study Day 16 due to a high rate of mortality. Survival rates were similar among all treatment groups at the final doses. At the highest dose of 50 mg/kg, lorcaserin exposures relative to human at 10 mg BID were 8 and 4 (males and females, respectively), and lorcaserin sulfamate (M1) exposures were 66 and 74 (males and females, respectively) times M1 exposure in humans at 10 mg BID (Table 3). Neither treatment related toxicity nor carcinogenic effects were observed. Treatment related neoplasms were not found at any dose.

2-YEAR CARCINOGENICITY STUDY IN RATS

A rat carcinogenicity study evaluated lorcaserin doses of 10, 30, and 100 mg/kg. The exposure multiples of lorcaserin at the highest dose were 56 and 84 (males and females, respectively) times the human exposure at 10 mg BID. Plasma exposure multiples for lorcaserin sulfamate (M1), the major circulating metabolite, were 136 (males) and 225, (females) times M1 exposure in humans at 10 mg BID. M1 exposures were more than 10 times lorcaserin exposures in all preclinical species studied. Based upon structure (a stable sulfamate conjugate of a non-genotoxic parent), M1 is not expected to be genotoxic. Direct evidence of this absence of genotoxicity is provided by the *in vivo* rat micronucleus assay, which used lorcaserin doses of up to 250 mg/kg.

Significant general toxicity was observed in males at the 100 mg/kg dose. In males, body weight loss of greater than 10% occurred at Week 51, and by Week 99, a 28% reduction was observed. Additional observations included general poor health and excess mortality; because of these findings the male high dose group was terminated at Week 100 at the

request of the FDA. In light of these findings, data from this dose should be interpreted with caution.

Female Rats

In female rats, mammary gland neoplasia was increased by lorcaserin over a very high background rate in control animals (Table 5). Mortality increased in high dose (100 mg/kg) females after Week 42 due to mammary gland tumors and in the 10 and 30 mg/kg dose groups thereafter. These tumors are secondary to lorcaserin-induced increases in serum prolactin, which is a well-documented cause of mammary neoplasia in rats.[56,57-61] Dopamine 2 (D2) blockers and serotonin 2A and 2C agonists have been associated with prolactin release.[62-64] Increases in serum prolactin were first demonstrated in male rats (Figure 5) after treatment with 30 and 100 mg/kg lorcaserin. Due to hormonal variability associated with the estrus cycle, a high rate of variability in serum prolactin was observed in hormonally intact female rats, which precluded demonstration of a drug effect. However, in ovariectomized, hormone-replaced animals, lorcaserin (100 mg/kg) treatment resulted in a 2-fold increase in serum prolactin (Figure 6). Although the role of prolactin in human breast cancer is not resolved,[65,66] evaluation of medications known to influence prolactin levels does not reveal any important association with risk of breast cancer.[67,68] In any event, lorcaserin did not increase serum prolactin in humans in a phase 3 study (Study APD356-011).

Table 5. Neoplasms in Female Rats and Lorcaserin Exposure Margins Above Human Exposure

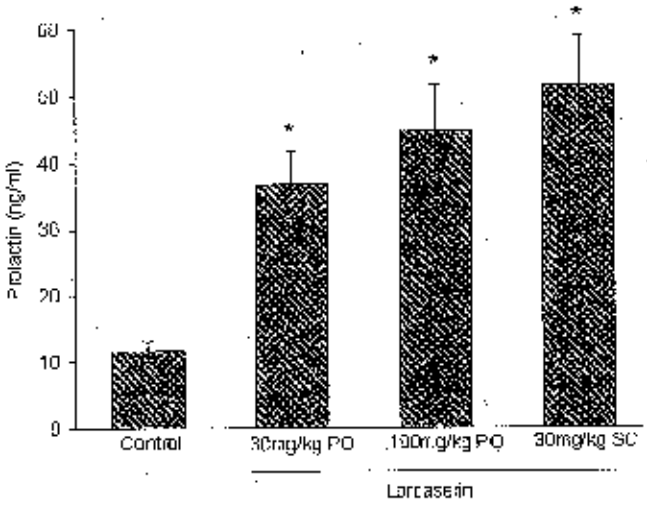
Dose (mg/kg)	0	10	30	100
Lorcaserin margin over human		7	24	84
M1 margin over human		41	88	225
Number of female rats	65	65	65	75
Mammary gland				
Adenocarcinoma[a]	28 (43%)	34 (52%)	35 (54%)	60[b] (80%)
Benign fibroadenoma[a]	20 (31%)	47[b] (72%)	54[b] (83%)	45[b] (60%)

a Trend is significant ($p < 0.0001$).

b Significantly different from control ($p < 0.0001$)

No other treatment-related neoplasms were observed in female rats, although systemic exposure was higher in females than in males (Table 3).

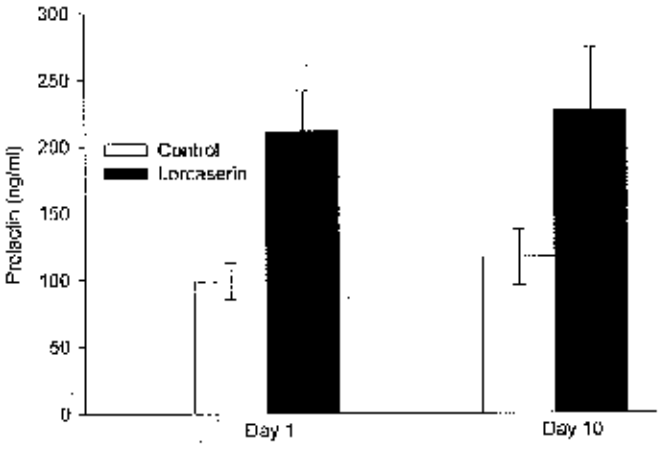
Figure 5. Lorcaserin Increases Serum Prolactin in Male Rats



Male S-D rats were treated with lorcaserin or vehicle control; 30 min after treatment, blood was obtained for prolactin analysis. Values are mean ± SEM, n = 15. *p < 0.01 relative to control (t-test or one way ANOVA with Student/Newman-Keuls test).

Source: DBR-08-031

Figure 6. Lorcaserin Increases Serum Prolactin in Ovariectomized Hormone Replaced Female Rats



Ovariectomized female S-D rats were implanted with subcutaneous pellets containing 2.5 mg estradiol and 35 mg progesterone. One wk later daily vehicle or lorcaserin (100mg/kg, PO) was initiated. Thirty min after treatment on days 1 and 10 blood was obtained for prolactin analysis. Values are mean ± SEM, N=10. * p <0.01, ** p<0.05 relative to control (t-test, Student/Newman-Keuls test).

Male Rats

In male rats, treatment related increases in neoplasms occurred in the mammary gland, as well as other tissues (Table 6). All of these tissues are sites of spontaneous neoplasms (MPI historical control data). Most of the tumor increases occurred in the high dose group (100 mg/kg). The incidence of liver neoplasms was not statistically significant. Margins over human exposure to lorcaserin and the M1 metabolite exist for each of these tumors, reaching 56 and 136, respectively, at the high dose where most tumor increases were found (Table 6).

Several distinct modes of action can account for the increases in neoplasms in each of these tissues. These involve hormone perturbation (mammary gland), metabolic overload (liver, thyroid) and toxicity/irritant effects (skin, brain).

Table 6. Neoplasms in Male Rats and Lorcaserin Exposure Margins Above Human Exposure

Dose (mg/kg)	0	10	30	100
Lorcaserin margin over human		5	17	56
M1 margin over human		36	68	136
Number of male rats	65	65	65	75
Mammary gland[a]				
Adenocarcinoma	0	0	2	2
Benign fibroadenoma[b]	0	1	1	6[b]
Liver[c]				
Hepatocellular adenoma	1	1	2	6
Hepatocellular carcinoma	1	3	3	4
Thyroid gland				
Follicular cell adenoma	0	5[d]	4	8[d]
Skin				
Squamous cell carcinoma[e]	0	0	4	5[e]
Brain				
Astrocytoma[f]	1	0	4	8[f]
Subcutis				
Benign fibroma[g]	3	7	11[g]	17[g]
Malignant schwannomas[h]	0	0	1	5[h]

a Adenocarcinoma/fibroadenoma combination; trend is significant ($p < 0.0001$). Significantly different from control at 30 mg/kg ($p = 0.0132$) and 100 mg/kg ($p = 0.0006$).

b Trend is significant ($p = 0.0001$). Significantly different from control at 100 mg/kg ($p = 0.002$).

c Adenoma/carcinoma individually or in combination: no statistically significant increase.

d Significantly different from control at 10 mg/kg ($p = 0.0423$) and 100 mg/kg ($p = 0.0139$).

e Trend is significant ($p = 0.0008$). Significantly different from control at 100 mg/kg ($p = 0.0245$

f Trend is significant ($p < 0.0001$). Significantly different from control at 100 mg/kg ($p = 0.0025$).

g Trend is significant ($p < 0.0001$). Significantly different from control at 30 mg/kg ($p = 0.0091$) and 100 mg/kg ($p < 0.0001$).

h Trend is significant ($p = 0.003$). Significantly different from control ($p = 0.0478$).

Table 6. Neoplasms in Male Rats and Lorcaserin Exposure Margins Above Human Exposure

Dose (mg/kg)	0	10	30	100
Lorcaserin margin over human		5	17	56
M1 margin over human		36	68	136
Number of male rats	65	65	65	75

Each of these tumors is discussed below.

Male Mammary Gland Tumors

Mammary gland adenocarcinoma was not significantly increased in male rats but fibroadenoma was increased at the high dose. The lorcaserin exposure margin was 17 relative to human exposure for mammary benign fibroadenoma. As in females, both of these mammary tumors are the result of increased serum prolactin, which is induced by lorcaserin (Figure 5).[69, 70] In male rats, lorcaserin treatment resulted in a 3.2 to 4.5-fold increase in serum prolactin levels. Prolactin, as discussed in the section on female mammary gland tumors, is not increased in humans at the recommended dose of lorcaserin, and hence this mode of action, even if relevant to humans, would not be operative at therapeutic doses.

Liver Neoplasia

There was no statistically significant increase in hepatocellular adenoma and carcinoma, but a non-significant trend was apparent. Development of rodent liver tumors is enhanced by hepatic biotransformation enzyme inducers.[71] This mechanism involves metabolic overload and is not relevant to humans. Phenobarbital is an example of an hepatic enzyme inducer (CYP and UGT enzymes) in rodents that is associated with hepatic neoplasia in rodents but not in humans.[40, 72, 73] CYP (and UGT) enzyme induction was observed in rats following repeated oral doses of 30 and 100 mg/kg lorcaserin.[74] Lorcaserin shows low potential for CYP induction in cultured human hepatocytes.[75]

Thyroid Follicular Cell Adenoma

Thyroid adenomas were significantly increased in low and high dose males. However, a rat-specific mechanism was identified: induction of UGT liver enzymes, the family of enzymes responsible for T4 (thyroxine) and T3 (triiodo-thyronine) metabolism. Rodent thyroid tumors are known to be associated with UGT inducers such as phenobarbital,[40, 75-80] and induction of UGT enzymes similar to that associated with phenobarbital was observed in rats following repeated oral doses of 10, 30, and 100 mg/kg lorcaserin.[81]

In rats, T4 and T3 have a much shorter half life than in humans due to the lack of thyroxine-binding globulin (TBG).[82] This absence makes rats more susceptible to thyroxine metabolism by UGT enzymes and renal elimination. Consequently, thyroid glands in rats are chronically stimulated by TSH causing glandular hypertrophy, and the rat thyroid gland is therefore particularly vulnerable to the consequences of liver UGT enzyme induction. In addition to the finding of follicular cell adenomas, further evidence of thyroid stimulation in

the rat carcinogenicity study was provided by an associated increased incidence of follicular cell hyperplasia, follicular cysts, and follicular cell hypertrophy.

The UGT enzyme mechanism is not considered relevant to humans.[83] Phenobarbital, a potent UGT (and CYP) inducer in both humans and rats, is only associated with thyroid tumors in the latter species. Based upon assessment of CYP enzyme induction, lorcaserin shows low potential for hepatic biotransformation enzyme induction in cultured human hepatocytes.[84]

Subcutaneous Fibroma and Schwannoma

In the subcutis, benign fibromas were significantly increased at the mid and high dose, and malignant schwannomas, tumors of nerve sheaths also known as neurinomas,[85] were significantly increased at the high dose. The increase in these tumors occurred at 17X and 56X the human exposure at the MRD, respectively. They were not observed in mice, which are susceptible to development of subcutaneous neoplasms.[86] Fibromas were also not observed in monkeys dosed with lorcaserin 125 mg/kg/day for 12 months. Rat subcutaneous neoplasms are known to increase with age[87] and to be elicited by a variety of irritant effects[88] including subcutaneously injected iron dextran.[45] It is possible that the increases in these tumors in male rats is due to their poor general condition, as reflected in a marked reduction in body weight, which could accelerate aging changes in the subcutaneous tissues.

Squamous Cell Carcinoma of the Skin

Squamous cell carcinoma of the skin was increased at the high dose, which resulted in a plasma drug exposure that was 56X that of human at the MRD. These tumors were not observed in female rats, or in mice, which are susceptible to development of epidermal neoplasms.[86, 89] As with the increased subcutaneous neoplasms, they are most likely due to the poor general condition of the high dose male animals, as reflected in marked reduction in body weight. Such weight reductions did not occur in females, which did not exhibit these neoplasms. Immunosuppression is known to enhance skin tumor development.[90, 91] The debilitation of male rats may have impaired their intrinsic immunosurveillance. The major inducer of these tumors in humans is UV light.

Brain Neoplasia

Astrocytomas were significantly increased in high dose male rats. This occurred at an exposure that was 56X that of human at the MRD. Recently, the presumed histogenesis of astrocytomas in rats has been called into question, with the consequences being that rat "astrocytomas" probably do not have a direct human counterpart.[92,93] Histological and immunohistochemical analysis of astrocytomas in rats using antibodies against GFAP (a marker for astrocytes) and antibodies against markers for macrophage lineage (ED-1) indicate that rat astrocytomas, in contrast to human, are not of astrocyte (glial cell) origin, but rather of monocytic origin (macrophage/microglia/dendritic cell).

A study of brain tissue from the rat carcinogenicity study was consistent with the evolving literature.[93] Immunohistochemical staining of the astrocytomas in the lorcaserin rat carcinogenicity study was conducted using antibodies against GFAP, anti-CD68 clone ED-1 and MHCII. All of the astrocytomas identified were GFAP negative and ED-1 positive, supporting the interpretation that the neoplastic cells comprising the tumors, referred to in the

rat carcinogenicity study as astrocytomas, were not derived from astrocytes but from macrophage or microglial cells.

These data are important for two reasons: 1) immune cell tumors of the CNS are rare in humans, and 2) generalized toxicity can be considered mitogenic for cells of macrophage lineage, thus providing a mechanism for the increased incidence of this tumor in male rats.

Acrylonitrile is a widely used synthetic intermediate in the manufacture of acrylic fiber, plastics and synthetic rubber. In chronic studies using rats, acrylonitrile causes a significant increase in brain tumors typically identified as astrocytomas.[94] Although there is a relatively high number of industrial workers exposed to acrylonitrile at levels equivalent to those in rats, epidemiological studies have shown no relationship between acrylonitrile exposure and brain tumors in humans.[95] The mechanism of acrylonitrile induced brain tumors in rats is not known. Evidence indicates, however, that acrylonitrile selectively induces oxidative stress in the rat brain;[96] thus a toxic mechanism appears to participate in brain tumor induction. In addition, it has been shown recently that, as with lorcaserin, acrylonitrile- induced rat "astrocytomas" appear to be of monocytic and not glial cell origin.[97]

In contrast, numerous studies of human glial neoplasms have used GFAP immunostaining to diagnose astrocytic neoplasms.[98, 99] Furthermore, results from GFAP immunostaining of human glial tumors has shown a significant relation with the present World Health Organization grading system of these tumors.[100, 101] Primary brain tumors of immune cell origin are rare in humans, constituting ~2.5% of the total, and most of these are lymphomas, of T-cell and B-cell origin.[102] Microgliomas could be included in this category. Congenital or acquired immunodeficiency is the only established risk factor for primary CNS lymphoma.[103] No chemical agent has yet been shown to cause tumors in the human nervous system.[104]

Incidences of Tumors in Females that Were Increased in Males

Only mammary tumors were increased in female rats, as described above. The following table displays the incidence in female rats of other tumors that were increased in males, demonstrating that the increased incidence of these tumors was sex specific despite higher exposures in females.

EXHIBIT S

FDAAC

September 16, 2010
8:00 AM ET

Abraham Thomas:	Good morning. I'd like to first remind everyone present to please silence your cell phones, Blackberries and other devices, if you have not already done so. I would also like to identify the FDA press contact, Ms. Karen Riley. We'll now go around the table and introduce the members of the Committee. Good morning, my name is Dr. Abraham Thomas. I'll be Acting Chair of the Endocrinologic and Metabolic Drugs Advisory Committee. I will now call the Endocrinologic and Metabolic Drugs Advisory Committee Meeting to order. We will start with myself. As I mentioned, I am Dr. Abraham Thomas, Division Head of Endocrinology at Henry Ford Hospital in Detroit, Michigan, and then with the FDA, Dr. Curtis Rosebraugh.
Curtis Rosebraugh:	Good morning, everybody. Curt Rosebraugh, Director, Office of Drug Evaluation II.
Eric Colman:	I'm Eric Colman, Deputy Director for DMEP.
Julie Golden:	Good morning. I'm Julie Golden, medical reviewer, DMEP.
Todd Bourcier:	Good morning. Todd Bourcier, pharm tox reviewer with DMEP.
Fred Alavi:	Good morning. Fred Alavi, pharm tox reviewer, DMEP.
Jodi Segal:	Good morning. Jodi Segal from Johns Hopkins University.
Allison Goldfine:	Allison Goldfine, Joslin Diabetes Center, Boston.
Ed Gregg:	Ed Gregg from CDC Atlanta.
Michael Proschan:	Michael Proschan. I'm a statistician with the National Institute of Allergy and Infectious Diseases.
Paul Tran:	Paul Tran, DFO for the Endocrine Committee.
Katherine Flegal:	Katherine Flegal, epidemiologist from the Centers for Disease Control and Prevention.

Lamont Weide:	Lamont Weide, Chief of Endocrinology, University of Missouri-Kansas City School of Medicine.
Eric Felner:	Eric Felner, pediatric endocrinologist at Emory University in Atlanta.
Jessica Henderson:	Jessica Henderson. I'm the Consumer Reviewer.
Pam Douglas:	Pam Douglas, cardiologist from Duke University.
Sanjay Kaul:	Good morning. Sanjay Kaul, cardiologist from Cedar Sinai Medical Center, Los Angeles.
Melanie Coffin:	Good morning. Melanie Coffin, Patient Representative.
Jacqueline Gardner:	Jacqueline Gardner, University of Washington, Seattle.
Heidi Connolly:	Heidi Connolly, cardiologist, Mayo Clinic.
Rick Veltri:	Rick Veltri, cardiology, Industry Representative.
Abraham Thomas:	For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.
Paul Tran:	Good morning. The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and temporary voting members of the Committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this Committee are in compliance with the federal ethics and conflict of interest law. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug & Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purpose of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of the safety and efficacy of a new drug application, NDA 22-529, with the proposed street name LORQESS, lorcaserine hydrochloride tablets, sponsored by Arena Pharmaceuticals as an adjunct to diet and exercise for weight management in patients with a body mass index, BMI, of equal to or greater than 30 kg/m2, or a BMI equal to or greater than 27 kg/m2 if accompanied by weight-related comorbidities. This is a particular matters meeting during which the specific matters related to Arena LORQESS will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements they may have made concerning the product at issue.

With respect to the FDA's invited Industry Representative, we would like to disclose that Dr. Enrico Veltri is participating in this meeting as a nonvoting Industry Representative acting on behalf of regulated industry. Dr. Veltri's role at this meeting is to represent industry in general and not any particular company. Dr. Veltri is a former employee of Merck.

We would like to remind members and temporary voting members that if the discussions involve any other product or firm not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the Committee of any financial relationship that they may have with any firm at issue. Thank you

Abraham Thomas: We will now proceed with the FDA opening remarks from Dr. Eric Colman. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Dr. Colman?

Eric Colman: Thank you. I would like to welcome back all the folks who were here yesterday for a second day, and also welcome those of you who are joining us for the first time. As you have heard, we are going to be talking about a new drug called lorcaserin, which is a 5-HT2C receptor agonist being developed for weight loss.

I want to mention one particular issue that relates to a question that we will be asking you, and that has to do with the potential for valvular heart disease. Given that this class of medication and data that suggests that activation of the 5-HT2B receptor is responsible for the valvulopathy that was observed with fenfluramine and dexfenfluramine, we were obviously very concerned with this compound, since it is somewhat of a chemical cousin to those drugs in terms of its interaction with the 5-H2 receptors.

At the beginning of the development plan, the Division spoke with the Company. We all agreed that echocardiograms would have to be done to best evaluate for the potential for valvulopathy. The question was, what was a reasonable sample size? I believe the Company initially proposed a noninferiority margin of 2, and we were uncomfortable with that degree of uncertainty. We felt 2 was a little too high. So, we had continued discussions. We ultimately settled on 1.5. I think that necessitated that their sample size go from a 3,000 or 4,000 to 7,000, but we felt that that was a reasonable place to start the process.

We were in the dark in some areas. For example, we had no idea what the incidents of valvular heart disease would be if you took a group of people at baseline who did not have it, followed them for a year on placebo, and then observed them to see how many actually developed FDA-defined valvulopathy. So, there were a lot of unknowns that we weren't aware of, and the only way to get some data was to start and see what you get.

So, I want to make it clear that the 1.5 was an initial goalpost just to allow us to proceed and get some data. From our standpoint, it was never -- the noninferiority margin is 1.5, so if you come in at 1.4, that is a game winner and there is no more discussion. We always anticipated it would be, we would look at the degree of uncertainty with a valvulopathy in context of the drug's efficacy, potentially other benefits of the drug, other potential risks of the drug. So, I just don't want to convey the message that 1.5 was the win-all number, because, again, we were working in the dark in many areas here.

Do we want to go over the questions?

Abraham Thomas: Questions to the Advisory Committee. No. 1: Has adequate evidence been provided to establish lorcaserin's efficacy as a weight loss drug? Are there additional studies that you would recommend pre- or post-approval to further evaluate lorcaserin's efficacy?

Question No. 2: Has adequate evidence been provided to assess the potential risk for lorcaserin's-induced valvular heart disease? A. Are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk? B. If approved, please discuss the need for monitoring and possible monitoring strategies.

Question 3: Has adequate evidence been provided to assess the potential risk to human subjects of lorcaserin-related neoplasm in rats? These neoplasms involve breast, brain, peripheral nerve, skin and subcutis. A. Are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk? B. If approved, please discuss the need for monitoring and possible monitoring strategies.

Question 4: Has adequate evidence been provided to assess and characterize the potential risk for psychiatric adverse events, such as dissociative disorders and depression/suicidality? A. Are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk? B. If approved, please discuss the need for monitoring, possible monitoring strategies, and contraindications for use.

Question 5: Has adequate evidence been provided to assess and characterize the potential risk for adverse events related to disorders of attention, memory, and other cognitive disorders? A. Are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk? B. If approved, please discuss the need for monitoring and possible monitoring strategies.

will review the medical need for weight loss, the overall benefits of weight loss, and the favorable risk/benefit profile of treatment with lorcaserin.

For purposes of full disclosure, the outside experts who will present information today to assist us in answering questions from the Committee have been compensated for their time. None of these experts own stock in Arena Pharmaceuticals.

In order to explain the rationale for lorcaserin development, I must first explain the role of serotonin in regulation of food intake and body weight. Serotonin is a major neurotransmitter with 14 known receptors in seven families. This breadth is important in understanding both the efficacy and liabilities of serotonergic approaches to weight management, as well as the need for the kind of selectivity that lorcaserin provides.

Serotonin was found to decrease food intake and reduce body weight in animals over four decades ago, leading to the development of serotonergic drugs for weight loss. Clinical experience with these drugs has demonstrated the need for selective agents.

The weight loss medications fenfluramine and dexfenfluramine were among the first to validate serotonin receptors as pharmacological targets for weight loss in humans. These drugs are nonselective with the potential to engage all 14 serotonin receptors. While they induced weight loss, they also increased the risk of serotonin-associated valvulopathy.

So, from this, we knew that it was important to target certain serotonin receptors. Subsequent studies have shown which to target and which to avoid. A strong body of evidence has implicated agonism of 2B receptors expressed on cardiac valvular interstitial cells in the valvulopathy, identifying a receptor to avoid, and studies in rodents taught us which receptor to target. These studies demonstrated the 2C receptor agonism could induce decreased food intake and produce weight loss. The efficacy of both selective and nonselective 2C agonists was blocked by selective antagonism further validating this target.

Furthermore, 2C knockout mice are hyperphagic, overweight, and resistant to agonists. This resistance can be overcome by selectively restoring these receptors in the hypothalamus.

We therefore designed lorcaserin as a selective serotonin 2C agonist. While lorcaserin has some functional activity at serotonin subtype 2 receptors A and B, it was specifically engineered to be highly potent at the 2C receptor, while avoiding activation of other serotonin receptors at therapeutic doses.

We first validated the pharmacology of lorcaserin in rats. In these animals we showed a similar receptor binding affinity to that observed in humans. Because of the selectivity of the 2C receptor, at therapeutic doses of lorcaserin we saw decreased food intake and weight loss in the rats. However, we did not see wet dog shakes or back muscle vesiculations, which are classic manifestations of 2A activation. And even at supratherapeutic doses, we did not demonstrate changes in heart valves associated with 2B activation.

In a moment, I will ask Dr. Williams to discuss his review of the preclinical carcinogenicity data. Dr. Williams is professor of the Department of Pathology at New York Medical College and is an internationally recognized expert in the field of carcinogenicity. He has published more than 500 papers on the topic including chapters in well recognized textbooks. He has been a member of the editorial board for a number of journals related to carcinogenicity and participated as a panel member or chair of

government-sponsored committees of the EPA, NIH, National Cancer Institute, and the World Health Organization. Dr. Williams will explain why the preclinical findings in the rat bioassay are not predictive of human risk.

Gary Williams: Thank you, Dr. Shanahan. Good morning. I am Gary Williams. Mr. Chairman, members of the Committee, as Dr. Shanahan indicated, my career has been dedicated in large part to studying the relevance of preclinical carcinogenicity findings to human cancer risk. I have done a complete review of the lorcaserin bioassay findings and related studies as well as the relevant literature that bears on the issues we are going to be addressing. And my conclusion, which is shown on the next slide, is that lorcaserin does not pose a cancer risk to humans at the recommended therapeutic dose.

To begin with, lorcaserin is not genotoxic, as demonstrated in a standard battery of preclinical *in vitro* and *in vivo* assays. It therefore does not directly induce neoplastic changes, and the tumor increases in the bioassays were due to secondary epigenetic processes.

Secondly, no treatment-related tumors were found in the mouse bioassay at doses up to the maximum tolerated dose. Then, all tumors of increased incidence in the rat are related to either toxicity from exceeding the maximum tolerated dose and/or to rodent-specific mechanisms. Tumors due to rodent-specific mechanisms are not relevant to humans.

Finally, adequate safety margins over human exposure exist for all tumors related to toxicity. I will now review the tumor findings in the rat.

This is a list of tumor types in Sprague-Dawley rats that were significantly increased and exceeded the historical control ranges for the tumor in the laboratory conducting the assay. With the absence of mammary gland tumors, the third line up from the bottom, all tumors of increased incidence were restricted to males. It is also important to note that all malignant tumors were found only at the high dose. The doses are indicated in the last column, which produced drug exposures 56 times greater in male rats and 84 times greater in female rats compared to what humans will see at the therapeutic dose.

Now, I might just pause to call attention to the fact that these exposures vastly exceed what is the norm for carcinogenicity bioassays. The International Conference on Harmonization to which the FDA is a party, has agreed that a 25-fold exposure margin is a pragmatic endpoint for the bioassay.

Importantly, all the tumors increased in the lorcaserin study are known to occur spontaneously in the rat strain used in the bioassay. And some of these, for example, astrocytomas, occurred in the control animals in the study. This supports the interpretation that the lorcaserin findings represent enhancement of intrinsic neoplasia.

Moreover, all the treatment-emergent tumors are all well known to be increased in other bioassays. And here I show a sample of other FDA-approved drugs that had findings in the rat bioassay involving the same tissues that were sites of tumors in the lorcaserin bioassay. And there are more examples, but this is just a selection from available material.

Looking at the lorcaserin data, there are three reasons why I concluded that the tumors increased in rats do not predict human risk at therapeutic dose, and these are toxicity at the high dose, rat-specific mechanisms not relevant to humans, and safety margins of

noncarcinogenic exposure over human exposure at the therapeutic dose. First I'll discuss the impact of toxicity in male rats.

This slide presents weight change in male rats over time. Over the course of the study, the control animals progressively gained weight, and their weight gain has been normalized to the line indicated by zero across the top of the chart. In contrast, all doses of lorcaserin caused reduced weight gain compared to controls. At the high dose, which is represented by the lower dark black line, there was significant decrease in weight relative to controls, which achieved a 10% reduction for the first part of the study, which is considered a maximally tolerated dose, and then progressed afterwards, finally reaching 28% by the end of the study.

Importantly, by week 69, the male rats on the high dose experienced absolute body weight loss, which is evidence of profound toxicity. If this were a pharmacological effect -- and, by the way, that does occur in the animals -- this effect would have occurred much earlier. One reason for the weight loss might have been the development of neoplasms, but this was not the case for all the rats.

This chart displays the weight curves for males without tumors. That means these are males that never developed tumors during the course of the study. Weight suppression exceeded 10% up to about week 40, and then progressed further, as shown in the dark line at the bottom. This clearly demonstrates the decrease in weight gain was occurring independent of tumor development.

In addition to these general effects, a variety of specific pathological findings also demonstrate toxicity in high-dose males. I will only focus on the first four, because these affected tissues that were targets for the increases in tumors. In the brain there was gliosis and mild focal mineralization. In the skin, atrophy of the epidermis, and in the liver, evidence of metabolic overload with observations of cystic degeneration, vacuolation and necrosis.

In addition, the fourth point, lymphoid depletion in the spleen and lymph nodes is an observation consistent with suppression of the immune system and may have contributed to the increased incidence of tumors, particularly skin tumors, which are known to be increased by impaired immunosurveillance. Importantly, these findings did not occur in female rats at the high dose even with the higher systemic exposures, demonstrating that the high dose was only toxic in males.

Taking into account the foregoing observations, the study director independently of Arena, concluded in the final study report that the high dose was toxic in males, as shown here. Based on these observations, I conclude that the three types of tumors shown here in bold are attributable to the tissue toxicities that I have mentioned.

Next, I will discuss implications of mechanisms. Recall that the mammary gland tumors were increased in female rats and high-dose male rats. The Sponsor considered several possibilities for these increases. Among them was increase in prolactin secretion, which is known to promote mammary neoplasia in rats. Indeed, lorcaserin increased prolactin in female and male rats. The documented increases were of short duration, but such increases may be sufficient to cause mammary tumors if they occur at a critical period, such as during development of the mammary gland when it is highly susceptible to tumorigenic stimuli, as I will discuss. Other relevant hormones assessed were not affected by lorcaserin.

The data on this chart show lorcaserin-stimulated prolactin release in Sprague-Dawley rats, the same strain used in the bioassay. On the left panel is the data from the study in eight-week-old female rats, and I emphasize eight weeks old. Accurately measuring prolactin was challenging because of the influence of diurnal and estra-cycle fluctuations in prolactin levels.

The Sponsored used an innovative approach of stabilizing the hormonal milieu in female rats and demonstrated that the increase occurs at 100 mg/kg body weight. That is the high dose in the bioassay.

Likewise, on the right-hand side, there is a dose-dependent increase in prolactin in males from 30 to 100 mg/kg. As I mentioned, the rats in these studies were weight weeks of age, a fact of importance in the following discussion.

I would now like to show two published scientific studies that document the exquisite sensitivity of the developing rat mammary gland to induction of cancer and response to prolactin. These studies should be viewed against the fact that the rats in the lorcaserin bioassay were started on treatment at about 42 days of age, which is standard practice in bioassays but is well before sexual maturity and full development of the mammary gland.

The importance of this timing is illustrated in the classic work of Charles Huggins shown on this chart. In this study, Sprague-Dawley rats, the same strain used in the lorcaserin studies, were given a single administration of the polycyclic aromatic hydrocarbon, 3-methyl-colanthrine, starting at 25 days of age. Short-term exposure to this compound between 25 and 75 days induced high incidences of mammary gland tumors. Incidentally, this study was part of the body of work for which Dr. Huggins was awarded the Nobel Prize.

It has been known since the 1960s that prolactin plays a role in mammary tumorigenesis in rodents. The effect of prolactin during mammary glad development was demonstrated by Stringer and coworkers in the study shown here. Daily administration of the dopamine antagonist, perphenazine, in female Sprague-Dawley rats, same strain as in lorcaserin studies, at eight weeks of age produced prolactin increases similar to what I described in the rats' dose with lorcaserin.

This prolactin increase led to a nine-fold increase in breast volume and related increases in epithelial cell compartments within 14 days of administration. These changes could predispose to cancer development, but the study was not continued long enough to identify a cancer outcome. And, in fact, I have found no study that has addressed this aspect.

Nevertheless, the study clearly demonstrates the responsiveness of the developing mammary gland to increases in prolactin. Thus, lorcaserin-mediated prolactin increases, which were documented at eight weeks of age, as previously noted, could elicit similar effects. These effects could potentially lead to mammary cancer in rats. This is supported by the observation that in the lorcaserin bioassay, palpable mammary gland tumors appeared by week 30 in 10% of the high dose group. And this very early onset of neoplasia, I think, provides compelling evidence that there was something initiated during the pre-pubertal period of exposure in these animals.

Importantly, in humans, prolactin is not a risk factor for breast cancer. Drugs that produce increases in prolactin and mammary neoplasia in rats, such as antipsychotic medications, have not been associated with breast cancer in humans. In any event, as

indicated in the last bullet, lorcaserin did not increase prolactin in humans in clinical trials.

In contrast to the prolactin findings, no other relevant hormone was found to be altered by lorcaserin treatment. Notably, this includes estradiol, an insulin-like growth Factor I, both of which are known to enhance mammary gland neoplasia.

Accordingly, I conclude that the mammary gland tumors are attributable to increased prolactin at a critical stage of development. In addition, I agree with the FDA that the increases in liver and thyroid tumors arise from a well established mechanism of metabolic overload of the liver, leading to an induction of enzymes including those involved in the metabolism of thyroid hormones. These mechanisms, like the prolactin mechanism, are not relevant to humans.

Lastly, I will address safety margins. Now, as I previously explained, lorcaserin was not genotoxic and therefore was not directly carcinogenic. The nongenotoxic mechanisms for mammary gland, liver and thyroid tumors, which I have discussed, have thresholds. Exposure below those thresholds conveys on risk of cancer development. In any margin below the threshold provides additional assurance of safety. In either the mouse or the rat bioassays, margins of safety were demonstrated for all tumors.

I agree with the FDA assessment of most margins; however, the FDA reviewer arrived at two conclusions shown here: Safety margin could be based on fibroadenoma incidence, and that mammary fibroadenoma and mammary adenocarcinoma should be combined for safety margin calculation. I do not agree with these conclusions for several reasons.

To begin with, fibroadenoma and carcinoma are different types of neoplasms. Carcinoma is an epithelial neoplasm, whereas, fibroadenoma is an epithelial stromal neoplasm. I have consulted all authoritative pathology and toxicology texts known to me on this issue, and I find no support for combining these different tumor types. Moreover, benign fibroadenoma is not a precursor to carcinoma, which, by the way, is also the case in humans. These tumors, therefore, should be considered separately.

In this table, we see that in rats there are 17-fold or greater safety margins for all of the malignant tumors. There are four-fold or greater margins of safety in either rats or mice. The tumor, for which I have an assessment different from that of FDA, is benign fibroadenoma.

First of all, the prolactin mechanism, which I believe to be the basis for the increase in these neoplasms, is not relevant to humans and hence the safety margin is not needed for assurance of human safety. Secondly, fibroadenoma is a benign neoplasm, and increases in rats have not been established to denote a human cancer risk.

So, in summary, lorcaserin is not genotoxic. All observed neoplasms can be ascribed to toxicity or another rodent-specific mechanism, and safety margins exist for all tumors. These considerations lead me to my conclusion that lorcaserin does not pose a cancer risk to humans at the recommended therapeutic dose. Thank you.

Bill Shanahan — Thank you, Dr. Williams. We will now turn our attention to our clinical efficacy data. The clinical trial program for lorcaserin consisted of 18 studies involving 8,576 patients and subjects. The objectives of the program were to demonstrate that lorcaserin could safely effect clinically meaningful weight loss in patients for whom weight management is medically indicated -- obese patients and significantly overweight patients with at least one-related comorbidity.

Bill Shanahan: We don't have any explanation for that, but typically, yeah, I think a comment was made yesterday that LDL typically doesn't drop with weight loss, but we don't have an explanation.

Lamont Weide: And the other question relates to the cancer issue, and I think that will come up multiple times today. In slide C-82, while the numbers are low. I mean, the numbers of patients receiving this are currently low, and I notice that there were no cancers in the placebo group. There were two people with lung cancer and two people with multiple myeloma in that group, while in the rats the tumors seemed to be more breast and brain related. Any comments on that?

Bill Shanahan: Dr. Anderson?

Christy Anderson: I'll point out first that this is just a partial listing and only includes some of the terms. If we look at a full listing of the neoplasm terms, we see that there is no imbalance in the total number of terms between lorcaserin and placebo. I am showing a slide now which for unknown reasons has a box around basal cell carcinoma. The important point on this slide is that -- let's switch to a different slide. The important point on this slide is that the total number of neoplasms is approximately the same in placebo and lorcaserin.

Perhaps even more importantly, if we look down the line at the sorts of things that did appear in the rats, like breast cancer, it is pretty much balanced between the lorcaserin and placebo group. The one [excess] event in lorcaserin b.i.d. group was actually in a patient who was on placebo at the time of diagnosis in the second year of the NINE trial.

Across other cancer types, if we lump all skin cancers, there is no more skin cancer incidence in the lorcaserin group than the placebo group, and we see basically none of the neurologic system tumors that we saw on the rodents.

Pam Douglas: I have two questions on the cardiovascular side effects. On slide 82, you mentioned that there were four myocardial infarction, acute MI events in the group. My understanding is that they were not adjudicated, and I was wondering if this also included acute coronary syndromes or just documented MIs and they were not adjudicated? That's the first question.

Christy Anderson: Within the events that we showed in the SAE summary, we only used selected MedDRA-preferred terms that showed up. We did a more thorough search of AE terms potentially related to ischemic cardiovascular events. Within the context of the clinical trial conduct, there was no adjudication. However, we did perform a post hoc adjudication.

We formed a group of external experts, cardiologists associated with TEMI, who have expertise in clinical cardiovascular events outcomes. The independently created a charter, reviewed our SAE terms, and then adjudicated the events, which are shown on this slide.

When they did put together all of the acute coronary syndrome, MI and related events, you see there if you focus on the final column, which is the pooled Phase III data, six events in placebo, five events in lorcaserin b.i.d. Obviously, the event right here is really low, but there is no evidence that there is an imbalance in the treatment groups.

Pam Douglas: Thank you. The second question as regarding valvulopathy. On slide 94, you said that the power was 80%, yet the numbers of individuals, at least in slide 96, are actually quite

So, that concludes my talk, and I would like to invite Dr. Fred Alavi to the podium to present our perspective on the tumor findings in rodents with lorcaserin.

Fred Alavi: Thank you. Good morning. I will present the results of the lorcaserin carcinogenicity assessment in rats and mice. First, I will provide an overview of the tumor response to lorcaserin in rats and mice; then I will discuss in more detail our view of the relevance of mammary tumors and nervous system tumors identified in rats. I will also address the parent gender and specificity of tumor response in rodents, and will end with a summary of our findings.

As with all pharmaceutical compounds for chronic clinical indications, the potential carcinogenicity of lorcaserin was assessed in two-year lifetime exposure studies in Sprague-Dawley rats and CD1 mice. Overall, lorcaserin was identified as nongenotoxic carcinogen in rats but was not tumorigenic in mice. I will present the findings in rats and then address the negative findings in mice near the end of my talk.

Lorcaserin doses of 10, 30 and 100 mg/kg were orally administered to rats for a scheduled period of two years. Lorcaserin exposure at these doses in male rats was approximately 5, 17 and 55 times higher than the clinical dose, and in females, 7, 24 and 82 times higher than the clinical dose.

The Division and the FDA's Executive Carcinogenicity Assessment Committee concluded that multiple tumor types were increased in male rats at exposure approximately 17-fold higher than the clinical dose.

These tumors which occurred at mid-dose of 30 mg/kg consisted of mammary fibroadenoma, astrocytoma, and Schwannoma, as well as fibroma and squamous carcinoma of skin subcutis.

These tumors were also seen at higher dose of 100 mg/kg. Additional tumors identified at this dose included liver and thyroid adenoma. The nontumorigenic low dose of 10 mg/kg provided a relative narrow five-fold safety margin to the clinical exposure.

In females, mammary neoplasms were observed at all doses, all lorcaserin, with lowest dose being seven times the clinical dose. Because even the lowest dose of lorcaserin was associated with mammary tumors, no safety margin to clinical exposure was identified.

Among tumor types observed in rats, the mammary tumors were of particular concern for the following reasons. Tumors were identified in both sexes; tumors occurred in all doses in females; tumors occurred near clinical exposure or at least within seven-fold of clinical exposure with no safety margin identified in females.

In males, the lorcaserin-related mammary tumors consisted of fibroadenoma and adenocarcinoma, and the incidences at 30 mg/kg and above exceeded the historical background range. Also, these tumors were fatal in cases, particularly at 100 mg/kg. In females, the lorcaserin-related mammary tumors consisted of significant increase in fibroadenoma at all doses, and adenocarcinoma at high dose, although in numerical increase seen at both low and mid-dose.

The incidents of tumors also exceeded the high historical background range and the control group, which can complicate to some degree detection of drug-related effect. However, our analysis demonstrates that a number of deaths related to benign and

malignant mammary tumors increased with dose, and that mean survival decreased over time over the same dose range.

Furthermore, higher doses were associated with multiple mammary tumor sites. Therefore, we are confident that lorcaserin increased mammary tumors at all doses in females. Also, we viewed the increased incidents of fibroadenoma and adenocarcinoma with equal concern, as both tumor types were fatal in rats.

The Applicant has proposed that the following mode of action for lorcaserin-related mammary tumors are likely to take place: Activation of 5-HT2C or off-target activation of 5-HT2A, resulting in increased pituitary prolactin output which is linked to induction of mammary hyperplasia and neoplasm in rodents; antidopaminergic and antipsychotic drugs such as haloperidol are known to result in robust and persistent increase in serum prolactin in rodents, and to some extent in humans.

Antidopaminergic drugs over time produce mammary tumors in rodents via this mechanism. The relevance of this mode of action to human risk is unresolved, but rodents are clearly susceptible to this mode of action.

We disagree with Applicant that the mechanistic studies submitted in NDA adequately implicate a role for prolactin in lorcaserin tumorigenic mode of action for the following reasons:

First, lorcaserin does not result in a robust sustained increase in prolactin levels. As the Sponsor has shown in the left panel, single dose of lorcaserin given to male rats modestly increase serum prolactin, though the response was much less than the response to haloperidol. However, this small acute increase in prolactin was not sustained as serum prolactin after 55 weeks of dosing was, if anything, about 50% less in lorcaserin treated group compared to control groups. This is all the mechanistic studies we could find for male rats.

In females, a single dose of lorcaserin did not increase serum prolactin, although haloperidol significantly increased prolactin levels. After 55 weeks of dosing, immunoreactive prolactin in the pituitary of lorcaserin-treated females increased marginally over the control group, but this increase did not correlate the serum prolactin levels which, again, were similar to the control groups.

Also, the pituitary staining apparently did not correlate with the mammary tissue findings, with the study reports stating that there were no correlations between the incidents of mammary gland prolactin stain and the incidents of pituitary gland stain in females at all dose levels.

Now, variable levels of sex hormones can lead to variable levels of serum prolactin, which the Applicant cited as the potential reason for the negative findings in the female rats. Therefore, the Applicant proposed that controlled levels of sex hormones were necessary to detect the prolactin response to lorcaserin in female rats.

So, to show this effect, female rats were ovariectomized, implanted with estrogen and progesterone, and then treated with lorcaserin. And, as the Sponsor has shown, lorcaserin marginally increased serum prolactin as shown by the black bars, compared to the effect of hormone alone, shown by yellow bars.

By comparison, haloperidol produced a robust increase regardless of hormone status, and this marginal increase of lorcaserin occurred only in ovariectomized and hormonally

supplemented female rats. These conditions bare little resemblance to those experienced by the female rats that were evaluated in the two-year carcinogenicity study.

There are two additional points that bear consideration. First, lorcaserin marginally increased serum prolactin under rather contrived conditions, but the positive controlled haloperidol very robustly increased prolactin regardless of the conditions, whether they were sexually intact, ovariectomized, or hormone supplemented.

Second, dexfenfluramine was found to modestly increase serum prolactin under the conditions where lorcaserin did not, as shown here in sexually intact and ovariectomized females. Presumably, this response to dexfenfluramine is related to its serotonergic properties. However, despite the modest increase in serum prolactin, dexfenfluramine did not produce mammary tumors in two-year rat bioassay.

To summarize the relevance of mammary tumors, lorcaserin increased mammary tumors within seven-fold of clinical exposure with no safety margin identified. It is our opinion that the mechanistic studies do not adequately support a role for prolactin in lorcaserin's tumorigenesis mode of action. And without a tumorigenic mode of action, monitoring of prolactin in clinical studies is of questionable relevance. And it is our view that the relevance of lorcaserin-related mammary tumors in rodents, [that the obese patient population cannot be dismissed.]

We are also concerned with the appearance of nervous system tumors with lorcaserin, particularly the increased incidents of astrocytoma, for the following reasons: The CNS is the site of drug action for lorcaserin, and lorcaserin preferentially partitions the brain tissue, and the partition varies by species, which complicates the estimation of the safety margin.

Finally, tumorigenic mode of action was not at risk, which limits the risk assessment to differences in exposure between animals and humans.

Upon the review of the data, the Division and the Carcinogenicity Assessment Committee concluded that numerical and statistically significant increase in astrocytoma and malignant Schwannoma in male rats was related to drug treatment at doses of 30 and 100 mg/kg. Nervous system tumors, i.e., astrocytoma tumors, were not significantly increased in female rats.

Estimated safety margin to clinical exposure is complicated by the finding that lorcaserin partitions to the brain relative to the plasma by approximately 25-fold in rats and 10-fold in monkeys. Brain partitioning in humans is unknown, but it is assumed by the Sponsor to resemble that in monkeys. It should be stressed that this is an assumption at this point.

The safety margins change depending on which assumption is applied. So, if partitioning in humans resemble monkeys as proposed by the Sponsor, then the brain tumors occurred at 50 times the clinical exposure with a safety margin of 14-fold, which reduces our concern. But if brain levels in humans are in fact higher or approach that in rats, then brain tumors occur at 17 multiples of clinical exposure with much narrower safety margin of five-fold, which we believe is the risk.

A mode of action for astrocytoma was not formally addressed. However, the Applicant proposed that the cellular origin of rat astrocytoma may be monocytic; therefore, may not have a cellular counterpart to human astrocytoma. Withdraws from astrocytes, and they cite the recent publication by Nagatani, et al. However, it is our opinion that the cellular original -- cellular lineage of rat astrocytoma remains unresolved in the literature. The

histochemical differences between rodents and primate astrocytoma are well known, but these tumors are nevertheless categorized as astrocytoma based on other morphological similarities.

Moreover, even the authors of the Nagatani paper concluded that the cellular origin of rat astrocytoma may be monocytic, but may also drive from neuronal progenitor specifically radial glial cells.

More relevant to the purpose of risk assessment, it is important to recognize that these rodent tumor bioassays are a large part of hazard identification, and that an identified hazard from these studies may or may not predict side-to-side or tumor type concordance in humans. It is our view that an outcome of astrocytoma in rats identified a tumor hazard, probably a brain tumor hazard for humans.

Since tumorigenic mode of action was not identified for this finding, we are unable to determine if key events in mode of action are similar or unrelated to human biology. Therefore, it is premature to dismiss the relevance of this finding hazard.

In summary, lorcaserin increased astrocytoma in male rats, but without a tumorigenic mode of action, risk assessment is based on the exposure differences between animals and humans. Depending on the assumption of brain partition in humans, astrocytoma occurs at 17-fold, or 50-fold higher than the clinical exposure. It is our view that relevance of lorcaserin-related astrocytoma in rats to the obese patient population is uncertain.

Next, I would like to address three additional considerations regarding the tumor results in rats and mice. An argument has been made that tumors in high-dose males were associated with significant toxicity, which complicates interpretation of tumor etiology, specifically citing increased mortality and up to 28% loss of body weight in high-dose male rats.

We disagree with this argument for the following reasons: First, most of the excess morality in the high dose group was caused by lorcaserin-related tumors, not generalized toxicity. The Division and Carcinogenicity Assessment Committee concluded that maximum tolerated dose, or MTD, was not exceeded in the study. Second, we do not consider weight loss for lorcaserin as evidence of generalized toxicity.

For example, weight loss of 30% or more with other investigational obesity drugs have prolonged survival and reduced tumor burden in two-year rat studies. Finally, lorcaserin-related tumors also occurred at the mid-dose, which was not associated with the excess morality or weight loss.

Another argument has been made that most tumors were confined to male rats, not females, suggesting a gender-specific effect for lorcaserin. While gender specificity is certainly plausible, the contribution of other factors should also be considered, particularly the observation that female rats on average died seven to 17 weeks earlier than male counterparts in mid and high dose, especially.

So, the total duration of drug exposure is actually less in females than I males. Also, the effect of high mammary tumor burden in females under the emergence of other tumor type is still unknown.

Lastly, the argument has been made that tumors were observed only in rats and were not seen in mice suggesting a species of specific tumor response to lorcaserin. On this point

we disagree, because the highest dose exposure in mice as shown by the first three bars in each graph nearly equal to the lowest drug exposure in rats. So, the lack of tumor response in mice were more likely to reflect the substantially lower drug exposure than species specificity of tumor response to lorcaserin.

In summary, lorcaserin is a nongenotoxic carcinogen induced in multiple tumor types in rats, mammary neoplasms occurred [in] clinical exposure with tumorigenic mode of action remain unresolved; brain neoplasm occur at uncertain multiples of clinical exposure; Schwannoma and skin subcutis neoplasms occur at 17-fold multiples of clinical exposure; and, finally, the difference in survival and drug exposure may explain the apparent gender and species specificity of tumor response. Thank you.

Julie Golden: Good morning, Chairman Thomas, members of the Committee. Today I will be presenting the Division's perspective on the lorcaserin clinical development program. I will start by presenting a brief overview of the regulatory history of other obesity drugs, to give you a sense for some of our considerations as lorcaserin development proceeded.

Then, I will briefly describe the lorcaserin clinical program and summarize some of the efficacy findings and how they relate to the criteria defined in the draft FDA Weight Management Guidance. I will then spend the rest of the time discussing safety.

I will start by presenting some of the echocardiographic findings evaluating valvular regurgitation. I will then discuss findings related to depression and suicide, cognition and serotonin excess.

To address some of the animal carcinogenicity findings, I will briefly discuss breast neoplasms and prolactin measurements in the clinical trials. Finally, I will discuss adverse events that could be related to the abuse liability of lorcaserin.

So, as you know, there are short- and long-term weight loss drugs currently approved in the United States. The short-term drugs include the amphetamine congeners, some of which are still commonly used despite general medical agreement that obesity requires chronic therapy. The currently approved long-term weight loss drugs are sibutramine, which you discussed yesterday, and orlistat.

Fenfluramine and dexfenfluramine were removed from the US market in the late '90s after an association with cardiac valvular fibrosis and insufficiency was reported. Finally, safety issues have kept some drugs from reaching the US market, most notably, rimonabant.

The Fen-Phen craze was really borne from the publication of a study by Weintraub and colleagues in 1992, in which 121 obese patients were administered fenfluramine and phentermine for up to four years. Despite the fact that weight loss over the long term was modest, and less than half the patients completed the study, prescriptions for fenfluramine and phentermine soared in the mid '90s.

In 1996, dexfenfluramine, a isomer of fenfluramine, was approved for long-term treatment in patients considered at high risk from their obesity. That is, a BMI greater than or equal to 30, or greater than or equal to 27 in association with weight-related comorbidities such as hypertension, diabetes, and hyperlipidemia.

In 1997, Connolly and colleagues reported that 24 women with no history of heart disease had developed unusual cardiac valvular morphology and regurgitation of left and right-sided heart valves after taking Fen-Phen for up to 28 months. The authors noted

palpitations, headache and vomiting in study days one and five. In the BLOSSOM trial, a 29-year-old white female experienced vertigo, nausea, vomiting, diarrhea, and increased blood pressure after concomitant treatment with dextromethorphan approximately eight weeks into the trial.

In conclusion, the imbalance of potential serotonin-related adverse events seen in the lorcaserin Phase III program was primarily due to chills and tremor. As with any serotonergic agent, serotonin syndrome remains a theoretical concern.

Because of the lorcaserin-related increase in mammary tumors in the rat carcinogenicity study, clinical development of breast cancer was obviously a concern. Midway through Phase III development, the Sponsor raised the possibility of a prolactin-mediated cause for mammary tumors in rats.

Given the known acute effect of lorcaserin on prolactin and modest support in the epidemiological literature for an association between prolactin and breast cancer in humans, an effort was undertaken to characterize the effect of lorcaserin on acute and chronic prolactin concentrations in humans. These slides will briefly describe both findings in the clinical trials.

The Phase III trials did not identify a meaningful difference between groups in the numbers of patients who developed breast neoplasms. However, given the relatively short duration and relatively young patient population, we would not expect an increased risk of cancer in the clinical trials.

In terms of prolactin, the normal range is 2.5 to 17 ng/mL in men, and 1.9 to 25 ng/mL in women. There is variability in prolactin concentrations during the day, and peak values are approximately two to three times that of the nadir.

Symptomatic hyperprolactinemia seen with antipsychotic medications is usually associated with prolactin concentrations greater than five to ten times the upper limit of normal. Prolactin concentrations were measured in a subset of patients in the BLOSSOM trial at pre-dose and two hours post-dose at baseline in weeks 4, 12, 24 and 52.

To mimic the prolactin assessment conducted in the Nurses Health Study, pre-dose prolactin concentrations were divided into quartiles at each time point. Lorcaserin is associated with prolactin quartile increases from pre-dose to post-dose. Note, however, that patients even in the highest quartile still had prolactin concentrations well below the range typically seen with symptomatic hyperprolactinemia.

When we compare baseline values to post-baseline values across the trial, a similar proportion of patients in each group experienced an increase in prolactin quartile. There was a small imbalance in the number of patients in the lorcaserin 10 mg b.i.d. group with prolactin concentrations greater than two times the upper limit of normal. Only one patient treated with lorcaserin had a prolactin value greater than five times the upper limit of normal, and his prolactin was also greater than five times the upper limit of normal at baseline. No patient had a prolactin value greater than 10 times the upper limit of normal.

So, in conclusion, despite the fact that no increase in breast cancer was identified in the trials, in our view, given the relatively young patient population and two year or less trial duration, we would not expect to see an increase in breast cancer even if lorcaserin was associated with a moderate to large increasing risk.

that they can to exclude that this may be a major a problem as it could be. But because of the many exclusions that were included in this study in terms of the patients that were not studied because of clinical reasons, there may have to be some labeling issues that address the fact that certain populations weren't studied.

Finally, instead of just looking at claims databases for adverse events in regard to heart disease, there should be a reporting mechanism set up that would allow the earlier detection of a safety signal if the medication is approved. Is there any comments or changes from the panel? Okay, I'll go on to Question 3:

Has adequate evidence been provided to assess the potential risk to human subjects of lorcaserin-related neoplasms in rats? These neoplasms involve breast, brain, peripheral nerve, skin and subcutis. Are there additional animal or clinical studies that you would recommend pre- or post-approval to further assess this potential risk? If approved, please discuss the need for monitoring and possible monitoring strategies. Dr. Henderson?

Jessica Henderson: I didn't have any problems with the efficacy of weight loss, but this neoplasm risk is my number one concern for risk. And probably within that area, the fact that there was no safety margin in the female rats, I'd like to see if we could have more animal studies to see if that can be determined, safety margin. And also definitely we would need to keep a registry, if this drug were approved. Because, as it was already brought out, most of the people in the trial are younger women, and this is a short duration. So, we would have to have a long-term registry.

Abraham Thomas: Okay. Any other comments?

Jessica Henderson: Oh, and also maybe animal studies and follow-up on the pups of the rats who had been on the drug.

Abraham Thomas: Dr. Gregg?

Ed Gregg: Yeah, I have to admit I was kind of spooked by the same thing, and particularly the assessment that there are mammary tumor risk all the way across the whole spectrum of dosage, and the statement from the FDA that no safety margin was identified. I do feel a bit unqualified to make a judgment as to how we translate risk from rat study to humans. And so I'd actually love it if there were a bit more discussion around this and somebody could either make me feel better or not.

Abraham Thomas: Dr. Gardner?

Jacqueline Gardner: I concur completely and don't know how to make that leap, and also don't know how to suggest studies that would help us make that leap, and so someone who can help us do that. But I do know that even if we decided to proceed with adequate – with what we perceive to be or suggest to be adequate warnings, it is going to be very difficult for women to hear that there might be an increased risk of breast cancer with a weight loss drug, and to -- it would – I don't know how we could do it. So, how can we learn more about this and what would we recommend to the Sponsor and the FDA?

Abraham Thomas: Dr. Proschan?

Michael Proschan: I would also like to echo that sentiment. I mean, I really feel lost on this. When the Company made their presentation on this point, I thought, gee, that makes sense. And then when the FDA made their presentation, I thought, gee, that makes sense, too, and I

have absolutely no idea now to translate from animals to people. So, I feel particularly lost on this one.

Abraham Thomas: Dr. Segal?

Jodi Segal: Well, estrogen is still on the market. Some drugs cause a little elevated risk of breast cancer. There is still a use for them. Can I ask the FDA a question? Is it sometimes better to approve drugs even if you have to pull them later? Is there a certain number of drugs that you're just going to have to get rid of later?

Unidentified Participant: Especially with weight loss drugs.

Unidentified Participant: Well, I guess if you voted to approve it, your name would be on the vote thing, and then if we yanked it, how would you feel about that? So, yeah, I can't answer that question.

Jodi Segal: But meaning some drugs you won't be collecting the data until post-approval possibly. That is why there are post-approval studies.

Abraham Thomas: One possibility is at least whether it's post- or pre-approval is that the age range of these women are quite low. If you think about breast cancer, these are women in their late forties. The risk would go up, especially later on. You might want to look at an older population and see what that risk is. Dr. Douglas?

Pam Douglas: Yeah, I started to stay something in answer to the first question when we talked about the selected population, we didn't mention age. And it is selected for age. So, the age limit of 65 excludes a large number of patients who are at risk not only -- at higher risk not only for breast cancer, but also heart disease.

Abraham Thomas: Dr. Goldfine?

Allison Goldfine: So, I'll let this -- this might be a little bit of a question for the FDA, but I think in general we get more concerned about the tumor potential when it's across two animal species, and what concerned me was the fact that the dosing in the mouse seemed inadequate. And I am asking whether or not you would have more confidence in the safety or risk if you actually did across two.

And before you answer that, I want to say that the comment about a registry was brought up, and I think that for something that would be very rare, like a brain cancer, that may actually be adequate to detect very early signal, but I'm not sure that for something as common as breast cancer that it would be an adequate way.

You really wouldn't know the background rates and it's not really going to -- it will be problematic for interpretation and therefore if one moved into the older, higher risk previously, CVD, diabetic populations, where one might have increased backgrounds of breast cancer, this might also sort out within a trial that addresses some of our other concerns as well. So, can I ask about the animal species then?

Fred Alavi: The mouse carcinogenicity study initially was designed to test up to 100 mg/kg body weight. And unfortunately that dose caused significant mortality within the first two weeks. So, doses had to be readjusted lower, and that is -- we found out at the end of exposures were also very low.

Allison Goldfine: Do you think there would be adequate other second species to test in that might shed -- because, again, one is often highlighted when it's more than one.

EXHIBIT T

Guidance for Industry

S1C(R2) Dose Selection for Carcinogenicity Studies

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

September 2008
ICH

Revision 1

Guidance for Industry

S1C(R2) Dose Selection for Carcinogenicity Studies

Additional copies are available from:

Office of Training and Communication
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Room 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and
Manufacturers Assistance; HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 1-800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm.

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

September 2008
ICH

Revision 1

Contains Nonbinding Recommendations

TABLE OF CONTENTS

EXH. T
P. 148

Contains Nonbinding Recommendations

Guidance for Industry[1]

S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION AND BACKGROUND (1)[2]

This guidance provides recommendations for dose selection for carcinogenicity studies of human pharmaceuticals. The guidance is intended to aid sponsors in selecting appropriate doses for rodent carcinogenicity studies.

FDA first issued the ICH guidance *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* in October 1994 and the addendum to the parent guidance *S1C(R) Addition of a Limit Dose and Related Notes* in July 1997. In November 2005, ICH incorporated the addendum to the parent guidance (S1C(R1)). In March 2008, ICH further revised the guidance (S1C(R2)).[3] This revised guidance includes the changes made by ICH in November 2005 and March 2008.

---

[1] This guidance was developed within the Expert Working Group (Safety) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, March 2008. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, March 2008.

[3] Specifically, note 2 of the parent guidance was deleted, the text referring to the notes was revised, and the addendum was integrated in the text. The pharmacokinetic endpoint of 25 was declared to be applicable also for pharmaceuticals with positive genotoxicity signals. This change has implications on "Refinement" (one of the 3Rs) in enhancing the welfare (i.e., reducing the pain or discomfort) of the animals at the maximally tolerated dose (MTD). Guidance terminology was revised to comply with FDA's good guidance practices regulation (21 CFR 10.115).

EXH. T
P. 149

Contains Nonbinding Recommendations

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Traditionally, carcinogenicity studies for chemical agents have relied upon the maximally tolerated dose (MTD) as the standard method for high dose selection (Note 1). The MTD is generally chosen based on data derived from toxicity studies of 3 months' duration.

In the past, the criteria for high dose selection for carcinogenicity studies of human pharmaceuticals have not been uniform among international regulatory agencies. In Europe and Japan, dose selection based on toxicity endpoints or attaining high multiples of the maximum recommended human daily dose (>100x on a milligram (mg)/kilogram (kg) basis) has been accepted. However, in the United States, dose selection based on the MTD has traditionally been considered the only appropriate practice. All regions have used a maximum feasible dose as an appropriate endpoint.

For pharmaceuticals with low rodent toxicity, use of the MTD can result in the administration of very large doses in carcinogenicity studies, often representing high multiples of the clinical dose. This has led to the concern that exposures in rodents greatly in excess of the intended human exposures might not be relevant to human risk; because they so greatly alter the physiology of the test species, the findings might not reflect what would occur following human exposure.

Ideally, the doses selected for rodent bioassays for pharmaceuticals should provide an exposure to the agent that (1) allows an adequate margin of safety over the human therapeutic exposure, (2) is tolerated without significant chronic physiological dysfunction and is compatible with good survival, (3) is guided by a comprehensive set of animal and human data that focus broadly on the properties of the agent and the suitability of the animal, and (4) permits data interpretation in the context of clinical use.

In order to achieve international harmonization of requirements for high dose selection for carcinogenicity studies of pharmaceuticals, and to establish a rational basis for high dose selection, the ICH Expert Working Group on Safety initiated a process to arrive at common, scientifically based criteria for high dose selection. Several features of pharmaceutical agents distinguish them from other environmental chemicals and can justify a guidance that might differ in some respects from other guidances. This should enhance the relevance of the carcinogenicity study for pharmaceuticals. Thus, much knowledge might be available on the pharmacology, pharmacokinetics, and metabolic disposition in humans. In addition, there will usually be information on the patient population, the expected use pattern, the range of exposure, and the toxicity and/or side effects that cannot be tolerated in humans. Diversity of the chemical and pharmacological nature of the substances developed as pharmaceuticals, and the diversity of mechanisms of carcinogenesis, call for a flexible approach to dose selection. This document proposes that any one of several approaches could be useful for dose selection, and should provide for a more rational approach to dose selection for carcinogenicity studies for pharmaceuticals. These include: (1) toxicity-based endpoints; (2) pharmacokinetic endpoints; (3) saturation of absorption; (4) pharmacodynamic endpoints; (5) maximum feasible dose; (6) limit dose; and (7) additional endpoints.

Contains Nonbinding Recommendations

Consideration of all relevant animal data and integration with available human data is paramount in determining the most appropriate endpoint for selecting the high dose for the carcinogenicity study. Relevant pharmacokinetic, pharmacodynamic, and toxicity data should be considered in the selection of doses for the carcinogenicity study, regardless of the primary endpoint used for high dose selection.

In the process of defining such a flexible approach, it is recognized that the fundamental mechanisms of carcinogenesis are only poorly understood at the present time. Further, it is also recognized that the use of the rodent to predict human carcinogenic risk has inherent limitations, although this approach is the best available option at this time. Thus, while the use of plasma levels of drug-derived substances represents an important attempt at improving the design of the rodent bioassay, progress in this field calls for continuing examination of the best method to detect human risk. This document is therefore intended to serve as guidance in this difficult and complex area, recognizing the importance of updating the specific provisions outlined below as new data become available.

A. General Considerations for the Conduct of Dose-Ranging Studies (1.1)

The considerations involved when undertaking dose-ranging studies to select the high dose for carcinogenicity studies are the same regardless of the final endpoint utilized.

1. In practice, carcinogenicity studies are carried out in a limited number of rat and mouse strains for which there is reasonable information on spontaneous tumour incidence. Ideally, rodent species/strains with metabolic profiles as similar as possible to humans should be studied (Note 2).
2. Dose-ranging studies should be conducted for both males and females for all strains and species to be tested in the carcinogenicity bioassay.
3. Dose selection is generally determined from 90-day studies using the route and method of administration that will be used in the bioassay.
4. Selection of an appropriate dosing schedule and regimen should be based on clinical use and exposure patterns, pharmacokinetics, and practical considerations.
5. Ideally, both the toxicity profile and any dose-limiting toxicity should be characterized. Consideration should also be given to general toxicity, the occurrence of preneoplastic lesions and/or tissue-specific proliferative effects, and disturbances in endocrine homeostasis.
6. Changes in metabolite profile or alterations in metabolizing enzyme activities (induction or inhibition) over time should be understood to allow for appropriate interpretation of studies.

B. Toxicity Endpoints in High Dose Selection (1.2)

ICH 1 agreed to evaluate endpoints other than the MTD for the selection of the high dose in carcinogenicity studies. These were to be based on the pharmacological properties and toxicological profile of the test compound. There is no scientific consensus on the use of toxicity endpoints other than the MTD. Therefore, the ICH Expert Working Group on Safety has agreed

to continue use of the MTD as a useful toxicity-based endpoint for high dose selection for carcinogenicity studies.

The following definition of the MTD is considered consistent with those published previously by international regulatory authorities (Note 1): The top dose or maximum tolerated dose is that which is predicted to produce a minimum toxic effect over the course of the carcinogenicity study. Such an effect can be predicted from a 90-day dose range-finding study in which minimal toxicity is observed. Factors to consider are alterations in physiological function that would be predicted to alter the animal's normal life span or interfere with interpretation of the study. Such factors include: no more than 10% decrease in body weight gain relative to controls; target organ toxicity; significant alterations in clinical pathological parameters.

C. Pharmacokinetic Endpoints in High Dose Selection (1.3)

A systemic exposure representing a large multiple of the human area under the exposure curve (AUC) (at the maximum recommended daily dose) can be an appropriate endpoint for dose selection for carcinogenicity studies for pharmaceuticals that have similar metabolic profiles in humans and rodents and low organ toxicity in rodents (i.e., high doses are well tolerated in rodents). The level of animal systemic exposure should be sufficiently great compared to exposure to provide reassurance of an adequate test of carcinogenicity.

It is recognized that the doses administered to different species might not correspond to tissue concentrations because of different metabolic and excretory patterns. Comparability of systemic exposure is better assessed by blood concentrations of parent drug and metabolites than by administered dose. The unbound drug in plasma is thought to be the most relevant indirect measure of tissue concentrations of unbound drug. The AUC is considered the most comprehensive pharmacokinetic endpoint since it takes into account the plasma concentration of the compound and residence time in vivo.

There is, as yet, no validated scientific basis for use of comparative drug plasma concentrations in animals and humans for the assessment of carcinogenic risk to humans. However, for the present, and based on an analysis of a database of carcinogenicity studies performed at the MTD, the selection of a high dose for carcinogenicity studies that represents a 25- to-1 exposure ratio of rodent to human plasma AUC of parent compound and/or metabolites is considered pragmatic (Note 3).

D. Criteria for Comparisons of AUC in Animals and Man for Use in High Dose Selection (1.4)

The following criteria are especially applicable for use in determining a pharmacokinetically-defined exposure for high dose selection.

1. Rodent pharmacokinetic data are derived from the strains used for the carcinogenicity studies using the route of compound administration and dose ranges planned for the carcinogenicity study (Notes 4, 5 and 6).

Contains Nonbinding Recommendations

2. Pharmacokinetic data are derived from studies of sufficient duration to take into account potential time-dependent changes in pharmacokinetic parameters that might occur during the dose ranging studies.
3. Documentation is provided on the similarity of metabolism between rodents and humans (Note 7).
4. In assessing exposure, scientific judgement is used to determine whether the AUC comparison is based on data for the parent, parent and metabolite(s), or metabolite(s). The justification for this decision is provided.
5. Interspecies differences in protein binding are taken into consideration when estimating relative exposure (Note 8).
6. Human pharmacokinetic data are derived from studies encompassing the maximum recommended human daily dose (Note 9).

E. Saturation of Absorption in High Dose Selection (1.5)

High dose selection based on saturation of absorption measured by systemic availability of drug-related substances can be considered. The mid and low doses selected for the carcinogenicity study should take into account saturation of metabolic and elimination pathways.

F. Pharmacodynamic Endpoints in High Dose Selection (1.6)

The utility and safety of many pharmaceuticals depend on their pharmacodynamic receptor selectivity. Pharmacodynamic endpoints for high dose selection will be highly compound-specific and can be considered for individual study designs based on scientific merits. The high dose selected should produce a pharmacodynamic response in dosed animals of such magnitude as would preclude further dose escalation. However, the dose should not produce disturbances of physiology or homeostasis that would compromise the validity of the study. Examples include hypotension and inhibition of blood clotting (because of the risk of spontaneous bleeding).

G. Maximum Feasible Dose (1.7)

Currently, the maximum feasible dose by dietary administration is considered to be 5% of diet. International regulatory authorities are re-evaluating this standard. It is believed that the use of pharmacokinetic endpoints (AUC ratio) for dose selection of low toxicity pharmaceuticals, discussed in this guidance, should significantly reduce the number of instances where high doses are selected based on feasibility criteria.

When routes other than dietary administration are appropriate, the high dose can be limited based on considerations including practicality and local tolerance.

EXH. T
P. 153

Contains Nonbinding Recommendations

H. Limit Dose (1.8)

In determining the high dose for carcinogenicity studies using the approaches outlined in this guidance it is appropriate to limit this dose to 1500 mg/kg/day (Note 10). This limit dose applies where the maximum recommended human dose does not exceed 500 mg/day (Note 11).

Data should be provided comparing exposure of rodents and humans to drug and metabolites primarily to support dose selection for and interpretation of the carcinogenicity study. Based on such information, there might be cases where the limit of 1500 mg/kg/day is not applicable because it cannot be assured that animal exposure after 1500 mg/kg/day is sufficiently high compared to the exposure achieved in humans. The rodent systemic exposure at 1500 mg/kg/day should be greater by at least an order of magnitude than human exposure measured at the intended human therapeutic dose. (If this is not the case, efforts should be made to increase the rodent exposure or to reconsider the animal model in a case-by-case approach.) If the human dose exceeds 500 mg/day the high dose can be increased up to the maximum feasible dose.

I. Additional Endpoints in High Dose Selection (1.9)

It is recognized that there might be merit in the use of alternative endpoints not specifically defined in this guidance on high dose selection for rodent carcinogenicity studies. Use of these additional endpoints in individual study designs should be based on scientific rationale. Such designs should be evaluated based on their individual merits (Note 12).

J. Selection of Middle and Low Doses in Carcinogenicity Studies (1.10)

Regardless of the method used for the selection of the high dose, the selection of the mid and low doses for the carcinogenicity study should provide information to aid in assessing the relevance of study findings to humans. The doses should be selected following integration of rodent and human pharmacokinetic, pharmacodynamic, and toxicity data. The rationale for the selection of these doses should be provided. While not all-encompassing, the following points should be considered in selection of the middle and low doses for rodent carcinogenicity studies:

1. Linearity of pharmacokinetics and saturation of metabolic pathways
2. Human exposure and therapeutic dose
3. Pharmacodynamic response in rodents
4. Alterations in normal rodent physiology
5. Mechanistic information and potential for threshold effects
6. The unpredictability of the progression of toxicity observed in short-term studies

II. SUMMARY (2)

This guidance outlines six criteria for selection of the high dose for carcinogenicity studies of therapeutics: the maximum tolerated dose, 25-fold AUC ratio (rodent:human), dose-limiting

pharmacodynamic effects, saturation of absorption, maximum feasible dose, and limit dose. The use of other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design should be considered based on scientific rationale and individual merits. In all cases, appropriate dose ranging studies should be conducted. All relevant information should be considered for dose and species/strain selection for the carcinogenicity study. This information should include knowledge of human use, exposure patterns, and metabolism. The availability of multiple criteria for dose selection will provide greater flexibility in optimizing the design of carcinogenicity studies for therapeutic agents.

III. NOTES (3)

Note 1

The following are considered equivalent definitions of the toxicity-based endpoint describing the maximum tolerated dose:

The U.S. Interagency Staff Group on Carcinogens has defined the MTD as follows:

> The highest dose currently recommended is that which, when given for the duration of the chronic study, is just high enough to elicit signs of minimal toxicity without significantly altering the animal's normal lifespan due to effects other than carcinogenicity. This dose, sometimes called the maximum tolerated dose (MTD), is determined in a subchronic study (usually of 90 days duration) primarily on the basis of mortality, toxicity, and pathology criteria. The MTD should not produce morphologic evidence of toxicity of a severity that would interfere with the interpretation of the study. Nor should it comprise so large a fraction of the animal's diet that the nutritional composition of the diet is altered, leading to nutritional imbalance.
>
> The MTD was initially based on a weight gain decrement observed in the subchronic study; i.e., the highest dose that caused no more than a 10% weight gain decrement. More recent studies and the evaluation of many more bioassays indicate refinement of MTD selection on the basis of a broader range of biological information. Alterations in body and organ weight and clinically significant changes in hematologic, urinary, and clinical chemistry measurements can be useful in conjunction with the usually more definitive toxic, pathologic or histopathologic endpoints.
>
> (Environmental Health Perspectives, Vol. 67, pp. 201-281, 1986)

The Ministry of Health and Welfare in Japan prescribes the following:

> The dose in the preliminary carcinogenicity study that inhibits body weight gain by less than 10% in comparison with the control and causes neither death due to toxic effects nor remarkable changes in the general signs and laboratory examination findings of the animals is the highest dose to be used in the full-scale carcinogenicity study.
>
> (Toxicity test guideline for pharmaceuticals, Chapter 5, pg. 127, 1985)

The Committee on Proprietary Medicinal Products of the European Community prescribes the following:

> The top dose should produce a minimum toxic effect, for example a 10% weight loss or failure of growth, or minimal target organ toxicity. Target organ toxicity will be

demonstrated by failure of physiological functions and ultimately by pathological changes.

(Rules Governing Medicinal Products in the European Community, Vol. III, 1987)

Note 2

This does not imply that all possible rodent strains should be surveyed for metabolic profile, but rather that standard strains used in carcinogenicity studies should be examined.

Note 3

In order to select a multiple of the human AUC that would serve as an useful endpoint for dose selection for carcinogenicity studies, a retrospective analysis was performed on data from carcinogenicity studies of therapeutics conducted at the MTD for which there was sufficient human and rodent pharmacokinetic data for comparison of AUC values.

In 35 drug carcinogenicity studies carried out at the MTD for which there were adequate pharmacokinetic data in rats and humans, approximately 1/3 had a relative systemic exposure ratio less than or equal to 1, and another 1/3 had ratios between 1 and 10.

An analysis of the correlation between the relative systemic exposure ratio, the relative dose ratio (rat mg/kg:human mg/kg MRD), and the dose ratio adjusted for body surface area (rat mg/M2 MTD:human mg/M2 MRD), performed in conjunction with the above-described database analysis, indicates that the relative systemic exposure corresponds better with dose ratios expressed in terms of body surface area rather than body weight. When 123 compounds in the expanded FDA database were analysed by this approach, a similar distribution of relative systemic exposures was observed. In the selection of a relative systemic exposure ratio (AUC ratio) to apply in high dose selection, consideration was given to a ratio value that would represent an adequate margin of safety, would detect known or probable human carcinogens, and could be attained by a reasonable proportion of compounds.

To address the issue of detection of known or probable human carcinogenic pharmaceuticals, an analysis of exposure and/or dose ratios was performed on International Agency for Research on Cancer (IARC) class 1 and 2A pharmaceuticals with positive rat findings. For phenacetin, sufficient rat and human pharmacokinetic data are available to estimate that a relative systemic exposure ratio of at least 15 was found to produce positive findings in a rat carcinogenicity study. For most of 14 IARC 1 and 2A drugs evaluated with positive carcinogenicity findings in rats, there is a lack of adequate pharmacokinetic data for analysis. For these compounds, the body surface area adjusted dose ratio was employed as a surrogate for the relative systemic exposure ratio. The results of this analysis indicated that using doses in the rodent corresponding to body surface area ratios of 10 or more would identify the carcinogenic potential of these pharmaceuticals.

As a result of the evaluations described above, a minimum systemic exposure ratio of 25 can be considered as a useful pharmacokinetic endpoint for high dose selection. This value was attained by approximately 25% of compounds tested in the FDA database (see Note 10), is high enough to detect known or probable (IARC 1, 2A) human carcinogenic drugs, and represents an adequate margin of safety. Those pharmaceuticals tested using a 25-fold or greater AUC ratio for

Contains Nonbinding Recommendations

the high dose will have exposure ratios greater than do 75% of pharmaceuticals tested previously in carcinogenicity studies performed at the MTD.

Note 4

The rodent AUCs and metabolite profiles can be determined from separate steady-state kinetic studies, as part of the subchronic toxicity studies, or dose-ranging studies.

Note 5

AUC values in rodents are usually obtainable using a small number of animals, depending on the route of administration and the availability of data on the pharmacokinetic characteristics of the test compound.

Note 6

Equivalent analytical methods of adequate sensitivity and precision should be used to determine plasma concentrations of pharmaceuticals in rodents and humans.

Note 7

It is recommended that in vivo metabolism be characterized in humans and rodents, if possible. However, in the absence of appropriate in vivo metabolism data, in vitro metabolism data (e.g., from liver slices, uninduced microsomal preparations) can provide appropriate support for the similarity of metabolism across species.

Note 8

While in vivo determinations of unbound drug might be the best approach, in vitro determinations of protein binding using parent and/or metabolites as appropriate (over the range of concentrations achieved in vivo in rodents and humans) might be used in the estimation of AUC unbound. When protein binding is low in both humans and rodents, or when protein binding is high and the unbound fraction of drug is greater in rodents than in humans, the comparison of total plasma concentration of drug is appropriate. When protein binding is high and the unbound fraction is greater in humans than in rodents, the ratio of the unbound concentrations should be used.

Note 9

Human systemic exposure data can be derived from pharmacokinetic monitoring in normal volunteers and/or patients. The possibility of extensive inter-individual variation in exposure should be taken into consideration. In the absence of knowledge of the maximum recommended human daily dose, at a minimum, doses producing the desired pharmacodynamic effect in humans should be used to derive the pharmacokinetic data.

Note 10

Review of the FDA carcinogenicity database of nearly 900 carcinogenicity tests indicated that about 20 tests had been conducted that used doses of 1000 mg/kg or greater as the highest dose tested. About 10 of these tests were considered as having demonstrated a carcinogenic response. Seven of these were positive only at or above 1000 mg/kg. Regulatory action has resulted from some of these cases. Based on these results, the limit dose for carcinogenicity testing should be 1500 mg/kg rather than 1000 mg/kg to eliminate the risk that a carcinogen will not be able to be identified as a result of adoption of a limit dose of 1000 mg/kg.

Note 11

It has been agreed that if a drug is only positive in rodents at doses above those producing a 25-fold exposure over exposure in humans, such a finding would not be considered likely to reflect a relevant risk to humans.

It has been shown that systemic exposure comparisons between rodents and humans are better estimated by a dose using mg/m^2 than using mg/kg (see Note 3 above). Therefore, the human dose should be at least 25-fold lower on a mg/m^2 basis than the high dose in the carcinogenicity study. The factor 6-7 (6.5) is used to convert rat doses from mg/kg to mg/m^2 and the factor 40 is used to convert human doses from mg/kg to mg/m^2. Thus, the estimated systemic exposure ratio of 25-fold rodent/human is equal to about a 25-fold mg/m^2 ratio or a 150-fold mg/kg ratio (150 = 25 x 40/6.5). Therefore a human dose below 10 mg/kg/day (about 500 mg/day or less) could be tested in rats at 1500 mg/kg as the high dose.

Note 12

Additional pharmaceutical-specific endpoints to select an appropriate high dose are currently under discussion (e.g., additional pharmacodynamic, pharmacokinetic, and toxicity endpoints, as well as alternatives to a maximum feasible dose).

EXHIBIT U

Moderator: Robert Hoffman
December 22, 2010
7:30 a.m. CT

Operator: Good morning and welcome to the Arena Pharmaceuticals conference call. At this time I would like to turn the call over to Arena's Chief Financial Officer, Mr. Robert Hoffman. Please go ahead.

Robert Hoffman: Thank you. Good morning and welcome to Arena Pharmaceuticals conference call. I'm Robert Hoffman, Arena's Chief Financial Officer. Joining me on the call are Jack Lief our President and Chief Executive Officer, Dominic Behan our Chief Scientific Officer, Bill Shanahan our Chief Medical Officer and Christy Anderson our Vice President of Lorcaserin Development.

Before I turn the call over to Jack, I'd like to point out that we will make forward-looking statements during this conference call. Such forward-looking statements include statements about our views related to the complete response letter, discussions with the FDA, and potential resubmission of the Lorcaserin NDA, the process, timing, and outcomes of regulatory review, the potential approval and commercialization of Lorcaserin, (R and A) size strategy and plans, our internal and collaborative programs, financial guidance and other statements that are not historical facts.

Such statements include the words plan, will, expect, or similar words. You're cautioned to not place undue reliance on these forward-looking statements which are only predictions that reflect the company's beliefs, expectations, and assumptions based on currently available information, and speak only as of the time they are made.

Risks and uncertainties that could cause actual results to differ materially from those described in our forward-looking statements include: regulatory authorities may not find data and other information related to our studies and trials sufficient for approval, the regulatory process is uncertain, our response to the CRL for the Lorcaserin NDA may not be submitted in a timely manner, or the information provided in such response may not satisfy the FDA.

The FDA may request additional information or have additional recommendations related to the Lorcaserin NDA, unexpected or unfavorable new data, decisions by (ASI) related to our marketing supply agreement, and the commercialization of Lorcaserin. The timing, results, and cost of clinical trials, pre-clinical studies, and research activities, our ability to obtain adequate funding, satisfactory resolution of litigation, and other risks identified in our (FCC) reports.

For a discussion of these and other factors, please refer to the risk factors described in our filings with the FCC. For forward-looking statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Now I'll turn the call over to our President and Chief Executive Officer, Jack Lief.

Jack Lief: Thanks Robert. Good morning, happy holidays and thank you for joining us. The purpose of this morning's call is to provide you with information regarding our plan to address the issues raised in the Lorcaserin complete response letter or CRL that we received from the FDA in October.

Following receipt of the CRL we requested an end of review meeting with the agency. Our goal for this meeting was to obtain additional clarity on the FDA's position and discuss our plans to respond to the CRL. We and (ASI) accomplished that goal. The discussions during the meeting, along with the FDA's written communication prior to the meeting, have provided us with further guidance and reinforced our position that we have a path forward to seek approval of Lorcaserin.

We expect to receive the FDA meeting minutes in January but based on guidance we've received so far, we are already making progress on responding to the FDA's recommendations and expect to resubmit the Lorcaserin NDA by the end of 2011.

As we continue discussions with the FDA to refine elements of our plans, we may identify ways to shorten this timeline. The majority of our activities relate to the three non-clinical issues outlined in the CRL. (Dr. Anderson) will review these and other activities involved in addressing the CRL. Christy?

Christy Anderson: Thanks Jack. I will first summarize each of the three non-clinical topics that Jack mentioned. The first non-clinical issue was diagnostic uncertainty in the classification of mammary masses in female rats. As we discussed previously, we provided interim, preliminary tissue diagnoses from our two year rat carcinogenicity study to the FDA which will prepare while the study was being conducted in addition to the final peer review study report that was generated when this study was completed.

Some of the preliminary tissue diagnosis for mammary tumors differed from the spinal diagnoses in the study report. In particular, some mammary tumor types were re-characterized from benign to malignant and vice versa. To address this issue, we have already convened a pathology working group of five independent pathologists to review the relevant tissues from the rat carcinogenicity study and to re-adjudicate the diagnoses of female rat mammary tumors in a blinded fashion as requested by the agency. The agency has reviewed and agreed to our protocol.

The second non-clinical issue was an unresolved exposure response relationship for Lorcaserin emergent mammary adenocarcinoma. The FDA has asked that we demonstrate the mechanism by which Lorcaserin causes mammary tumors in rats and that this mechanism is reasonably irrelevant to human risk.

Based on our discussions with the FDA, we believe that the agency accept that prolactin release, if demonstrated, is a viable mechanism for tumors in rats, and that prolactin mediated mammary tumors in rats are reasonably irrelevant to human risk.

We also note that the agency has previously accepted this mechanism for other drugs such as anti-psychotics that induce prolactin release and mammary tumors in rodents. To establish that Lorcaserin's effect on mammary tumors is prolactin mediated, the FDA has requested experimental evidence that demonstrates clear, persistent increases in prolactin in intact female rats at doses of Lorcaserin associated with mammary tumors in rats.

As you may recall, in the experiment submitted with the NDA, we demonstrated prolactin increases in female rats by controlling experimental variability using ovariectomized hormone replaced animals. With additional experimentation we've identified ways to control the sources of variability in measurement of prolactin in intact female rats and believe that we will be able to demonstrate persistent increases in serum prolactin in these animals. To address this issue we have initiated non-clinical studies to provide the requested evidence to the agency.

The third non-clinical issue was an unidentified mode of action and unclear safety margins for Lorcaserin emergent brain astrocytoma. This issue involves the observation of astrocytomas in the carcinogenicity study in male rats that received the highest doses of Lorcaserin. The agency asks that in the absence of information about the mechanism by which these tumors form, we clarify the safety margin in rats relative to humans.

In other words, the agency asks that we try to estimate the Lorcaserin concentrations in the human brain as compared to the rat brain. To address this issue we've initiated several non-clinical experiments. We also plan to initiate a small clinical study to enroll approximately ten volunteers who will be dosed with Lorcaserin for about a week followed by parallel cerebrospinal fluid and blood collection.

Although Lorcaserin cannot be readily measured in the human brain, the concentration in cerebrospinal fluid, which can be measured, will provide an additional estimate of brain levels. We'd also like to discuss a labeling issue. This is one area where we plan to seek additional clarity. The FDA stated in the CRL that based on its review of the material submitted in the NDA, it would recommend placement of Lorcaserin in Schedule IV of the Controlled Substances Act.

The agency also communicated that completing certain pre-clinical studies and submitting data in our complete response will provide new information that will be reviewed and considered in the abuse potential assessment and final scheduling recommendation. We're preparing to initiate these studies pending additional discussions with the Controlled Substances staff.

Lastly the FDA requested that we submit the final study report for BLOOM-DM. Last month we announced top line results from this trial that we've shared with the agency and the final study report is now complete. The agency has stated that they will review the data when we submit our application and that the data will contribute to the agency's overall benefit-risk assessment of Lorcaserin.

Based on the BLOOM-DM results, we believe that Lorcaserin can help address the weight management treatment challenges of obese and overweight patients with Type 2 diabetes, and that the data supports the benefit-risk profile of Lorcaserin. We look forward to the FDA's review of the BLOOM-DM results and to presenting more detailed data at upcoming medical meetings. I will now turn the call back to Jack.

Jack Lief: Thanks Christy. In summary, we are encouraged by the outcome of the end of review meeting. We have additional clarity on our next steps as we seek to obtain the FDA's approval of Lorcaserin.

We're confident that we have a path forward to pursue and look forward to continued collaboration with (ASI) along the way. Arena and (ASI) are committed to resubmitting a thorough response to the CRL as soon as

James Birchenough: And just a follow up on the re-adjudication of the mammary masses. There was obviously this reclassification from the interim reports to the final report. How do you get this diagnostics uncertainty? It seems like adenocarcinoma should be something that both pathologists can pick up. And what gives you confidence that the final report was really the accurate representation of adenocarcinoma burden? And following Bill's question, will you share that data as well?

Jack Lief: I'll let Bill Shanahan address that question.

Bill Shanahan: So with the carcinogenicity studies, we provided interim updates to the agency that were based on initial impressions by a single pathologist. And the working process at the CRO and in many CROs is that the data are the final peer review, the analysis. So this is based on a final analysis. And that's why there, in some cases, were some changes between the initial impression before the final peer review. And that's what's caused the issue.

Male: So just (inaudible) all be clear, we sent draft reports periodically to the agency while the study was going on. This is not a normal process but the agency requested this. We complied of course. And then the actual data is generated by the final peer reviewed process, which has a final report.

And now, we have this panel of five experts who have re-reviewed all of the data in a completely blinded fashion and are preparing such a report. So we'll have a very robust process and database to work off.

James Birchenough: OK, thanks guys.

Jack Lief: Sure.

Operator: Our next question comes from Carol Werther of SSRP. Please go ahead.

Carol Werther: Thank you. What scope of these additional trials? Are they going to be larger than what you did previously? And how can the process be speeded up?

Jack Lief: Yes so as Christy mentioned, most of the work is pretty clinical. And you know we're in the process of finalizing the protocols and initiating studies. You know we hope as we progress we may identify opportunities to accelerate the timeline to file even quicker than the end of next year. But we'll see how that works out. Christy, do you have anything to add to that?

Christy Anderson: Sure I mean in making the estimate of timing we've included a lot of time for you know setting up contracts with various CROs, a lot of time for creating the documents. If we can accelerate the process of contracts and make our internal processes for creating the documents more efficient we can significantly contract the period of time that it'll take to make the submission.

Since we're only in the process now of identifying and contracting with CROs, we gave a pretty conservative estimate of how long these things will take. So within the next few weeks we'll have a much more accurate estimate of how long this whole process will take.

Jack Lief: But right now we feel very confident that we plan on re-filing at the end of 2011.

Carol Werther: So the duration of the trials is pretty short then?

Jack Lief: Yes.

Carol Werther: And did the agency ask you to look at any other animal species?

Jack Lief: No.

Carol Werther: OK. And can you just give us an idea of how expensive do you think these trials are going to be?

Jack Lief: Sure. So you know at this time we can provide a preliminary estimate of the external costs of the outlying activities. We don't think the cost will exceed a few million dollars. We'll provide financial guidance for next year on our

fourth quarter conference call that will include our estimate of Arena's portion of the cost. I recall that we shared our costs with (ASI). Our guidance remains that we expect to end this year, 2010, with approximately $150 million in cash.

Carol Werther: Thank you.

Operator: Our next question comes from Thomas Wei of Jefferies & Company. Please go ahead.

Thomas Wei: Thanks. I just wanted to follow-up on (Jim)'s question on what exactly the FDA has agreed on in terms of the prolactin elevation. So did they – did they agree that you know this prolactin elevation that occurs within the early maturity of the rats is sufficient to prove that there might be a rat memory tumor effect that's not relevant to humans? Did they – did they agree with this bromocriptine example that you raised?

Jack Lief: Dominic?

Dominic Behan: I was simply using that as an example in the literature, short-term exposure to prolactin appears to be very important. With the agency, we discussed a range of experimentation that would be appropriate for them to see persistent increases in prolactin.

So again, we're you know finalizing the protocols in that regard. We think all these experiments can be fit within the 2011 time frame and we'll have more clarity as we move forward. But that's what we're comfortable with and with communicating currently. The good news is I think we got a significant level of clarity in terms of what we need to achieve here.

Thomas Wei: And with whatever timeframe it is that you do end up running this study for, should it be interpreted as a failed trial if you show a transient increase early on in the dosing period but at the last study follow-up there's no prolactin elevation? Would that basically not meet with the FDA as laying out for you?

Phil Nadeau: Yes, I think you know in general the diagnoses are clear, but we have to make sure that these changes for you know can be accommodated in the FDA's eyes. And with this final blinded review should provide a – there are five independent you know highly trained pathologists who are reviewing these slides independently. And that will give us I think a very accurate final accounting.

Jack Lief: And the agency has been very helpful in approving our protocols for the re-adjudication and that sort of thing. So this is all pretty clear for us.

Thomas Wei: Thanks.

Jack Lief: Sure.

Operator: Our next question comes from Steve Byrne of Bank of America. Please go ahead.

Steve Byrne: I was wondering if you'd discussed the BLOOM-DM data with the FDA and specifically whether or not they had any comments about the (inaudible) cases in the Lorcaserin treated patients.

Jack Lief: Yes, so I'll let Christy Anderson address that question.

Christy Anderson: We basically told the FDA that the BLOOM-DM data will be available to them in a study report very quickly. They told us at the (inaudible) review, the BLOOM-DM data when we provide the complete response. So they basically said it's a review issue.

We'll provide them the echo data in the same format that we provided with the other studies. The same analyses will be provided. In addition, the FDA asked that we provide the same integrated analyses that we provided in the (NDA) but that we include the BLOOM-DM data.

In addition, we will provide some more sophisticated integrated analyses where we basically pool the BLOOM, BLOSSOM and BLOOM-DM data and

No. 14-55633

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

TODD SCHUENEMAN, on behalf of himself and all others similarly situated,

Plaintiff-Appellant,

v.

ARENA PHARMACEUTICALS, INC., et al.,

Defendants-Appellees,

On Appeal from the United States District Court for the Southern District of California
Honorable Cathy Ann Bencivengo
Case No. 3:10-cv-01959-CAB-BLM

DEFENDANTS-APPELLEES' SUPPLEMENTAL EXCERPTS OF RECORD
VOLUME II OF II
(PAGES 243-334)

William E. Grauer
Koji F. Fukumura
Mary Kathryn Kelley
Ryan E. Blair
Cooley LLP
4401 Eastgate Mall
San Diego, CA 92121-1909
(858) 550-6139

Attorneys for Defendants-Appellees

TABLE OF CONTENTS
VOLUME I OF II

Page

Page

Page

TABLE OF CONTENTS
VOLUME II OF II

Page

EXHIBIT W

Summary of FDA-Approved Drugs with Labels Containing Information on Rat/Mouse Carcinogenicity Studies and Relevant Public Disclosures Preceding FDA Approval

Drug & Manufacturer	*FDA Approval Date*	*Discussion in Labeling: Rat/Mouse Carcinogenicity Data*	*Relevant Public Disclosures Preceding FDA Approval*
Caduet (Atorvastatin) Manufacturer: **Pfizer**	01/30/04	• "In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose." (*See* p. 189.) • "A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day ***resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.***" (*See* p. 189.)	• 1/22/04 Form 8-K: "This product has been developed in a wide range of dosing combinations and, when approved, will provide a unique, novel treatment for patients with hypertension and high cholesterol -- resulting in better patient outcomes because both conditions will be treated simultaneously, not one at a time." (*See* p. 195.)

Drug & Manufacturer	FDA Approval Date	Carcinogenicity Data	Relevant Public Disclosures Preceding FDA Approval
Geodon / Zeldox (Ziprasidone) Manufacturer: **Pfizer**	02/05/01	• "In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increased incidence of tumors relative to controls. ***In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m2 basis).***" (*See* p. 198-199.)	• Q2FY2000 Form 10-Q: "In the first quarter of 2000, we refiled with the FDA the [NDA] for the oral dosage form of the anti-psychotic Zeldox, including new data requested by the FDA. An FDA advisory committee reviewed this compound on July 19 and voted to recommend its approval. The various committee members who commented expressed their opinion that Zeldox should be approved for first-line therapy, but should be labeled to provide adequate information to physicians and patients as to the effect of the drug on the QTc interval prolongation of the electrocardiogram. Zeldox will now go though the FDA's final review and labeling stages." (*See* p. 201.)

Drug & Manufacturer	FDA Approval Date	Disclosure Of Positive Rat/Mouse Carcinogenicity Data	Relevant Public Disclosures Preceding FDA Approval
Kuvan (Sapropterin) Manufacturer: **BioMarin**	12/13/07	• "A 2-year carcinogenicity study was conducted in F-344 rats, and a 78-week carcinogenicity study was conducted in CD-1 mice. In the 104-week oral carcinogenicity study in rats, sapropterin doses of 25, 80, and 250 mg/kg/day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg/day, respectively, based on body surface area) were used. In the 78-week oral carcinogenicity study in mice, sapropterin doses of 25, 80, and 250 mg/kg/day (0.1, 0.3, and 2 times the recommended human dose, respectively, based on body surface area) were used. ***In the 2-year rat carcinogenicity study, there was a statistically significant increase in the incidence of benign adrenal pheochromocytoma in male rats treated with the 250 mg/kg/day (about 2 times the maximum recommended human dose, based on body surface area) dose, as compared to vehicle-treated rats.*** The mouse carcinogenicity study showed no evidence of a carcinogenic effect, but the study was not ideal due to its duration of 78 instead of 104 weeks." (*See* p. 204-205.)	• FY2006 Form 10-K: "On January 16, 2007, we announced positive results from the Phase 3 diet study of Kuvan for PKU in 4 to 12 year-old patients. Results showed that all pre-specified safety and efficacy end-points were met. Kuvan treatment caused a significant increase in phenylalanine (Phe) tolerance as well as a reduction in blood phenylalanine levels. In the primary end-point, Kuvan enabled a mean increase of 20.9 mg/kg/day of Phe supplementation for those patients on Kuvan, representing a doubling of their baseline intake . . . ***On December 18, 2006, we announced positive results from the open label extension study of the pivotal Phase 3 study of Kuvan. Results confirm that all pre-specified safety and efficacy endpoints were met, and data demonstrated the long-term safety and tolerability of Kuvan as a treatment to control blood Phe levels across a range of doses in PKU patients.***" (*See* p. 207-208.)
Lexapro (Escitalopram) Manufacturer: **Forest Laboratories**	08/14/02	• "Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. ***There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.***" (*See* p. 212.)	• FY2002 Form 10-K: "Clinical trials demonstrate that Lexapro is a more potent selective serotonin reuptake inhibitor ("SSRI") than its parent compound and confirm the antidepressant activity of Lexapro in all clinical measures of depression." (*See* p. 214.)

EXH. W
P. 179

Drug & Manufacturer	FDA Approval Date	Disclosures in NDA re: Rat/Mice Carcinogenicity Data	Relevant Public Disclosures Preceding FDA Approval
Lunesta / Estorra (Eszopiclone) Manufacturer: **Sepracor**	12/15/04	• "In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). ***However, in a carcinogenicity study in Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown.***" (*See* p. 217-218.) • "In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD." (*See* p. 218.)	• FY2002 Form 10-K: "We studied ESTORRA in the 3 mg dosage strength for adults and in the 2 mg dosage strength for treatment of the elderly population. ***The NDA contains data from a total of 24 clinical trials, which included more than 2,700 adult and elderly subjects, and more than 60 preclinical studies.*** We conducted a total of six randomized, placebo-controlled, Phase III studies, including one with a positive control, for the treatment of insomnia in both adult and elderly patients. We also completed a double-blind, placebo-controlled, 6-month chronic efficacy and safety trial, which included 788 subjects for the treatment of chronic insomnia. We followed this efficacy and safety trial with a 6-month open-label extension to study safety for up to 12 months." (*See* p. 220.)

EXH. W
P. 180

Drug & Manufacturer	FDA Approval Date	Disclosures of Label Re: Rat/Mouse Carcinogenicity Data	Relevant Public Disclosures Preceding FDA Approval
Protonix (Pantoprazole) Manufacturer: **Wyeth**	02/02/00	• "In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day… ***In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.*** " (*See* p. 224.) • "Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies." (*See* p. 225.) • "In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the	• 1998 Form 10-K: "Protonix suppresses acid production and has minimal potential for interacting with other medications. Protonix is the first U.S. product in its class that is formulated both in tablet and intravenous form, the latter for patients who cannot take medications orally or who are at increased risk of gastric ulceration and bleeding." (*See* p. 228.)

EXH. W
P. 181

Drug & Manufacturer	FDA Approval Date	Disclosures in Label re: Rat/Mouse Carcinogenicity Data	Relevant Public Disclosures Preceding FDA Approval
		recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. ***Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.*** " (*See* p. 225.) • "In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia." (*See* p. 225.)	

Drug & Manufacturer	FDA Approval Date	Disclosures in Label re Rat/Mouse Carcinogenicity Study Data	Relevant Public Disclosures Preceding FDA Approval
Vytorin (Simvastatin) Manufacturer: **Merck**	07/23/04	• "In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day." (*See* p. 231.) • "***In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).***" (*See* p. 231.) • "***A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in***	• 7/21/04 Form 8-K: "Clinical trials have shown that patients taking ezetimibe with simvastatin achieved significantly greater reductions in LDL cholesterol across the dosing ranges studied than leading statin therapies. As a result, VYTORIN is expected to be well positioned to compete in the critical and growing high-efficacy space of the cholesterol-lowering market, especially now with new recommendations for even lower LDL cholesterol goals." (*See* p. 236.) • 3/15/04 Form 8-K: "VYTORIN (ezetimibe/simvastatin) was well tolerated and had an overall safety profile similar to simvastatin in the study; there were no clinically or statistically significant differences in the incidence of muscle enzyme elevations (five to 10 times or more than 10 times the upper limit of normal) or consecutive liver enzyme elevations (ALT or AST more than three times the upper limit of normal)." (*See* p. 247.)

Drug A/ Manufacturer	FDA Approval Date	Carcinogenesis/Mutagenesis/Impairment of Fertility Data	Teratogenic/Fetotoxic/Embryotoxic Data
		females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose." (See p. 231.)	

EXH. W
P. 184

Drug & Manufacturer	FDA Approval Date	Disclosure of Diabetes, Rat Model, Carcinogenicity Data	Relevant Public Disclosures Preceding FDA Approval
Xopenex HFA (levalbuterol) Manufacturer: **Sepracor**	03/11/05	• ***"In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at, and above, dietary doses of 2 mg/kg/day (approximately 30 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m2 basis and approximately 15 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m2 basis).*** In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg/day (approximately 3800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m2 basis and approximately 1800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m2 basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg/day (approximately 500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m2 basis and approximately 240 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m2 basis)." (*See* p. 252.)	• 3QFY2004 Form 10-Q: "On May 12, 2004, we submitted our NDA to the FDA for XOPENEX HFA MDI for the treatment or prevention of bronchospasm in adults, adolescents and children 4 years of age and older with reversible obstructive airway disease, such as asthma and chronic obstructive pulmonary disease, or COPD. MDIs are hand-held, pressurized canisters that deliver inhaled medications directly to the lungs. ***Our MDI development program included approximately 1,870 pediatric and adult subjects and 54 studies (preclinical and clinical).*** In 2003, we completed our Phase III studies of XOPENEX HFA. *In each of the three, large-scale, pivotal Phase III trials that we conducted, the XOPENEX HFA MDI was well tolerated and met the targeted efficacy endpoints in both adults and children with asthma.* In the primary airway function measure, FEV1 (a test of lung function that measures the amount of air forcefully exhaled in one second), the XOPENEX HFA MDI produced statistically and clinically significant improvements relative to placebo ($p<0.001$). If the FDA delays or denies approval of our NDA for XOPENEX HFA MDI, then commercialization of this product candidate could be delayed or terminated, which would have a material adverse effect on our business." (*See* p. 254.)

PAGE INTENTIONALLY LEFT BLANK

EXH. W
P. 186

CADUET®
(amlodipine besylate/atorvastatin calcium) Tablets

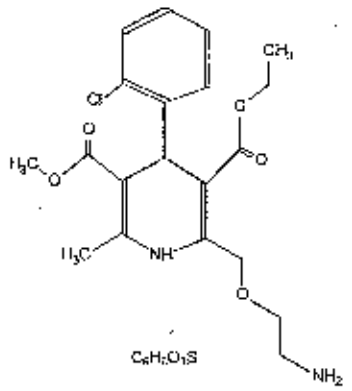
DESCRIPTION

CADUET® (amlodipine besylate and atorvastatin calcium) tablets combine the long-acting calcium channel blocker amlodipine besylate with the synthetic lipid-lowering agent atorvastatin calcium.

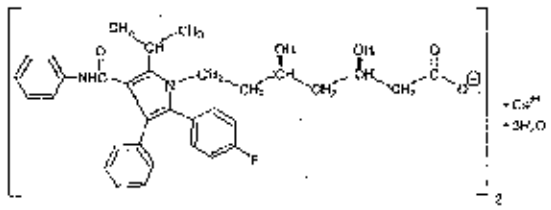
The amlodipine besylate component of CADUET is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

The atorvastatin calcium component of CADUET is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$.

The structural formulae for amlodipine besylate and atorvastatin calcium are shown below.



Amlodipine besylate



Atorvastatin calcium

CADUET contains amlodipine besylate, a white to off-white crystalline powder, and atorvastatin calcium, also a white to off-white crystalline powder. Amlodipine besylate has a molecular weight of 567.1 and atorvastatin calcium has a molecular weight of 1209.42. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol, and freely soluble in methanol.

CADUET tablets are formulated for oral administration in the following strength combinations:

EXH. W
P. 187

Table 1: CADUET Tablet Strengths

	5mg/ 10mg	5mg/ 20mg	5mg/ 40mg	5mg/ 80mg	10mg/ 10mg	10mg/ 20mg	10mg/ 40mg	10mg/ 80mg
amlodipine equivalent (mg)	5	5	5	5	10	10	10	10
atorvastatin equivalent (mg)	10	20	40	80	10	20	40	80

Each tablet also contains calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry® II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000 and talc) or Opadry® II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc and FD&C blue #2). Combinations of atorvastatin with 5 mg amlodipine are film coated white, and combinations of atorvastatin with 10 mg amlodipine are film coated blue.

CLINICAL PHARMACOLOGY

Mechanism of Action

CADUET

CADUET, is a combination of two drugs, a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) amlodipine (antihypertensive/antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin (cholesterol lowering agent). The amlodipine component of CADUET inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of CADUET is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The Amlodipine Component of CADUET

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

NDA 21-540
Page 22

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking CADUET.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Drug/Laboratory Test Interactions None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with amlodipine: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*. For the rat, the highest dose level was, on a mg/m^2 basis, about twice the maximum recommended human dose*.

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).

*Based on patient weight of 50 kg.

Studies with atorvastatin: In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased

FORM 8-K

CURRENT REPORT

PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of report: January 22, 2004
Date of earliest event reported: January 22, 2004

PFIZER INC.
(Exact name of registrant as specified in its charter)

Delaware	1-3619	13-5315170
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

235 East 42nd Street New York, New York (Address of principal executive offices)	10017 (Zip Code)

Registrant's telephone number, including area code:
(212) 573-2323

<PAGE>

Item 7(c). Exhibits

Exhibit 99 - Press Release of Pfizer Inc. dated January 22, 2004, reporting Pfizer's financial results for the fourth quarter of 2003 and for the year ended December 31, 2003.

Item 12. Results of Operations and Financial Condition

On January 22, 2004, Pfizer Inc. issued a press release announcing its financial results for the fourth quarter of 2003 and for the year ended December 31, 2003. A copy of the press release is furnished as Exhibit 99 to this report and is incorporated herein by reference.

SIGNATURE

Under the requirements of the Securities Exchange Act of 1934, the registrant has caused this report to be signed on its behalf by the authorized undersigned.

PFIZER INC.

By: /s/ Margaret M. Foran
Margaret M. Foran
Title: Vice President-Corporate Governance and Secretary

Dated: January 22, 2004

<PAGE>

EXHIBIT INDEX

Exhibit No.	Description
99	Press Release of Pfizer Inc. dated January 22, 2004, reporting

EXH. W
P. 190

Pfizer's financial results for the fourth quarter of 2003 and for
the year ended December 31, 2003.

</TEXT>
</DOCUMENT>
<DOCUMENT>
<TYPE>EX-99
<SEQUENCE>3
<FILENAME>c16650ex99.txt
<DESCRIPTION>PRESS RELEASE
<TEXT>

Exhibit 99

Pfizer Inc 2003 Performance Report

Pfizer Delivers Strong 2003 Financial Results

Quarterly Revenues Increase 52 Percent to $14.167 Billion,
Full-Year Revenues Grow 40 Percent to $45.188 Billion,
Reflecting Strong Growth from Pharmaceutical Industry's
Broadest Product Portfolio and Inclusion of
Post-Acquisition Results of Legacy Pharmacia

Financial Provisions Recorded for Two Legacy Warner-Lambert Legal Matters

---

Fourth-Quarter and Full-Year Reported Net Income of $602 Million and
$3.910 Billion, Respectively; Fourth-Quarter and Full-Year Reported
Diluted EPS of $.08 and $.54, Respectively

Fourth Quarter and Full-Year Adjusted Income* of $3.968 Billion and
$12.722 Billion, Respectively; Fourth-Quarter and Full-Year Adjusted
Diluted EPS* of $.53 and $1.75, Respectively

Pfizer Remains On Track to File an Industry-Record 20 Major NDAs in 2001-2006

Patient Access Programs Help More Than 1.5 Million Americans
Receive Pfizer Medicines During 2003

Expectations for Strong Growth in 2004

NEW YORK, Jan. 22 /PRNewswire-FirstCall/ -- Pfizer today reported financial results for the fourth quarter and full year of 2003.

"Our performance in the fourth quarter capped an exceptional year for Pfizer, one that offers clear evidence of the powerful momentum across all areas of our business," said Hank McKinnell, chairman and chief executive officer. "Highlights for 2003 included the achievement of our key financial goals; the rapid and effective integration of Pharmacia; the strong performance of key products in the face of new competition; successful launches of new products; continued advances of product candidates in our R&D pipeline; and ongoing development of our business through strategic acquisitions, licensing agreements, and divestitures. These outstanding results for 2003 were further enhanced by our significant progress in expanding patient access to medicines, continuing leadership in corporate governance, and new initiatives that underscore our commitment to good corporate citizenship."

Fourth-quarter and full-year revenues grew 52 percent and 40 percent to $14.167 billion and $45.188 billion, respectively. Revenue growth was driven by strong performances across a broad range of products, the inclusion of post-acquisition results of legacy Pharmacia products, and the weakening of the U.S. dollar relative to other currencies. Prior-year revenues used for comparative purposes reflect results of legacy Pfizer only.

EXH. W
P. 191

The Company's human pharmaceutical operations generated revenues of $12.441 billion, up 51 percent, in the fourth quarter and of $39.631 billion, up 40 percent, for the full year. Sales of Pfizer's Consumer Healthcare business were $937 million in the fourth quarter, up 42 percent, and were $3.042 billion for the full year, up 20 percent. Pfizer's Animal Health sales increased 57 percent in the period to $508 million and grew 43 percent for the full year to $1.598 billion.

Pfizer reported net income in the quarter of $602 million ($.08 per diluted share). This result included certain significant items of $1.524 billion, mainly relating to legal provisions recorded for two legacy Warner-Lambert legal matters: Rezulin personal-injury claims and a governmental investigation of marketing practices related to Neurontin; non-cash charges of $1.603 billion relating to purchase accounting for the Pharmacia acquisition; and merger-related costs of $239 million, all on an after-tax basis. Excluding these items, adjusted income and adjusted diluted EPS* were $3.968 billion and $.53, respectively.

Pfizer reported net income for full-year 2003 of $3.910 billion ($.54 per diluted share). This result included income from certain significant items of $620 million, mainly relating to gains on the sale of discontinued businesses and products of $2.285 billion, offset by $1.358 billion of legal provisions recorded for Rezulin personal-injury claims and governmental investigations of marketing practices related to Neurontin; non-cash charges of $8.742 billion relating to purchase accounting for the Pharmacia acquisition; and merger-related costs of $660 million, all on an after-tax basis. Excluding these items, adjusted income and diluted EPS* for full-year 2003 were $12.722 billion and $1.75, respectively.

Significant Achievements in Enhancement of Marketed Products and Development of New Product Candidates

"Our portfolio of leading medicines, which spans most major therapeutic categories, drove Pfizer's strong revenue growth in the fourth quarter and full-year 2003," said Karen Katen, executive vice president of the company and president of Pfizer Global Pharmaceuticals. "Pfizer is well-positioned for continued industry leadership in the years ahead."

In the fourth quarter, 14 products marketed by Pfizer remained at the top of their respective therapeutic categories -- more than any other company. These included eight of the world's 25 top-selling medicines, including Lipitor, the most widely prescribed medicine in the world. More than one billion prescriptions were written for Pfizer products last year. Pfizer's field sales organization continues to be recognized for excellence. For the ninth year in a row, physicians ranked Pfizer's U.S. sales organization number one in the industry, according to the recently completed Scott Levin/Verispan field image survey.

"While we fully supported our marketed products with new and substantial clinical efficacy and safety data as well as physician and patient education, we also prepared to launch major new products," said Ms. Katen. "For example, in January the combined cardiovascular field force will introduce Inspra for heart failure in the U.S. -- bringing a breakthrough treatment to market and further expanding our industry-leading cardiovascular portfolio.

"In neurology and ophthalmology, Pfizer's product offerings are also broad. Pfizer covers the therapeutic continuum for depression and social anxiety with our market-leading SSRI Zoloft and with the anxiolytic Xanax XR. We also have leading central-nervous-system products or product candidates for Alzheimer's disease, schizophrenia, migraine, epilepsy, neuropathic pain, multiple sclerosis, insomnia, and movement disorders. Our ophthalmology portfolio now includes the marketed products Zithromax for trachoma and Xalatan for glaucoma and will be supplemented with the Phase 3 candidate

Macugen for macular degeneration, in co-development with Eyetech Pharmaceuticals, Inc.

"While we maintain our longstanding commitment to widely used therapies, we have also clearly demonstrated that we can meet the critical medical needs of smaller, more targeted patient populations. Vfend, for example, treats deadly, invasive fungal infections in immuno-compromised patients -- a relatively small but critical need. Another example from our neuroscience portfolio is Rebif for multiple sclerosis (co-promoted with Serono S.A.). Pfizer's oncology portfolio and pipeline now include Camptosar for colon cancer, Ellence and Aromasin for breast cancer, and 15 oncology agents in development.

"Our proven commitment to serving patients goes beyond medicines. We are also serious about reaching underserved people in need. To that end, we provide access and health-education programs for vulnerable patient populations, like our Florida: A Healthy State initiative, and patient-assistance programs that last year helped more than 1.5 million underserved Americans receive our medicines free or at reduced cost.

"In spite of a challenging global operating environment and new competition in key worldwide markets, we have continued to focus on what we do best -- bringing our medicines to people who need them," Ms. Katen concluded.

Performance milestones for marketed products since the end of the third quarter of 2003 include the following:

Lipitor

-- The results of the REVERSAL (REVERSing Atherosclerosis with Aggressive Lipid Lowering) trial -- published at the November 2003 meeting of the American Heart Association -- showed the positive effects from aggressively lowering lipids on halting atherosclerosis progression. REVERSAL compared the effectiveness of Lipitor 80 mg with Pravachol 40 mg in reducing plaque buildup in patients with coronary artery disease who required cardiac catheterization or angiograms. Lipitor therapy reduced plaque volume in arterial vessels, while patients on Pravachol experienced a significant increase in plaque. The REVERSAL study reinforced results of the CARDS and ASCOT trials, which were terminated early due to overwhelmingly significant positive clinical evidence in patients treated with Lipitor.

-- Despite new competition, Lipitor gained more than one full share point in new prescriptions since early November, showing solid leadership as the statin of choice. This performance affirms physicians' trust in the efficacy and safety record of Lipitor, backed by 67 million patient years of experience.

Viagra

-- Viagra remains the premier treatment for erectile dysfunction, with unsurpassed safety and efficacy. Its clinical record was bolstered by a new study, presented in November at the European Society for Sexual Medicines, which showed that 79 percent of Viagra patients who tried two new phosphodiesterase V inhibitors for erectile dysfunction preferred not to switch to the new medicines. These results are consistent with long-term efficacy and patient-satisfaction studies showing that, after four years, 96 percent of men remain satisfied with Viagra.

Inspra

-- In October, the FDA approved Inspra for heart failure in patients who had suffered a heart attack. This indication was based on the EPHESUS study, which showed that adding Inspra to current heart-failure therapy in post-heart-attack patients resulted in a 15-

percent reduction in mortality.

Xalatan/Xalcom
-- Xalatan/Xalcom became the world's first ophthalmic treatment to achieve $1 billion in annual sales (includes sales of Xalatan/Xalcom during 2003 prior to our acquisition of Pharmacia in April). The product is a first-line therapy for glaucoma, the world's second-leading cause of blindness, with a strong efficacy and favorable side-effect profile.

Vfend
-- The FDA recently approved two important enhancements to Pfizer's novel antifungal treatment Vfend. In November 2003, Vfend was approved for use in the treatment of esophageal candidiasis, an opportunistic fungal infection in immuno-compromised patients. In December 2003, a new Vfend oral-suspension formulation was approved. In addition to the new oral suspension, Vfend is available in both tablet and intravenous forms.

Somavert
-- Somavert, an important new treatment for patients with the growth disorder acromegaly, is now available in six E.U. countries and is expected to be available throughout Europe in the first half of 2004. The first medicine in a class called growth-hormone-receptor antagonists, Somavert offers physicians a major advantage over existing therapies, such as surgery, radiation, and other pharmaceuticals.

Fosfluconazole
-- Fosfluconazole, the injectable pro-drug of Pfizer's leading antifungal agent Diflucan, was approved for marketing in Japan in October 2003.

2003 was also a productive year for Pfizer Global Research and Development. "The Pfizer pipeline is growing," said Dr. John LaMattina, President, Pfizer Global Research and Development. "The early-stage pipeline is benefiting from productive internal discovery research. The mid- and late-stage pipelines are growing, supplemented by targeted licensing and acquisition of late-stage candidates. We are on track to meet our goal of filing 20 major NDAs in the five-year period ending in 2006. To date, we have completed six of the 20 anticipated NDA filings, and we anticipate another productive year in 2004."

Development milestones achieved since the end of the third quarter of 2003 include the following:

Pregabalin
-- The FDA accepted the regulatory submission for pregabalin for the treatment of epilepsy, neuropathic pain associated with diabetic peripheral neuropathy, neuropathic pain associated with herpes zoster, and generalized anxiety disorder.

Geodon
-- The FDA accepted the regulatory submission for use of Geodon in treating mania.

Rextra
-- The U.S. regulatory submission for Rextra in the treatment of migraine was completed during the fourth quarter and accepted by the FDA.

Caduet
-- The European regulatory submission for Caduet, the Lipitor Norvasc one-pill combination, was completed during December 2003. In the

EXH. W
P. 194

U.S., regulatory review continues on the Caduet NDA, which was filed in March 2003. This product has been developed in a wide range of dosing combinations and, when approved, will provide a unique, novel treatment for patients with hypertension and high cholesterol -- resulting in better patient outcomes because both conditions will be treated simultaneously, not one at a time.

Esperion
-- The planned acquisition of Esperion Therapeutics, announced in December, would add a new acute-care dimension to Pfizer's cardiovascular portfolio. Lipitor and the product candidate Lipitor/torcetrapib represent chronic therapies to reduce LDL (or bad) cholesterol and raise HDL (or good) cholesterol. Esperion brings expertise and clinical-development compounds for acute, hospital-based treatments to regress arterial plaque in patients who have had a cardiovascular event. These complementary product offerings will further distinguish Pfizer's leadership position in cardiovascular medicine.

Advanced-stage clinical studies are continuing for the injectable COX-2-selective inhibitor Dynastat for pain and inflammation; Exubera, an inhalable form of insulin for type 1 and type 2 diabetes under co-development, co-manufacture, and co-marketing with Aventis, with the participation of Nektar Therapeutics; varenicline for smoking cessation; Lipitor-torcetrapib for cholesterol disorders; lasofoxifene for osteoporosis and other indications; indiplon for insomnia, under co-development with Neurocrine Biosciences, Inc.; Macugen for macular degeneration and macular edema, under co-development with Eyetech Pharmaceuticals, Inc.; Daxas (roflumilast) for chronic obstructive pulmonary disease and asthma, under co-development with Altana Pharma; capravirine for HIV/AIDS; a Zithromax/chloroquine combination for malaria; sumanirole for Parkinson's disease; asenapine for neurological disorders, under co-development with Akzo Nobel's Organon healthcare unit; edotecarin for colorectal cancer; and SU-11248, an angiogenesis inhibitor for treatment of gastrointestinal and other cancers.

Expectations for Strong Growth in 2004

David Shedlarz, executive vice president and chief financial officer, noted, "2003 has been a very successful year, characterized by numerous challenges met and opportunities seized. During the year, we made substantial progress in the integration of Pharmacia, sustained the strong performance of our current major products, blunted the impact of emerging product competition, continued the replenishment of our research pipeline, reinforced our network of development partnerships, and made substantial progress toward resolving legacy legal issues.

"The many successes of the past year help give Pfizer a strong platform for growth in 2004, given the dimensions of our product portfolio, our operational capabilities, and our financial depth and flexibility.

"Our expectations for strong financial performance in 2004 remain substantially unchanged. We are comfortable with targets for 2004 revenue of about $54 billion, for 2004 adjusted income of $16.3 billion, and for 2004 adjusted diluted EPS of $2.13. We now project 2004 reported net income of $12.8 billion and 2004 reported diluted EPS of $1.68. Merger-related cost synergies totaled $1.3 billion in 2003, exceeding our previous estimate of about $1.0 billion. We now project merger-related cost synergies in 2004 of about $3.4 billion, an increase from our previous estimate of about $3.0 billion. We plan to spend about $7.9 billion in R&D during 2004.

Mr. Shedlarz concluded, "In the dynamic environment of today's worldwide pharmaceutical industry, Pfizer is uniquely well-positioned to sustain our strong and balanced performance, leverage past and future opportunities, reinforce and extend our differentiation from others in the industry, and

EXH. W
P. 195

PAGE INTENTIONALLY LEFT BLANK

EXH. W
P. 196

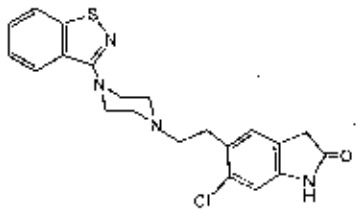
GEODON®
(ziprasidone HCl)
Oral Suspension

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Geodon (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

DESCRIPTION

GEODON® is available as Oral Suspension (ziprasidone hydrochloride) for oral administration. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Oral Suspension contains a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Oral Suspension is supplied for oral administration as ziprasidone 10 mg/mL in 60 mL (600

EXH. W
P. 197

certain antihypertensive agents.

(4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic Interactions

The Effect of Other Drugs on Ziprasidone

Carbamazepine - Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole - Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35–40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine - Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid - The coadministration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Lithium - Ziprasidone at a dose of 40 mg BID administered concomitantly with lithium at a dose of 450 mg BID for 7 days did not affect the steady-state level or renal clearance of lithium.

Oral Contraceptives - Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

Dextromethorphan - Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there

was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** under **PRECAUTIONS, General**).

Mutagenesis - Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility - Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

Pregnancy - Pregnancy Category C - In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

10-Q 1 0001.htm

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549
FORM 10-Q

X QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

For the quarterly period ended July 2, 2000

OR

TRANSITION REPORT PURSUANT TO SECTION 13
OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from_____to_____

COMMISSION FILE NUMBER 1-3619

PFIZER INC.
(Exact name of registrant as specified in its charter)

DELAWARE	13-5315170
(State of Incorporation)	(I.R.S. Employer Identification No.)

235 East 42nd Street, New York, New York 10017
(212) 573-2323
(Registrant's telephone number)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days.

YES X NO__

At August 8, 2000, 6,313,725,922 shares of the issuer's common stock were outstanding (voting).

FORM 10-Q

For the Quarter Ended
July 2, 2000

Table of Contents

EXH. W
P. 200

COSTS AND EXPENSES

Cost of Sales

Cost of sales decreased 2% in the second quarter and 3% in the first half of 2000 as compared with the prior year periods, while revenues increased 8% in the second quarter and 9% in the first half. In both periods, these results were mainly attributable to favorable product and business mix and improvements in manufacturing efficiency and to a lesser extent the impact of foreign exchange.

Selling, Informational and Administrative Expenses

Selling, informational and administrative expenses increased 8% in the second quarter and 7% in the first half of 2000 over the prior year periods. During the first half of 2000, we continued to provide strong support for our products; however, the growth rate of SI&A is slowing as we begin the integration of Pfizer with Warner-Lambert.

Research and Development Expenses

Research and development expenses increased 14% in both the second quarter and first half of 2000 over the prior year periods. Budgeted R&D spending is about $4.7 billion for the full year 2000.

In the second quarter of 2000, we filed the following indications with the U.S. Food and Drug Administration (FDA):

- Zoloft - Supplementary filings for long-term management of anxiety disorders (panic disorder, adult and pediatric obsessive-compulsive disorder and post-traumatic stress disorder)

In the first quarter of 2000, we refiled with the FDA the New Drug Application for the oral dosage form of the anti-psychotic Zeldox, including new data requested by the FDA. An FDA advisory committee reviewed this compound on July 19 and voted to recommend its approval. The various committee members who commented expressed their opinion that Zeldox should be approved for first-line therapy, but should be labeled to provide adequate information to physicians and patients as to the effect of the drug on the QTc interval prolongation of the electrocardiogram. Zeldox will now go through the FDA's final review and labeling stages. We plan to launch Zeldox in Sweden in September where it has already been approved for marketing and are in the process of seeking mutual recognition in Europe.

In October 1999, we received an approvable letter from the FDA for Relpax for the treatment of migraines. We are currently in labeling discussions with the FDA.

Ongoing or planned clinical trials for additional uses and dosage forms for our currently marketed products include:

Product	Indication
Norvasc	Pediatric hypertension
Zithromax	• Cardiovascular risk in patients with atherosclerosis (a process in

EXH. W
P. 201

PAGE INTENTIONALLY LEFT BLANK

EXH. W
P. 202

Kuvan™ (sapropterin dihydrochloride) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Kuvan safely and effectively. See full prescribing information for Kuvan.

Kuvan (sapropterin dihydrochloride) Tablets

Initial U.S. Approval: 2007

-----INDICATIONS AND USAGE-----

Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet (1).

----DOSAGE AND ADMINISTRATION----

The recommended starting dose of Kuvan is 10 mg/kg/day taken once daily.

Doses of Kuvan may be adjusted in the range of 5 to 20 mg/kg taken once daily. Blood Phe must be monitored regularly (2.1).

Kuvan should be taken orally with food to increase the absorption. Kuvan Tablets should be dissolved in 4 to 8 oz. (120-240 mL) of water or apple juice and taken within 15 minutes (2.2).

------DOSAGE FORMS AND STRENGTHS------

100 mg tablets (3).

----------CONTRAINDICATIONS----------

None (4).

-----WARNINGS AND PRECAUTIONS-----

Monitor Blood Phe Levels During Treatment:

Prolonged exposure to elevated blood Phe levels can injure the brain and reduce brain function. To ensure adequate blood Phe control, blood Phe levels must still be carefully monitored even though patients are receiving Kuvan which can reduce blood Phe levels (5.1).

Treat All Patients With a Phe-restricted Diet:

The initiation of Kuvan therapy does not eliminate the need for ongoing dietary management (5.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence >4%) in patients treated with Kuvan are headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting, and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

--------USE IN SPECIFIC POPULATIONS--------

Pregnancy Category C. This drug should be used during pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women. Women who are exposed to Kuvan during pregnancy are encouraged to enroll in the Kuvan patient registry (8.1, 17.5).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revision Date: 12/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

EXH. W
P. 203

SER 270

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kuvan is a synthetic form of BH4, the cofactor for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4 can activate residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

12.2 Pharmacodynamics

In PKU patients who are responsive to BH4 treatment, blood Phe levels decrease within 24 hours after a single administration of sapropterin dihydrochloride, although maximal effect on Phe level may take up to a month, depending on the patient. A single daily dose of Kuvan is adequate to maintain stable blood Phe levels over a 24-hour period. Twelve patients with blood Phe levels ranging from 516 to 986 µmol/L (mean 747 ± 153 µmol/L) were assessed with 24-hour blood Phe level monitoring following a daily morning dose of 10 mg/kg/day. The blood Phe level remained stable during a 24-hour observation period. No substantial increases in blood Phe levels were observed following food intake throughout the 24-hour period.

Doses above 20 mg/kg/day have not been evaluated in clinical studies.

12.3 Pharmacokinetics

Studies in healthy volunteers have shown comparable absorption of sapropterin dihydrochloride when tablets are dissolved in water or orange juice and taken under fasted conditions. Administration of dissolved tablets after a high-fat/high-caloric meal resulted in mean increases in Cmax of 84% and AUC of 87% (dissolved in water). However, there was extensive variability in individual subject values for Cmax and AUC across the different modes of administration and meal conditions. In the clinical trials of Kuvan, drug was administered in the morning as a dissolved tablet without regard to meals. The mean elimination half-life in PKU patients was approximately 6.7 hours (range 3.9 to 17 hr), comparable with values seen in healthy subjects (range 3.0 to 5.3 hr).

A population pharmacokinetic analysis of sapropterin that included patients between 9 and 49 years of age showed no effect of age on sapropterin dihydrochloride pharmacokinetics. Pharmacokinetics in patients <9 years and >49 years of age have not been studied.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted in F-344 rats, and a 78-week carcinogenicity study was conducted in CD-1 mice. In the 104-week oral carcinogenicity study in rats, sapropterin doses of 25, 80, and 250 mg/kg/day (0.2, 0.7, and 2 times the maximum recommended human dose of 20 mg/kg/day, respectively, based on body surface area) were used. In the 78-week oral carcinogenicity study in mice, sapropterin doses of 25, 80, and 250 mg/kg/day (0.1, 0.3, and 2 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, there was a statistically

significant increase in the incidence of benign adrenal pheochromocytoma in male rats treated with the 250 mg/kg/day (about 2 times the maximum recommended human dose, based on body surface area) dose, as compared to vehicle-treated rats. The mouse carcinogenicity study showed no evidence of a carcinogenic effect, but the study was not ideal due to its duration of 78 instead of 104 weeks.

Sapropterin was genotoxic in the *in vitro* Ames test at concentrations of 625 µg (TA98) and 5000 µg (TA100) per plate, without metabolic activation. However, no genotoxicity was observed in the *in vitro* Ames test with metabolic activation. Sapropterin was genotoxic in the *in vitro* chromosomal aberration assay in Chinese hamster lung cells at concentrations of 0.25 and 0.5 mM. Sapropterin was not mutagenic in the *in vivo* micronucleus assay in mice at doses up to 2000 mg/kg/day (about 8 times the maximum recommended human dose of 20 mg/kg/day, based on body surface area). Sapropterin, at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats.

14. CLINICAL STUDIES

14.1 Clinical Studies in PKU

The efficacy and safety of Kuvan were evaluated in 4 clinical studies in patients with PKU.

Study 1 was a multicenter, open-label, uncontrolled clinical trial of 489 patients with PKU, ages 8 to 48 years (mean 22 years), who had baseline blood Phe levels ≥450 µmol/L and who were not on Phe-restricted diets. All patients received treatment with Kuvan 10 mg/kg/day for 8 days. For the purposes of this study, response to Kuvan treatment was defined as a ≥30% decrease in blood Phe from baseline. At Day 8, 96 patients (20%) were identified as responders.

Study 2 was a multicenter, double-blind, placebo-controlled study of 88 patients with PKU who responded to Kuvan in Study 1. After a washout period from Study 1, patients were randomized equally to either Kuvan 10 mg/kg/day (N=41) or placebo (N=47) for 6 weeks. Efficacy was assessed by the mean change in blood Phe level from baseline to Week 6 in the Kuvan-treated group as compared to the mean change in the placebo group.

The results showed that at baseline, the mean (±SD) blood Phe level was 843 (±300) µmol/L in the Kuvan-treated group and 888 (±323) µmol/L in the placebo group. At Week 6, the Kuvan-treated group had a mean (±SD) blood Phe level of 607 (±377) µmol/L, and the placebo group had a mean blood Phe level of 891 (±348) µmol/L. At Week 6, the Kuvan- and placebo-treated groups had mean changes in blood Phe level of –239 and 6 µmol/L, respectively (mean percent changes of –29% (±32) and 3% (±33), respectively). The difference between the groups was statistically significant ($p < 0.001$) (Table 2).

10-K 1 d10k.htm FORM 10-K

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2006

Or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to
Commission file number: 000-26727

BioMarin Pharmaceutical Inc.
(Exact name of registrant issuer as specified in its charter)

Delaware	68-0397820
(State of other jurisdiction of Incorporation or organization)	(I.R.S. Employer Identification No.)
105 Digital Drive, Novato, California	94949
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number: (415) 506-6700
(Former name, former address and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:
Common Stock, $.001 par value
Preferred Share Purchase Rights
(Title of Class)
Securities registered under Section 12(g) of the Act:
None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers in response to Item 405 of Regulation S-K is not contained in this form, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act. (Check one): Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act.) Yes ☐ No ☒

Applicable only to issuers involved in bankruptcy proceedings during the proceeding five years:

Indicate by check mark whether the registrant has filed all documents and reports required to be filed by Sections 12, 13 or 15(d) of the Securities Exchange Act of 1934 subsequent to the distribution of securities under a plan confirmed by a court. Yes ☐ No ☐

Applicable only to corporate issuers:

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act are available free of charge at www.bmrn.com as soon as reasonably practicable after electronically filing such reports with the SEC. Additionally, these reports are available at the SEC's website at http://www.sec.gov. Information contained in our website is not part of this report.

A summary of our various commercial products and development programs, including key metrics as of December 31, 2006, is provided below:

Program	Indication	Orphan Drug Designation	Stage	Next Key Milestone	2006 Total Product Revenue (in millions)	2006 Research & Development Expense (in millions)
Naglazyme	MPS VI	Yes	Approved	N/A	$ 46.5	$ 9.7
Aldurazyme	MPS I	Yes	Approved	N/A	$ 96.3 (1)	N/A
Kuvan	PKU	Yes	Clinical	File NDA in Q2 2007	$ 18.7	$ 27.4
6R-BH4	Cardiovascular Indications	Not yet determined	Clinical	Phase II results in 2008	N/A	$ 8.9
Phenylase	PKU	Not yet determined	Preclinical	File IND in 2008	N/A	$ 4.5

(1) We have developed Aldurazyme through a 50/50 joint venture with Genzyme, BioMarin/Genzyme LLC, and recognize our 50% share of the net income of BioMarin/Genzyme LLC as Equity in the Income of BioMarin/Genzyme LLC in our consolidated statements of operations.

Recent Developments

Results From Phase 2 Clinical Study of BH4 in Poorly Controlled Hypertension

On February 20, 2007, we announced results from the Phase 2 clinical study of 6R-BH4 in poorly controlled hypertension. Results demonstrated that there was no statistically significant or clinically meaningful effect of 6R-BH4 on any efficacy or safety parameter measured, relative to placebo.

Positive Results From Phase 3 Diet Study of Kuvan (formerly referred to as Phenoptin) for PKU

On January 16, 2007, we announced positive results from the Phase 3 diet study of Kuvan for PKU in 4 to 12 year-old patients. Results showed that all pre-specified safety and efficacy end-points were met. Kuvan treatment caused a significant increase in phenylalanine (Phe) tolerance as well as a reduction in blood phenylalanine levels. In the primary end-point, Kuvan enabled a mean increase of 20.9 mg/kg/day of Phe supplementation for those patients on Kuvan, representing a doubling of their baseline intake.

Initiation of Phase 2 Clinical Trial of BH4 in Peripheral Arterial Disease

On January 4, 2007, we announced that the first patient has initiated treatment in the Phase 2 clinical study of 6R-BH4 for the treatment of symptomatic peripheral arterial disease. We expect to announce data from this study in the first half of 2008.

Remaining $51.4 Million of 3.50% Convertible Notes Due 2008 Converted to Common Stock

On December 22, 2006, we gave notice that we were calling for redemption of the remainder of the outstanding 3.50% Convertible Senior Subordinated Notes due June 15, 2008. Prior to the January 26, 2007 call date, all of the remaining noteholders elected to convert the notes into our common stock, pursuant to the terms of the notes. As a result, we issued approximately 3.7 million shares of common stock.

EXH. W
P. 207

Positive Results From Phase 3 Extension Study of Kuvan for PKU

On December 18, 2006, we announced positive results from the open label extension study of the pivotal Phase 3 study of Kuvan. Results confirm that all pre-specified safety and efficacy endpoints were met, and data demonstrated the long-term safety and tolerability of Kuvan as a treatment to control blood Phe levels across a range of doses in PKU patients.

Marketing Approval for Aldurazyme in Japan

On October 31, 2006, we announced that Japan's Ministry of Health, Labor and Welfare has granted marketing authorization for Aldurazyme in Japan.

Commercial Products

Naglazyme

Naglazyme is a recombinant form of N-acetylgalactosamine 4-sulfatase (arylsulfatase B) indicated for patients with mucopolysaccharidosis VI (MPS VI). MPS VI is a debilitating life-threatening genetic disease for which no other drug treatment currently exists and is caused by the deficiency of N-acetylgalactosamine 4-sulfatase (arylsulfatase B), an enzyme normally required for the breakdown of certain complex carbohydrates known as glycosaminoglycans (GAGs). Patients with MPS VI typically become progressively worse and experience multiple severe and debilitating symptoms resulting from the build-up of carbohydrate residues in all tissues in the body. These symptoms include: inhibited growth, spinal cord compression, enlarged liver and spleen, joint deformities and reduced range of motion, skeletal deformities, impaired cardiovascular function, upper airway obstruction, reduced pulmonary function, frequent ear and lung infections, impaired hearing and vision, sleep apnea, malaise and reduced endurance.

Naglazyme was granted marketing approval in the U.S. in May 2005 and in the E.U. in January 2006. Naglazyme has been granted orphan drug status in the U.S. and the E.U., which confers seven years of market exclusivity in the U.S. and 10 years of market exclusivity in the E.U. for the treatment of MPS VI, expiring in 2012 and 2016, respectively. However, different drugs can be approved for the same condition if they are determined to have a better safety and efficacy profile than Naglazyme. We market Naglazyme in the U.S. and E.U. using our own sales force and commercial organization. We have launched the product in the major markets of the E.U. and are continuing launch efforts on a country-by-country basis in the other E.U. countries. Additionally, we are receiving some revenue from named patient sales of Naglazyme in other countries. We have initiated commercial operations in Brazil during 2006 and are currently evaluating the option of using local partners in other countries as an alternative to direct marketing of Naglazyme. Naglazyme net product sales for 2006 totaled $46.5 million, as compared to $6.1 million for 2005.

Aldurazyme

Aldurazyme has been approved for marketing in the U.S., E.U., Japan and other countries for patients with mucopolysaccharidosis I (MPS I), for which no other drug treatment currently exists. MPS I is a progressive and debilitating life-threatening genetic disease that is caused by the deficiency of alpha-L-iduronidase, a lysosomal enzyme normally required for the breakdown of GAGs. Patients with MPS I typically become progressively worse and experience multiple severe and debilitating symptoms resulting from the build-up of carbohydrate residues in all tissues in the body. These symptoms include: inhibited growth, delayed and regressed mental development (in the severe form), enlarged liver and spleen, joint deformities and reduced range of motion, impaired cardiovascular function, upper airway obstruction, reduced pulmonary function, frequent ear and lung infections, impaired hearing and vision, sleep apnea, malaise and reduced endurance.

Aldurazyme has been granted orphan drug status in the U.S. and the E.U., which gives Aldurazyme seven years of market exclusivity in the U.S. and 10 years of market exclusivity in the E.U. for the treatment of MPS I, expiring in 2010 and 2013, respectively. However, different drugs can be approved for the same condition if they

PAGE INTENTIONALLY LEFT BLANK

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-440

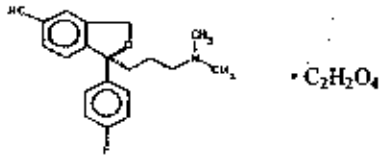
FINAL PRINTED LABELING

EXH. W
P. 210

LEXAPRO™
(escitalopram oxalate)

DESCRIPTION

LEXAPRO™ (escitalopram oxalate) is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



The molecular formula is $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ and the molecular weight is 414.40.

Escitalopram oxalate occurs as a fine white to slightly yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO), soluble in isotonic saline solution, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate, and insoluble in heptane.

LEXAPRO™ tablets are film coated, round tablets containing escitalopram oxalate in strengths equivalent to 5 mg, 10 mg or 20 mg escitalopram base. The 10 and 20 mg tablets are scored. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hydroxypropyl methyl cellulose, titanium dioxide, and polyethylene glycol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-

Ritonavir – Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Drugs Metabolized by Cytochrome P4502D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited in vivo data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in Cmax and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

Metoprolol - Administration of 20 mg/day Lexapro™ for 21 days resulted in a 50% increase in Cmax and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro™ and metoprolol had no clinically significant effects on blood pressure or heart rate.

Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of ECT and escitalopram.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

EXH. W
P. 212

10-K 1 forest10k2002.htm FOREST LABORATORIES, INC. 10-K MARCH 31, 2002

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark one)

[X] ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended March 31, 2002

[ ] TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period From _____ to _____

Commission File No. 1-5438

FOREST LABORATORIES, INC.

(Exact name of registrant as specified in its charter)

Delaware	**11-1798614**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification Number)*
909 Third Avenue	
New York, New York	**10022**
(Address of principal executive offices)	*(Zip code)*

(212) 421-7850
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $.10 par value	New York Stock Exchange
Rights, as adjusted, to purchase one quarter of one-hundredth share of Series A Junior Participating Preferred Stock, par value $1.00 per share	New York Stock Exchange

EXH. W
P. 213

physician's prescription, as well as non-prescription pharmaceutical products sold over-the-counter. Forest's most important United States products consist of branded ethical drug specialties marketed directly, or "detailed," to physicians by the Company's Forest Pharmaceuticals, Forest Therapeutics, Forest Healthcare and Forest Specialty Sales salesforces. The Company emphasizes detailing to physicians of those branded ethical drugs it believes have the most potential for growth, and the development and introduction of new products, including products developed in collaboration with licensing partners.

Forest's products include those developed by Forest and those acquired from other pharmaceutical companies and integrated into Forest's marketing and distribution systems. See "Recent Developments."

Forest is a Delaware corporation organized in 1956, and its principal executive offices are located at 909 Third Avenue, New York, New York 10022 (telephone number 212-421-7850).

Recent Developments

Lexapro™: In January 2002, Forest received an "approvable letter" from the United States Food and Drug Administration ("FDA") for Lexapro (escitalopram oxalate), a single isomer version of Forest's Celexa™ (citalopram HBr) for the treatment of depression. An approvable letter represents the final stage in the FDA approval process to market a pharmaceutical product in the United States. Forest anticipates receiving final FDA approval early in fiscal 2003. Citalopram is a racemic mixture with two mirror image molecules, the S- and R-isomers. The S-isomer of citalopram is the active isomer in terms of its contribution to citalopram's antidepressant effects, while the R-isomer does not contribute to the antidepressant activity. With Lexapro, the R-isomer has been removed, leaving only the active S-isomer. Clinical trials demonstrate that Lexapro is a more potent selective serotonin reuptake inhibitor ("SSRI") than its parent compound and confirm the antidepressant activity of Lexapro in all clinical measures of depression. Lexapro was developed by H. Lundbeck A/S, a Danish pharmaceutical firm which licenses this compound, as well as Celexa, to Forest. Lexapro has already been approved for sale in 10 European countries.

Celexa: Sales of Celexa, Forest's selective serotonin reuptake inhibitor for the treatment of depression were $1,087,794,000 for the fiscal year ended March 31, 2002. According to data published by IMS, an independent prescription audit firm, as of June 7, 2002 Celexa has achieved a 17.2% share of total prescriptions for antidepressants in the SSRI/SNRI category. Citalopram is currently marketed in most European countries and is the leading antidepressant in several European markets. Forest licenses the United States rights to Celexa from H. Lundbeck A/S.

Benicar™ Co-Promotion with Sankyo Pharma: In December 2001, Forest entered into a co-promotion agreement with Sankyo Pharma for the co-promotion in the United States of Benicar (olmesartan medoxomil) an angiotensin receptor blocker discovered and developed by Sankyo Pharma for the treatment of hypertension. The New Drug Application ("NDA") for Benicar was approved by the FDA in April 2002 and the product was commercially launched in the United States in May 2002.

Pursuant to the co-promotion agreement with Sankyo, Forest and Sankyo will share in the detailing of the product to physicians, hospitals, managed care organizations and other institutional users of pharmaceutical products over a six-year period. Forest will receive co-promotion income based upon the relative contribution of the two companies to the co-promotion effort, and will receive residual payments following the end of the co-promotion period based on sales levels achieved.

PAGE INTENTIONALLY LEFT BLANK

EXH. W
P. 215

NDA 21-476 Approved Labeling Text
Dated December 15, 2004

R_x only

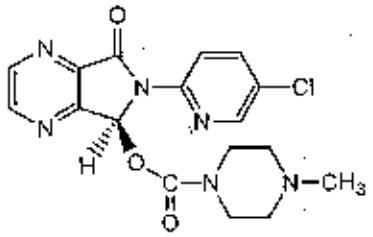
C-IV

LUNESTA™ (eszopiclone) TABLETS
1 mg, 2 mg, 3 mg

PRESCRIBING INFORMATION

DESCRIPTION:

LUNESTA (eszopiclone) is a nonbenzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. The chemical name of eszopiclone is (+)-(5S)-6-(chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazin-5-yl 4-methyl- piperazine-1-carboxylate. Its molecular weight is 388.81, and its empirical formula is $C_{17}H_{17}ClN_6O_3$. Eszopiclone has a single chiral center with an (*S*)-configuration. It has the following chemical structure:



Eszopiclone is a white to light-yellow crystalline solid. Eszopiclone is very slightly soluble in water, slightly soluble in ethanol, and soluble in phosphate buffer (pH 3.2).

Eszopiclone is formulated as film-coated tablets for oral administration. LUNESTA tablets contain 1 mg, 2 mg, or 3 mg eszopiclone and the following inactive ingredients: calcium phosphate, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, and triacetin. In addition, both the 1 mg and 3 mg tablets contain FD&C Blue #2.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

The precise mechanism of action of eszopiclone as a hypnotic is unknown, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. Eszopiclone is a nonbenzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties.

EXH. W
P. 216

Drugs That Inhibit CYP3A4 (Ketoconazole)

CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days. C_{max} and $t_{1/2}$ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Drugs That Induce CYP3A4 (Rifampicin)

Racemic zopiclone exposure was decreased 80% by concomitant useof rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

Drugs Highly Bound To Plasma Protein

Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

Drugs With A Narrow Therapeutic Index

Digoxin

A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.

Warfarin

Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (*R*)- or (*S*)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25 mg oral dose of warfarin.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Carcinogenesis

In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and

an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD — i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis

Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation assay, in an unscheduled DNA synthesis assay, or in an *in vivo* mouse bone marrow micronucleus assay.

(*S*)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* ^{32}P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Impairment Of Fertility

Eszopiclone was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopiclone decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m^2 basis). Other effects included increased pre-implantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

10-K 1 a2105467z10-k.htm 10-K
QuickLinks -- Click here to rapidly navigate through this document

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2002

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission file number 0-19410

Sepracor Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**22-2536587**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
84 Waterford Drive, Marlborough, Massachusetts	**01752**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **(508) 481-6700**

Securities registered pursuant to Section 12(b) of the Act: **NONE**

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $.10 par value

EXH. W
P. 219

racemic mixture, or a racemate. These two isomers are generally referred to as (S)-isomers (left) and (R)-isomers (right). While isomers have identical molecular weights and physical properties, they show remarkable selectivity within biological systems and therefore can have different

biological actions. In many cases, only one isomer of the racemic drug is responsible for the drug's efficacy. The other may be an unnecessary component or may cause side effects. Typically, in our product development process, we separate racemic mixtures containing two isomers into compounds containing only one isomer.

Active Metabolites

An active metabolite is a therapeutically active compound produced by the metabolism of a parent drug. Drugs administered to treat diseases are sometimes transformed, or metabolized, within the body into a variety of related chemical forms known as metabolites, some of which may have therapeutic activity. Metabolites that have therapeutic activity are known as active metabolites. Active metabolites can also be synthesized in the laboratory. During preclinical and clinical testing of a parent drug, subjects are exposed to the active metabolite of the parent drug. Therefore, a developer of an active metabolite may be able to rely upon certain known clinical information of the parent drug in its NDA submission for the active metabolite, including safety data. In some cases, this can eliminate the need for certain clinical studies and significantly expedite the development process of an active metabolite drug.

The majority of the scientific and medical research conducted by us is directed toward discovering differences between isomers derived from racemates or active metabolites derived from parent drugs. In contrast to traditional new drug development, the safety and efficacy of the racemates and parent drugs of our pharmaceuticals under development are often well understood before clinical trials begin. Parent drugs have been successfully taken through clinical studies and may have been on the market for years. We evaluate isomers or active metabolites in a highly accelerated and focused manner. Our directed research effort allows us to identify potential advantages in our candidates such as improvements in potency, onset of action, duration of activity, dosage, additional indications, or meaningful reductions in side effects or adverse reactions.

Recent Product and Pipeline Developments

ESTORRA. In January 2003, we submitted an NDA to the FDA seeking clearance to market ESTORRA™ brand eszopiclone 2 mg and 3 mg tablets for the treatment of transient and chronic insomnia. We studied ESTORRA in the 3 mg dosage strength for adults and in the 2 mg dosage strength for treatment of the elderly population.

The NDA contains data from a total of 24 clinical trials, which included more than 2,700 adult and elderly subjects, and more than 60 preclinical studies. We conducted a total of six randomized, placebo-controlled, Phase III studies, including one with a positive control, for the treatment of insomnia in both adult and elderly patients. We also completed a double-blind, placebo-controlled, 6-month chronic efficacy and safety trial, which included 788 subjects for the treatment of chronic insomnia. We followed this efficacy and safety trial with a 6-month open-label extension to study safety for up to 12 months.

According to the National Sleep Foundation, insomnia affects approximately 50 million people in the United States. Insomnia symptoms may include difficulty falling asleep, awakening frequently during the night, awakening too early in the morning, or awakening feeling unrefreshed. Causes of insomnia can include depression, anxiety, pain and other medical conditions, as well as environmental factors such as jet lag or shift work.

Pursuant to the Prescription Drug User Fee Act, the FDA has 60 days to determine whether to accept the ESTORRA NDA submission for filing.

ASTELIN®. In August 2002, we signed an agreement with MedPointe Inc. for the co-promotion of ASTELIN (azelastine HCl), a nasal-spray antihistamine. ASTELIN is the only antihistamine that has

EXH. W
P. 220

been approved by the FDA for the treatment of symptoms for both seasonal allergic rhinitis in adults and children 5 years of age and older and non-allergic vasomotor rhinitis in adults and children 12 years and older.

Under the terms of the multi-year agreement, our sales force markets ASTELIN to pulmonologists, allergists, pediatricians and primary care physicians in United States hospitals and clinics. We are entitled to receive a percentage of net sales above an agreed upon annual baseline sales level, if those sales levels are achieved. Each company is responsible for its own selling expenses.

SOLTARA™. On March 7, 2002, the FDA issued a "not approvable" letter for our NDA for SOLTARA brand tecastemizole 15 mg and 30 mg capsules. A "not-approvable" letter is issued if the FDA believes that the application contains insufficient information for an approval action.

The FDA identified three primary issues that it determined were not adequately addressed in our NDA in light of certain aspects of tecastemizole's pharmacokinetics and potential for accumulation in tissue. Two of the issues pertained to observations from safety studies in animals that were not observed in humans: phospholipidosis, an adaptive storage response to drug administration, and cardiomyopathy, a pathologic condition of the heart muscle. A third issue concerned the need for additional assurance of the absence of any potential for QTc prolongation, which is an effect on electrical impulse conduction in the heart.

The FDA expressed the concern that, because it takes normal and cardiac compromised patients a long time to eliminate tecastemizole from their system, which is known as a long terminal elimination phase, our safety evaluations were not of sufficient duration to provide adequate safety data in patients after the tecastemizole is eliminated. The period of time after elimination is known as tissue steady-state.

Due to SOLTARA's extended terminal elimination phase, the FDA also concluded that we would need to evaluate the concentration of the drug in tissue after prolonged exposure in order to quantify the potential for tecastemizole accumulation in target organs.

In April 2002, we met with the FDA to discuss issues outlined in the "not approvable" letter for SOLTARA. In October 2002, we met with the FDA to discuss initiation of additional preclinical and clinical studies of SOLTARA. Contingent upon favorable results of these preclinical and clinical studies, we expect to include additional preclinical and clinical studies in addition to re-analyzed existing tecastemizole data as part of a proposed amendment to the SOLTARA NDA.

Contingent upon successful completion of additional studies and re-analysis of existing tecastemizole data, we believe that we will be in a position to amend the SOLTARA NDA to seek marketing approval in the first half of 2004. There can be no assurance whether or when we will amend the SOLTARA NDA or, if amended and filed, whether or when SOLTARA will be approved. We do not expect the SOLTARA NDA to receive FDA approval, if at all, before 2005.

XOPENEX® for children six to eleven years old. In January 2002, we received FDA approval for XOPENEX brand levalbuterol HCl inhalation solution for the treatment or prevention of bronchospasm in children six to eleven years old with reversible obstructive airway disease, such as asthma. XOPENEX is marketed for use in a nebulizer at dosage strengths of 0.31 mg and 0.63 mg for pediatric patients. We have marketed XOPENEX inhalation solution at dosage strengths of 0.63 mg and 1.25 mg for patients 12 years of age and older since May 1999.

XOPENEX MDI. In January 2002 we announced initiation of a scale-up and manufacturing collaboration with 3M Drug Delivery Systems Division, referred to in this report as 3M, for a XOPENEX hydrofluoroalkane (HFA) metered-dose inhaler (MDI).

The collaboration combines our short-acting beta-agonist, XOPENEX, and 3M's expertise in manufacturing MDIs, the device most commonly used by patients for the treatment of asthma and

chronic obstructive pulmonary disease, or COPD, using HFA technology. We are currently conducting large-scale clinical

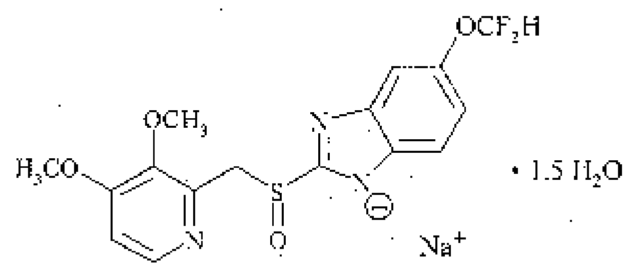
PAGE INTENTIONALLY LEFT BLANK

EXH. W
P. 222

PROTONIX®
(pantoprazole sodium)
Delayed-Release Tablets

DESCRIPTION

The active ingredient in PROTONIX® (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX is supplied as a delayed-release tablet for oral administration. Each delayed-release tablet contains 45.1 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg pantoprazole) with the following inactive ingredients: anhydrous sodium carbonate NF, mannitol USP, crospovidone NF, povidone USP, calcium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, yellow iron oxide NF, propylene glycol USP, methacrylic acid copolymer NF, polysorbate 80 NF, sodium lauryl sulfate NF, and triethyl citrate NF.

PROTONIX®
(pantoprazole sodium)
Delayed-Release Tablets

Information for Patients

Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, or warfarin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day.. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

PROTONIX®
(pantoprazole sodium)
Delayed-Release Tablets

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, , the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy
Teratogenic Effects
Pregnancy Category B
Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

-----BEGIN PRIVACY-ENHANCED MESSAGE-----
Proc-Type: 2001,MIC-CLEAR
Originator-Name: webmaster@www.sec.gov
Originator-Key-Asymmetric:
MFgwCgYEVQgBAQICAf8DSgAwRwJAW2sNKK9AVtBzYZmr6aGjlWyK3XmZv3dTINen
TWSM7vrzLADbmYQaionwg5sDW3P6oaM5D3tdezXMm7z1T+B+twIDAQAB
MIC-Info: RSA-MD5,RSA,
X8vUVQDtLpuG/uXg3Hyj9DyNTHCI7N1t9PG433LV0WUlYcD1MelD1kN15s+evI3y
LpydQlo2yJu4IwX4CglpSA==

<SEC-DOCUMENT>0000005187-99-000005.txt : 19990330
<SEC-HEADER>0000005187-99-000005.hdr.sgml : 19990330
ACCESSION NUMBER: 0000005187-99-000005
CONFORMED SUBMISSION TYPE: 10-K405
PUBLIC DOCUMENT COUNT: 16
CONFORMED PERIOD OF REPORT: 19981231
FILED AS OF DATE: 19990329

FILER:

COMPANY DATA:
COMPANY CONFORMED NAME: AMERICAN HOME PRODUCTS CORP
CENTRAL INDEX KEY: 0000005187
STANDARD INDUSTRIAL CLASSIFICATION: PHARMACEUTICAL PREPARATIONS [2834]
IRS NUMBER: 132526821
STATE OF INCORPORATION: DE
FISCAL YEAR END: 1231

FILING VALUES:
FORM TYPE: 10-K405
SEC ACT:
SEC FILE NUMBER: 001-01225
FILM NUMBER: 99576215

BUSINESS ADDRESS:
STREET 1: 5 GIRALDA FARMS
CITY: MADISON
STATE: NJ
ZIP: 07940
BUSINESS PHONE: 9736605035

MAIL ADDRESS:
STREET 1: 5 GIRALDA FARMS
CITY: MADISON
STATE: NJ
ZIP: 07940
</SEC-HEADER>
<DOCUMENT>
<TYPE>10-K405
<SEQUENCE>1
<TEXT>

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 1998	Commission file number 1-1225

AMERICAN HOME PRODUCTS CORPORATION
(Exact name of registrant as specified in its charter)

Delaware (State or other jurisdiction of incorporation or organization)	13-2526821 (I.R.S. Employer Identification Number)
Five Giralda Farms, Madison, NJ (Address of Principal Executive Offices)	07940-0874 (Zip Code)

Registrant's telephone number, including area code (973) 660-5000

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange On Which Registered
$2 Convertible Preferred Stock, $2.50 par value	New York Stock Exchange
Common Stock, $.33 - 1/3 par value	New York Stock Exchange

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes X No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. [X]

<PAGE>

State the aggregate market value of the voting stock held by nonaffiliates of the registrant. (The aggregate market value shall be computed by reference to the price at which the stock was sold, or the average bid and asked prices of such stock, as of a specified date within 60 days prior to the date of filing).

Aggregate market value at March 15, 1999 $87,622,897,443

Indicate the number of shares outstanding of each of the registrant's classes of common stock, as of the latest practicable date (applicable only to corporate registrants).

	Outstanding at March 15, 1999
Common stock, $0.33 1/3 par value	1,311,375,350

Documents Incorporated by Reference: List hereunder the following documents if incorporated by reference and the part of the Form 10-K into which the document is incorporated: (1) any annual report to security holders; (2) any proxy or information statements; and (3) any prospectus filed pursuant to Rule 424(b) or (c) under the Securities Act of 1933 (the listed documents should be clearly described for identification purposes).

(1) 1998 Annual Report to Shareholders - In Parts I, II and IV
(2) Proxy Statement filed March 26, 1999 - In Part III

<PAGE>

PART I

ITEM 1. BUSINESS

General

American Home Products Corporation (the "Company" or "AHPC"), a Delaware corporation organized in 1926, is currently engaged in the discovery, development, manufacture, distribution and sale of a diversified line of products in three primary businesses: Pharmaceuticals, Consumer Health Care and Agricultural Products. Pharmaceuticals include branded and generic ethical pharmaceuticals, biologicals, antibiotics, and animal biologicals and pharmaceuticals. Principal products include women's health care products, cardiovascular products, neuroscience therapies, anti-inflammatory and gastroenterology drugs, anti-infectives, vaccines, biopharmaceuticals, oncology therapies and infant nutritionals. Principal animal health products include vaccines, pharmaceuticals, endectocides and growth implants. Consumer Health Care products include analgesics, cough/cold/allergy remedies, nutritional supplements including vitamins, minerals and herbal products, and hemorrhoidal, antacid and asthma relief items sold over-the-counter. Agricultural Products include crop protection and pest control products such as herbicides, insecticides, fungicides and plant growth regulators.

In July 1998, the Company purchased the vitamin and nutritional supplement products business of Solgar Vitamin and Herb Company Inc. and its related affiliates ("Solgar") for approximately $495 million in cash.

In February 1998, the Company sold the Sherwood-Davis & Geck medical devices business for approximately $1.770 billion. This transaction completed the Company's exit from the medical devices business.

In December 1997, the Company sold the stock of Storz Instrument Company and affiliated companies, a global manufacturer and marketer of ophthalmic products, and certain related assets for approximately $380 million.

In February 1997, the Company purchased the Hoechst animal health business of Roussel S.A. for approximately $460 million.

In December 1996, the Company purchased the remaining equity interest in the biopharmaceutical company, Genetics Institute, Inc. ("G.I."), that it did not already own for approximately $1.279 billion.

In November 1996, the Company sold a majority interest in the American Home Foods business for approximately $1.503 billion. The Company initially retained a 20% equity interest in International Home Foods, the successor to American Home Foods. During 1998 and 1997, the Company sold its remaining equity interest in International Home Foods.

<PAGE>

In late 1994, the Company purchased the outstanding common stock of American Cyanamid Company ("Cyanamid"). The aggregate purchase price to acquire all of Cyanamid including acquisition-related fees and expenses was approximately $9.6 billion.

Additional information relating to the Solgar, Roussel S.A., and G.I. acquisitions, the Sherwood Davis & Geck, Storz and American Home Foods dispositions, and certain other acquisitions and divestitures is set forth in Notes 2 and 3 of the Notes to Consolidated Financial Statements in the Company's 1998 Annual Report to Shareholders and is

14

<PAGE>
Hemophilia, an inherited blood-clotting disorder, is caused by a deficiency in specialized proteins that promote the normal clotting process. Approximately 40,000 people in North America, Europe and Japan suffer from hemophilia A--the result of a deficiency of the factor VIII protein. Another 8,000 people have hemophilia B, in which the factor IX protein is the missing link in the clotting chain.

Until the early 1980s, human plasma-derived products that carried the possibility of viral transmission were the only therapies available to treat hemophilia, prompting efforts to produce products by recombinant DNA technology. In 1983, the first recombinant factor VIII product, cloned and discovered by Genetics Institute (G.I.), a unit of Wyeth-Ayerst, became the first such treatment commercially available. Not only was it a breakthrough for patients with hemophilia A, but the product represented one of the most significant technical achievements within the biotechnology industry.

In 1997, G.I. again launched a breakthrough recombinant product -- ReFacto Coagulation Factor IX (Recombinant) - which provided hemophilia B patients with the first plasma-free as well as albumin-free treatment option. Now G.I. is planning to introduce ReFacto Antihemophilic Factor (Recombinant) - a second-generation recombinant factor VIII for hemophilia A sufferers, which, unlike other recombinant factor VIII products, is formulated without the use of human serum albumin and reduces the potential for disease from blood-borne viral contamination. FDA and European regulatory review of ReFacto is actively under way.

[PHOTO]

"For several years, I thought I had indigestion. There would be times when I literally couldn't swallow my food. I tried drinking milk or taking antacids, but they provided only temporary relief."

Robert Owen, Age 54

SYNTONIX
RECOVERING FROM REFLUX

For some people, it feels like mild heartburn. Others think they have suffered a heart attack. In actuality, both extremes represent the symptoms of gastroesophageal reflux disease (GERD) -- a condition in which gastric acid flows up from the stomach and damages the lining of the esophagus. The disease interferes with eating and sleeping and tends to dominate almost every aspect of life.

GERD can occur for many reasons, including excess secretion of gastric acid. This acid is produced by "proton pumps" in enzyme system in the cells of the stomach. While the stomach can handle acidic conditions, the esophagus cannot. When the walls of the esophagus are exposed to stomach acid, the result is sour taste, inflammation or irritation and, in severe cases, ulcers or.

In the early 1990s, proton pump inhibitor (PPI) drugs were developed to turn off the final pathway of acid production. Revolutionizing the field of acid control, this class of compounds today is the most effective treatment for GERD symptoms and for the healing of esophageal inflammation.

In mid-1998, Wyeth-Ayerst filed two New Drug Applications with the FDA for a new PPI--Protonix (pantoprazole). Protonix suppresses acid production and has minimal potential for interacting with other medications. Protonix is the first I.V. product in its class that is formulated both in tablet and intravenous form, the latter for patients who cannot take medications orally or who are at increased risk of gastric ulceration and bleeding.

15

<PAGE>
Pneumococcal Conjugate Vaccine

Defending
[Photo of two infants]

Worldwide, more than 1.2 million children under the age of five die as a result of pneumococcal disease. And as pneumococcus bacteria have become increasingly resistant to the antibiotics most commonly used to treat its infection, there is an urgent need for a vaccine effective in infants and young children.

In a Phase III clinical trial involving more than 38,000 children, Wyeth-Ayerst's pneumococcal conjugate vaccine -- which contains the serotypes that have been shown to be most commonly associated with drug resistance -- tested 100 percent effective against very rare "type invasive pneumococcal disease. The special conjugation process used in making this vaccine dramatically enhances its ability to produce high protective levels of antibodies in infants and very young children relative to the current polysaccharide vaccine. This vaccine is formulated to protect against the seven strains of pneumococci that cause approximately 80 percent of invasive pneumococcal disease and 65 percent of pneumococcal otitis media infections among young children in the United States.

With the pivotal clinical trial supporting a 7 license coming ahead of schedule because of these positive results, the FDA granted the vaccine Fast Track regulatory filing status in January 1999. The product license application for meningitis and bacteremia is expected to be completed in May 1999; a supplemental filing is planned for otitis media.

16

PAGE INTENTIONALLY LEFT BLANK

EXH. W
P. 229

XXXXXXX

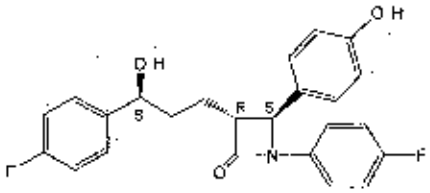
VYTORIN™ 10/10
(EZETIMIBE 10 MG/SIMVASTATIN 10 MG TABLETS)
VYTORIN™ 10/20
(EZETIMIBE 10 MG/SIMVASTATIN 20 MG TABLETS)
VYTORIN™ 10/40
(EZETIMIBE 10 MG/SIMVASTATIN 40 MG TABLETS)
VYTORIN™ 10/80
(EZETIMIBE 10 MG/SIMVASTATIN 80 MG TABLETS)

DESCRIPTION

VYTORIN contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

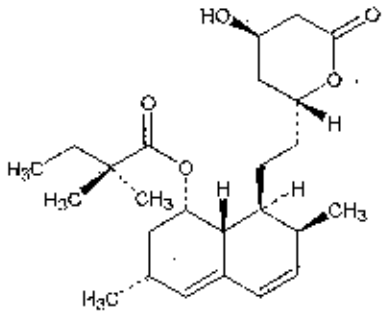
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:



Simvastatin, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57.

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Its structural formula is:



VYTORIN is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20), 40 mg of simvastatin (VYTORIN 10/40), or 80 mg of simvastatin (VYTORIN 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.

EXH. W
P. 230

vitro in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis

<DOCUMENT>
<TYPE>8-K
<SEQUENCE>1
<FILENAME>y99243e8vk.txt
<DESCRIPTION>FORM 8-K
<TEXT>
<PAGE>

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

JULY 21, 2004
Date of Report (Date of Earliest Event Reported)

SCHERING-PLOUGH CORPORATION
(Exact name of registrant as specified in its charter)

NEW JERSEY	1-6571	22-1918501
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification Number)

2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033
(Address of principal executive offices, including Zip Code)

(908) 298-4000
(Registrant's telephone number, including area code)

<PAGE>
ITEM 5. OTHER EVENTS AND REGULATION FD DISCLOSURE

2004 Second Quarter Earnings Press Release

Schering-Plough issued a press release titled "Schering-Plough Reports Financial Results for 2004 Second Quarter" on July 21, 2004, and the press release is attached to this 8-K as Exhibit 99.1. Schering-Plough also issued related Supplemental Data, which is attached to this 8-K as Exhibit 99.2.

Disclosure Notice for Forward Looking Statements

Cautionary Factors That May Affect Future Results (Cautionary Statements Under the Private Securities Litigation Reform Act of 1995)

This 8-K, including each exhibit, the comments of Schering-Plough officers during our earnings teleconference/webcast on July 21, 2004 at 7:00 am (EDT), and other written reports and oral statements made from time to time by the company may contain "forward-looking statements" within the meaning of the Securities Litigation Reform Act of 1995. Forward-looking statements relate to expectations or forecasts of future events. They use words such as "anticipate," "believe," "could," "estimate," "expect," "forecast," "project," "intend," "plan," "potential," "will," and other words and terms of similar meaning in connection with a discussion of potential future events, circumstances or future

operating or financial performance. You can also identify forward-looking statements by the fact that they do not relate strictly to historical or current facts.

In particular, forward-looking statements include statements relating to future actions, ability to access the capital markets, prospective products, the status of product approvals, future performance or results of current and anticipated products, sales efforts, development programs, expenses and programs to reduce expenses, the cost of and savings from reductions in work force, the outcome of contingencies such as litigation and investigations, growth strategy and financial results.

Any or all forward-looking statements here or in other publications may turn out to be wrong. Actual results may vary materially, and there are no guarantees about Schering-Plough's financial and operational performance or the performance of Schering-Plough stock. Schering-Plough does not assume the obligation to update any forward-looking statement.

Many factors could cause actual results to differ from Schering-Plough's forward-looking statements. These factors include inaccurate assumptions and a broad variety of other risks and uncertainties, including some that are known and some that are not. Although it is not possible to predict or identify all such factors, they may include the following:

- A significant portion of net sales are made to major pharmaceutical and health care products distributors and major retail chains in the United States. Consequently, net sales and quarterly growth comparisons may be affected by fluctuations in the buying patterns of major distributors, retail chains and other trade buyers. These fluctuations may result from seasonality, pricing, wholesaler buying decisions or other factors.

- Competitive factors, including technological advances attained by competitors, patents granted to competitors, new products of competitors coming to the market, new indications for competitive products or generic prescription or OTC competition as Schering-Plough's products mature and patents expire on products.

<PAGE>

- Increased pricing pressure both in the United States and abroad from managed care organizations, institutions and government agencies and programs. In the United States, among other developments, consolidation among customers may increase pricing pressures and may result in various customers having greater influence over prescription decisions through formulary decisions and other policies.

- The potential impact of the Medicare Prescription Drug, Improvement and Modernization Act of 2003; possible other U.S. legislation or regulatory action affecting, among other things, pharmaceutical pricing and reimbursement, including Medicaid and Medicare, involuntary approval of prescription medicines for over-the-counter use; and other health care reform initiatives and drug importation legislation. Legislation or regulations in markets outside the U.S. affecting product pricing, reimbursement or access. Laws and regulations relating to trade, antitrust, monetary and fiscal policies, taxes, price controls and possible nationalization.

- Patent positions can be highly uncertain and patent disputes are not unusual. An adverse result in a patent dispute can preclude commercialization of products or negatively impact sales of existing products or result in injunctive relief and payment of financial remedies.

- Uncertainties of the FDA approval process and the regulatory approval and review processes in other countries, including, without limitation, delays in approval of new products.

- Failure to meet Good Manufacturing Practices established by the FDA and other governmental authorities can result in delays in the approval of products, release of products, seizure or recall of products, suspension or revocation of the authority necessary for the production and sale of products, fines and other civil or criminal sanctions. The resolution of manufacturing issues with the FDA discussed in Schering-Plough's 10-Ks, 10-Qs and 8-Ks are subject to substantial risks and uncertainties. These risks and uncertainties, including the timing, scope and duration of a resolution of the manufacturing issues, will depend on the ability of Schering-Plough to assure the FDA of the quality and reliability of its manufacturing systems and controls, and the extent of remedial and prospective obligations undertaken by Schering-Plough.

- Difficulties in product development. Pharmaceutical product development is highly uncertain. Products that appear promising in development may fail to reach market for numerous reasons. They may be found to be ineffective or to have harmful side effects in clinical or pre-clinical testing, they may fail to receive the necessary regulatory approvals, they may turn out not to be economically feasible because of manufacturing costs or other factors or they may be precluded from commercialization by the proprietary rights of others.

- Efficacy or safety concerns with respect to marketed products, whether or not scientifically justified, leading to recalls, withdrawals or declining sales.

- Major products such as CLARITIN, CLARINEX, INTRON A, PEG-INTRON, REBETOL Capsules, REMICADE and NASONEX accounted for a material portion of Schering-Plough's 2003 revenues. If any major product were to become subject to a problem such as loss of patent protection, OTC availability of the Company's product or a competitive product (as has been disclosed for CLARITIN and its current and potential OTC competition), previously unknown side effects; if a new, more effective treatment should be introduced; generic availability of competitive products; or if the product is discontinued for any reason, the impact on revenues could be significant. Also, such

<PAGE>

information about important new products, such as ZETIA, or important products in our pipeline such as VYTORIN, may impact future revenues.

- Unfavorable outcomes of government (local and federal, domestic and international) investigations, litigation about product pricing, product liability claims, other litigation and environmental concerns could preclude commercialization of products, negatively affect the profitability of existing products, materially and adversely impact Schering-Plough's financial condition and results of operations, or contain conditions that impact business operations, such as exclusion from government reimbursement programs.

- Economic factors over which Schering-Plough has no control, including changes in inflation, interest rates and foreign currency exchange rates.

- Instability, disruption or destruction in a significant geographic region - due to the location of manufacturing facilities, distribution facilities or customers - regardless of cause, including war, terrorism, riot, civil insurrection or social unrest; and natural or man-made disasters,

including famine, flood, fire, earthquake, storm or disease.

- Changes in tax laws including changes related to taxation of foreign earnings.

- Changes in accounting standards promulgated by the American Institute of Certified Public Accountants, the Financial Accounting Standards Board or the SEC, or the Public Company Accounting Oversight Board that would require a significant change to Schering-Plough's accounting practices.

For further details and a discussion of these and other risks and uncertainties that may impact Schering-Plough's forward looking statements, see Schering-Plough's past and future SEC filings.

ITEM 7. FINANCIAL STATEMENTS AND EXHIBITS

(c) Exhibits. The following exhibits are filed with this 8-K:

99.1 Press release titled "Schering-Plough Reports Financial Results for 2004 Second Quarter"

99.2 Supplemental Financial Data

ITEM 12. RESULTS OF OPERATIONS AND FINANCIAL CONDITION

Schering-Plough today issued a press release titled "Schering-Plough Reports Financial Results for 2004 Second Quarter" and provided additional supplemental financial data. The press release is attached to this 8-K as Exhibit 99.1. The supplemental financial data is attached to this 8-K as Exhibit 99.2.
<PAGE>

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Schering-Plough Corporation

By: /s/Douglas J. Gingerella
Douglas J. Gingerella
Vice President and Controller

Date: July 21, 2004
<PAGE>
Exhibit Index

The following exhibits are filed with this 8-K:

99.1 Press release titled "Schering-Plough Reports Financial Results for 2004 Second Quarter"

99.2 Supplemental Financial Data

</TEXT>
</DOCUMENT>

<DOCUMENT>
<TYPE>EX-99.1
<SEQUENCE>2
<FILENAME>y99243exv99w1.txt
<DESCRIPTION>PRESS RELEASE
<TEXT>
<PAGE>

Exhibit 99.1

[Logo Schering-Plough]

News Release

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

FOR RELEASE: IMMEDIATELY

Media Contact: Steve Galpin, Jr.
(908) 298-7415
Investor Contacts: Alex Kelly
Lisa M. DeBernardine
Janet M. Barth
(908) 298-7436

SCHERING-PLOUGH REPORTS FINANCIAL RESULTS FOR 2004 SECOND QUARTER

KENILWORTH, N.J., July 21, 2004 - Schering-Plough Corporation (NYSE: SGP) today reported financial results for the 2004 second quarter, including lower comparative sales and earnings versus the 2003 period. The financial results reflect difficult comparisons with the year-ago period and were affected by several factors, including: lower sales for certain key profit-generating products and the impact from the loss of U.S. exclusivity on REBETOL for hepatitis C; an expense related to a licensing agreement for a new antibiotic in development; the absence of INTRON A revenues; higher interest expense from the long-term debt issued in the 2003 fourth-quarter; investments in sales and marketing support; additional spending in connection with Food and Drug Administration (FDA) consent decree, compliance and quality-system obligations; and costs associated with efforts to reduce overall payroll and related expenses.

"Second quarter results are consistent with the tough financial comparisons we expected for 2004," said Fred Hassan, Schering-Plough chairman and CEO. "While we still expect 2004 to be a difficult year and for earnings - excluding unusual items - to be below those of 2003, we are also starting to see some early signs of sequential stabilization versus the prior quarter. We are encouraged by the continuing steady growth of ZETIA for high cholesterol. And we are looking forward to the U.S. approval and launch of our cholesterol-lowering agent VYTORIN, which will offer patients a powerful new treatment option for high cholesterol. The potential of this exciting product may also benefit from the new and more aggressive cholesterol-lowering recommendations just issued by health experts for patients at high risk of heart attacks. We have said that VYTORIN will be pivotal to achieving our anticipated turnaround beginning in 2005, so its U.S. approval will mark an important event for this company."

<PAGE>

VYTORIN (ezetimibe/simvastatin) is a new cholesterol-lowering therapy being developed and marketed in partnership with Merck & Co., Inc. VYTORIN contains ZETIA (ezetimibe), a cholesterol-absorption inhibitor discovered by Schering-Plough, and Merck's Zocor (simvastatin) statin product in a single tablet. The dual-inhibition product has been approved for marketing in several countries, including Germany and Mexico. Clinical trials have shown that patients taking ezetimibe with simvastatin achieved significantly greater reductions in LDL cholesterol across the dosing ranges studied than leading statin therapies. As a result, VYTORIN is expected to be well positioned to compete in the critical and growing high-efficacy space of the cholesterol-lowering market, especially now with new recommendations for even lower LDL cholesterol goals.

"Physicians' positive experience with ZETIA is generating enthusiasm in the marketplace," Hassan added. "With our partner Merck, we look forward to a successful launch of VYTORIN in the world's largest pharmaceutical market and the world's largest treatment category."

Hassan said Schering-Plough is relentlessly pursuing cost reductions in conjunction with its drive to upgrade the company's global infrastructure in facilities, technologies and organizational terms. "We have achieved the goal we set for ourselves with the Value Enhancement Initiative," said Hassan, "and we're continuing to look for ways to extract costs that can be reinvested more productively elsewhere." Announced in August 2003, the VEI program was designed to increase efficiencies and achieve annual savings in excess of $200 million that can then be reinvested. Savings are being reinvested in growth-driving priorities in research, manufacturing and compliance, licensing and other opportunities, and in strengthening the company's sales forces to prepare for the global launch of VYTORIN.

EXH. W
P. 236

"Although we still face considerable challenges, I am pleased with the overall progress we are making," added Hassan. "We are working through the Stabilization and Repair phases of our five-stage Action Agenda and continue to look forward to a turnaround anticipated to begin in 2005. Our commitment to business integrity, quality and compliance remains at the center of this strategy."

Second Quarter 2004 Results

Schering-Plough reported a loss for the 2004 second quarter of $60 million or 4 cents in diluted earnings per share compared with net income of $162 million and diluted earnings per share of 12 cents in the 2003 period. The company recorded a charge to R&D expense in the 2004 second quarter of $80 million, or 4 cents per diluted share (as measured using the company's effective tax rate), related to an upfront payment in conjunction with the licensing from Toyama Chemical Co. Ltd. of garenoxacin, a quinolone antibiotic in development. Special charges in the 2004 second quarter totaled $42 million or

-2-

<PAGE>

2 cents per diluted share (as measured using the company's effective tax rate). The special charges related to employee-termination costs stemming from reductions in the company's global workforce.

Second quarter 2004 net sales of $2.1 billion were 7 percent lower than the $2.3 billion in the 2003 period and included a favorable foreign exchange impact of 5 percent. Second quarter sales of Prescription Pharmaceuticals totaled $1.6 billion, down 12 percent, while Consumer Health Care sales rose 19 percent to $317 million and Animal Health sales grew 9 percent to $196 million. Consolidated U.S. net sales were $837 million, down 21 percent, and net sales outside the United States were $1.3 billion, up 5 percent, including a 6 percent favorable impact from foreign exchange and the seasonal aspect of the allergy business. Outside the United States, sales for the second quarter of 2004 reflected unfavorable comparisons due to the absence of LOSEC revenues in Europe, as the company's agreement with AstraZeneca ended in the 2003 third quarter; LOSEC revenues in the 2003 second quarter were $39 million.

Global cholesterol franchise sales, which include ZETIA and VYTORIN, totaled $247 million in the 2004 second quarter compared with sales of $173 million in the comparable 2003 period. ZETIA has now been approved in 65 countries. In the United States, more than 9 million prescriptions have been written for the product since its U.S. launch in November 2002, according to IMS Health. The company utilizes the equity method of accounting for its cholesterol joint venture with Merck. Under the equity method, the company records its share of the operating profits less its share of the research and development costs in "Equity income from cholesterol joint venture." U.S. ZETIA sales exceeded a pre-defined annual sales level, as stipulated in the joint venture contract, during the second quarter of 2004. As a result, profit from U.S. sales of ZETIA will be split 50/50 for the remainder of the year, down from a previously higher profit split. "Equity income from cholesterol joint venture" for Schering-Plough totaled $77 million in the 2004 second quarter. Operating profit excludes the cost of the company's sales forces throughout the world. The company noted that it incurs substantial costs, such as selling, general and administrative costs, that are not reflected in the "Equity income from cholesterol joint venture" and are borne by the overall cost structure of Schering-Plough.

Prescription Pharmaceuticals sales in the 2004 second quarter reflected a significant decline in sales for the company's hepatitis C products versus the year-ago period, as expected, due to ongoing competition in a market that has been contracting. Global sales of PEG-INTRON were down 42 percent to $144 million. Sales of REBETOL were down 55 percent to $98 million due to branded competition and the 2004 second quarter launch of U.S. generic competition, which is expected to result in sharply reduced REBETOL sales going forward. The company has been successful in gaining acceptance by physicians and patients of its new PEG-INTRON REDIPEN precision-dosing pen for hepatitis C patients following the product's February launch in the U.S. market.

-3-

<PAGE>

The company's allergy franchise continued to face intense competitive pressures in the United States. Second quarter 2004 global CLARINEX sales were $226 million, up 3 percent. Sales outside the United States climbed 38 percent to $100 million in the second quarter due to market share gains and continued conversion from prescription CLARITIN. U.S. sales declined 13 percent to $126 million due to the continued contraction in the U.S. prescription antihistamine market, stemming from the late-2002 introduction of over-the-counter (OTC) CLARITIN and other branded and non branded nonsedating antihistamines, coupled with market share declines. Global NASONEX sales were down 11 percent to $156 million primarily due to trade buying patterns in 2003 coupled with a decline in U.S. market share. In international markets, NASONEX sales of $57 million were 18 percent higher due to market share gains and market growth.

Leading the prescription products recording higher sales in the 2004 second quarter was REMICADE, a treatment for immune-mediated inflammatory disorders

that Schering-Plough markets in countries outside the United States (excluding Japan and certain Far East markets) for rheumatoid arthritis, Crohn's disease and ankylosing spondylitis. REMICADE sales in the 2004 second quarter rose 44 percent to $162 million, benefiting from greater medical use and expanded indications. Oncology products posting higher sales in the quarter included TEMODAR, a treatment for certain types of brain tumors, up 17 percent to $102 million; and CAELYX, for the treatment of ovarian cancer, metastatic breast cancer and Kaposi's sarcoma, up 34 percent to $35 million. Sales of SUBUTEX, a treatment for opiate addiction sold in certain countries outside the United States, rose 3 percent to $47 million.

In Consumer Health Care, sales rose 19 percent to $317 million in the second quarter. Sales of OTC CLARITIN rose 22 percent to $117 million in the second quarter primarily due to trade inventory adjustments in the second quarter of 2003. Sun care sales rose 60 percent to $79 million due to the timing of orders and shipments, coupled with favorable weather conditions. Sales of foot care products rose 7 percent to $89 million.

Sales of Animal Health products totaled $186 million in the second quarter of 2004, up 9 percent, including a favorable foreign exchange impact of 6 percent.

The company's ratio of gross margin to sales was 62.2 percent for the 2004 second quarter versus 66.0 percent in the 2003 period. The lower ratio was primarily due to: lower production volumes coupled with increased spending related to the SUA consent decree and efforts to upgrade the company's global infrastructure; an unfavorable change in product sales mix (primarily higher sales of lower-margin products); and the absence of European LOSEC revenues. On a sequential basis, the company noted that the second quarter gross margin ratio was consistent with the prior quarter after factoring in the impact of seasonality with respect to CLARINEX sales. Schering-Plough said its

ongoing focus on operational excellence in all key functions, including compliance and quality, continues to increase the overall cost structure of the company.

Selling, general and administrative expenses rose 4 percent to $975 million in the second quarter of 2004, primarily reflecting the expansion of the field force to prepare for the VYTORIN launch as well as the impact of foreign exchange.

Research and development spending for the second quarter totaled $461 million, up 22 percent, including the $80 million milestone payment related to the Toyama agreement.

The "other, net" line reflects higher net interest expense from increased borrowings including higher borrowing costs associated with the long-term debt issued in the 2003 fourth quarter. As of June 30, 2004, the estimated annual effective tax rate was approximately 20 percent.

Recent Developments

The company also reviewed recent significant developments, including:

- European Union approval in June of REMICADE as first-line therapy for the treatment of early rheumatoid arthritis in combination with methotrexate.
- New Drug Application (NDA) for posaconazole oral suspension accepted for filing in July by the FDA for the treatment of certain invasive fungal infections in patients 13 years of age and older. The NDA was submitted to FDA in May.
- Definitive license agreement reached in June with Toyama Chemical Co. Ltd. for garenoxacin, Toyama's proprietary quinolone antibacterial agent in late stage development. Under the agreement, Toyama granted Schering-Plough exclusive rights to develop, own and sell garenoxacin worldwide, excluding Japan, Korea and China.
- Positive clinical results reported in June at the American Society of Clinical Oncology on TEMODAR (temozolomide) in increasing survival rates when used with radiation as first-line treatment in patients with glioblastoma multiforme, a common and aggressive form of brain cancer.
- Positive opinion issued in June by European Medicines Agency recommending approval of a shorter 24-week course of PEG-INTRON and REBETROL combination therapy for patients chronically infected with hepatitis C virus genotypes 2 or 3.
- In light of changing research and development priorities, a decision was made to seek outside partners for the future development of a pure anti-estrogen. Post-menopausal studies in Phase II had been on hold pending the outcome of FDA guidance on hormone replacement therapy products. This agent will no longer appear on the company's published Product Pipeline.

EXH. W
P. 238

<PAGE>

- Agreement reached in June with the U.S. Securities and Exchange Commission (SEC) to settle issues related to compliance with the books and records and internal accounting control provisions of the U.S. Foreign Corrupt Practices Act by a Schering-Plough subsidiary in Poland.

- Agreement reached in May with the Attorney General's Office of the State of Texas to settle issues related to reimbursement by Texas' Medicaid program of albuterol sulfate solution and inhaler asthma products.

- Moody's Investor Service on July 14 lowered its long-term senior unsecured credit rating on the company from "A3" to "Baa1" and confirmed its short-term credit rating of "Prime-2." Moody's reported that the company's ratings outlook is negative.

Second Quarter 2004 Conference Call and Webcast

Schering-Plough will conduct a conference call today at 7 a.m. (EDT) to review the second quarter results. To listen live to the call, dial 1-706-634-5223. A replay of the call will be available starting at approximately 10 a.m. on July 21 through 5 p.m. on July 23. To listen to the replay, dial 1-706-645-9291 and enter the conference ID #3994435.

A live audio webcast of the conference call also will be available to all interested parties by going to the Investor Relations section of the Schering-Plough corporate Web site, www.schering-plough.com, and clicking on the "Presentations/Webcasts" link. A replay of the webcast will be available starting at approximately 1 p.m. on July 21 through 5 p.m. on July 28.

DISCLOSURE NOTICE: The information in this press release includes certain "forward-looking" statements relating to the company's upstream prospects, earnings outlook, anticipated turnaround and resulting growth prospects, and savings goals relating to productivity and efficiency initiatives. Actual results may differ materially from forward-looking statements due to a number of risks and uncertainties, including the market visibility of the company's marketed and pipeline products, including the current and pipeline products in the company's joint venture with Merck; possible changes in business strategies and the ability to successfully implement those business strategies; general market and economic factors; competitive product development; market acceptance of new products; product availability; current and future branded, generic or OTC competition; federal and state regulations and legislation; the research and regulatory processes for new products and indications; existing and new manufacturing issues that may arise; trade buying patterns; patent positions; litigation and investigations; and instability or destruction in a geographic area important to the company due to reasons such as war. For further details and a discussion of these and other risks and uncertainties, see the company's past and future Securities and Exchange Commission filings,

<PAGE>

including the company's 8-K being filed today. The company does not assume any obligation to update any forward-looking statements.

Schering-Plough is a global science-based health care company with leading prescription, consumer and animal health products. Through internal research and collaborations with partners, Schering-Plough discovers, develops, manufactures and markets advanced drug therapies to meet important medical needs. Schering-Plough's vision is to earn the trust of the physicians, patients and customers served by its more than 30,000 people around the world.

# # #

53 0704

<PAGE>

SCHERING-PLOUGH CORPORATION

Report for the second quarter ended June 30 (unaudited):
(Amounts in millions, except per share figures)

<TABLE>
<CAPTION>
<S> <C> <C> <C> <C> <C> <C>

EXH. W
P. 239

	Second Quarter			Six Months		
	2004	2003	%	2004	2003	%
Net Sales	$ 2,147	$ 2,308	(7)	$ 4,110	$ 4,369	(6)
Cost of Sales	793	794	1	1,530	1,442	6
Selling, General and Administrative	979	938	4	1,893	1,780	6
Research and Development a/	451	369	22	824	691	19
Other, Net	43	(4)	N/M	70	8	N/M
Special Charges b/	42	20	N/M	112	20	N/M
Equity (Income)/Loss from Cholesterol Joint Venture	(77)	(26)	N/M	(154)	4	N/M
(Loss)/Income Before Income Taxes ..	(81)	227	N/M	(173)	444	N/M
Income Tax Benefit/(Expense)	16	(45)	N/M	35	(89)	N/M
Net (Loss)/Income	$ (65)	$ 182	N/M	$ (138)	$ 355	N/M
Diluted (Loss)/Earnings per Common Share	$ (0.04)	$ 0.12	N/M	$ (0.09)	$ 0.24	N/M
Effective Tax Rate	20.0%	20.0%		20.3%	20.0%	
Average Common Shares Outstanding - Diluted	1,472	1,471		1,471	1,471	
Actual Number of Common Shares Outstanding at June 30	1,472	1,469		1,472	1,469	

</TABLE>

N/M - Not a meaningful percentage

a/ Research and development in the second quarter 2004 and first six months of 2004 includes an $80 million upfront payment in conjunction with the licensing from Toyama Chemical Company LTD. of garenoxacin, a quinolone antibiotic in development.

b/ Special Charges for the second quarter ended June 30, 2004 included $42 million of employee termination costs. Special charges for the six months ended June 30, 2004 included $86 million of employee termination costs and $26 million of asset impairment charges primarily related to the company's anticipated exit from a small European research and development facility. Special Charges for 2003 included $20 million of asset impairment charges related to manufacturing facility assets.

The Company noted that it incurs substantial costs, such as selling, general and administrative costs, that are not reflected in the "Equity income from cholesterol joint venture" and are borne by the overall cost structure of Schering-Plough.

-6-

<PAGE>

SCHERING-PLOUGH CORPORATION

Report for the second quarter ended June 30 (continued):

Net Sales by Major Product:
(Dollars in Millions)

<TABLE>
<CAPTION>

<S>	<C>	<C>	<C>	<C>	<C>	<C>
	Second Quarter			Six Months		
	2004	2003	%	2004	2003	%
GLOBAL PHARMACEUTICALS	$1,544	$1,871	(17)	$3,135	$3,517	(11)
Clarinex / Aerius	225	219	3	356	392	(9)
Remicade	182	120	66	347	240	45
Nasonex	156	175	(11)	296	253	17
PEG-Intron	144	247	(42)	293	469	(38)
Temodar	102	87	17	188	146	28
Intron A	89	125	(29)	158	199	(21)
Rebetol	88	196	(55)	187	415	(55)
Claritin Rx *	82	90	(9)	173	179	(5)

EXH. W
P. 240

Integrilin	78	92	(15)	151	161	(6)
Subutex	47	36	31	91	66	37
Elocon	46	41	13	84	80	5
Caelyx	35	26	34	70	49	43
CONSUMER HEALTH CARE	317	288	10	629	559	12
OTC	150	135	11	286	291	(2)
OTC Claritin	77	67	22	234	255	(8)
FOOT CARE	89	83	7	166	145	14
SUN CARE	78	99	(21)	157	123	28
ANIMAL HEALTH	85	171	(50)	356	313	14
CONSOLIDATED NET SALES	$2,147	$2,303	(7)	$4,110	$4,389	(6)

</TABLE>

* Includes international sales of Claritin Rx only. Canadian sales of Claritin are now reported in the OTC Claritin line within Consumer Health Care. The prior period has been reclassified accordingly.

Global cholesterol franchise sales, which include Zetia and Vytorin, totaled $297 million in the 2Q11 second quarter and $436 million for the six month period.

NOTE: Certain prior period amounts have been reclassified to conform to the current year presentation.

Additional information about U.S. and international sales for specific products is available by calling the company or visiting the investor relations Web site at http://ir.schering-plough.com.

# # #

-5-

</TEXT>
</DOCUMENT>

FORM 8-K

Merck & Co. Inc. - MRK

Filed: March 15, 2004 (period: March 15, 2004)

Report of unscheduled material events or corporate changes.

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the

Securities Exchange Act of 1934

March 15, 2004

Date of Report (Date of Earliest Event Reported)

Schering-Plough Corporation

(Exact name of registrant as specified in its charter)

New Jersey	1-6571	22-1918501
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification Number)

2000 Galloping Hill Road
Kenilworth, NJ 07033

(Address of principal executive offices, including Zip Code)

(908) 298-4000

(Registrant's telephone number, including area code)

Item 7. Financial Statements and Exhibits

(c) Exhibits. The following exhibits are filed with this 8-K:

99.1 Press Release issued by MERCK/Schering-Plough Pharmaceuticals on March 8, 2004 titled "Ezetimibe with Simvastatin Provided Significantly Greater Reductions in LDL Cholesterol Compared to Lipitor and Zocor Across Dosing Ranges, New Studies Showed"

99.2 Press Release issued by MERCK/Schering-Plough Pharmaceuticals on March 10, 2004 titled "Adding ZETIA to Statin Therapy Produced Significant Reductions in LDL-Cholesterol in Community-Based Trial of More Than 3,900 Patients"

99.3 March 15, 2004 Investor Frequently Asked Questions and Answers

Item 9. Regulation FD Disclosure

Schering-Plough is filing several press releases and investor frequently asked questions (FAQs) about the products ZETIA and VYTORIN as exhibits to this 8-K. The press releases and FAQs are also available on Schering-Plough's Web site at www.schering-plough.com.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Schering-Plough Corporation

By: /s/ Robert J. Bertolini

Robert J. Bertolini

Executive Vice President and

Chief Financial Officer

Date: March 15, 2004

Exhibit Index

The following exhibit is filed with this 8-K:

99.1 Press Release issued by MERCK/Schering-Plough Pharmaceuticals on March 8, 2004 titled "Ezetimibe with Simvastatin Provided Significantly Greater Reductions in LDL Cholesterol Compared to Lipitor and Zocor Across Dosing Ranges, New Studies Showed"

99.2 Press Release issued by MERCK/Schering-Plough Pharmaceuticals on March 10, 2004 titled "Adding ZETIA to Statin Therapy Produced Significant Reductions in LDL-Cholesterol in Community-Based Trial of More Than 3,000 Patients"

99.3 March 15, 2004 Investor Frequently Asked Questions and Answers

Exhibit 99.1

MERCK / Schering-Plough Pharmaceuticals

News Release

Media Contacts:	Chris Loder	Investor Contact:	Mark Stejbach
	Merck & Co., Inc.		Merck & Co., Inc.
	908/423-3786		908/423-5185
	(Cell) 908/347-4949		
	Skip Irvine		Lisa DeBerardine
	Merck & Co., Inc.		Schering-Plough Corp.
	267/305-5397		908/298-7436
	(Cell) 215/806-6757		
	Denise Foy		Janet Barth
	Schering-Plough Corp.		Schering-Plough Corp.
	908/298-7616		908/298-7436
	(Cell) 908/670-0495		

Ezetimibe with Simvastatin Provided Significantly Greater Reductions in LDL Cholesterol Compared to Lipitor® and Zocor® Across Dosing Ranges, New Studies Showed

Ezetimibe with Simvastatin Provided LDL-C Reductions Ranging from 46 to 61 Percent

NEW ORLEANS, March 8, 2004 -- Results from Phase III clinical trials showed that patients taking ezetimibe with simvastatin experienced significantly greater reductions in LDL ("bad") cholesterol across the dosing ranges studied compared to reductions seen in patients taking Lipitor® (atorvastatin) or Zocor® (simvastatin), alone. Results from the studies, conducted in support of VYTORIN (ezetimibe/simvastatin), an investigational medicine, were presented here today at the 53rd Annual Scientific Meeting of the American College of Cardiology (ACC). Ezetimibe and simvastatin, the active ingredients in VYTORIN, achieve dual inhibition of two sources of cholesterol by inhibiting both cholesterol production in the liver and cholesterol absorption in the intestine.

"Results from these studies showed that ezetimibe with simvastatin provided significantly greater reductions in LDL cholesterol compared to atorvastatin or simvastatin alone. These results suggest that, if approved, this investigational medicine would offer physicians a different

treatment option which targets two sources of cholesterol through dual inhibition of both cholesterol production and absorption," said Christie Ballantyne, M.D., FACC, FACP, director of the Center for Cardiovascular Disease Prevention and professor of medicine at Baylor College

of Medicine/The Methodist DeBakey Heart Center in Houston.

- more -

Study Results

Ezetimibe with simvastatin provided greater LDL-C reductions compared to Lipitor

Results from a 24-week, 788-patient study of ezetimibe 10 mg taken with simvastatin (doses ranging from 10 mg to 80 mg) compared to atorvastatin monotherapy (doses ranging from 10 mg to 80 mg) showed significantly greater LDL-C reductions in patients taking ezetimibe with simvastatin compared to patients taking atorvastatin alone across the dosing ranges. The average LDL-C levels at baseline across treatment groups ranged from 179 mg/dL to 181 mg/dL.

The primary endpoint of this study was the efficacy comparison after the first six-week treatment period. After six weeks of therapy, patients taking ezetimibe 10 mg with simvastatin 10 mg and patients taking ezetimibe 10 mg with simvastatin 20 mg experienced greater LDL-C reductions (46 percent and 50 percent, respectively) compared to atorvastatin 10 mg, which produced a 37 percent reduction (p<0.01 for each versus atorvastatin). In addition, as each treatment group was titrated through the dosing ranges (by doubling the respective statin dose up to a maximum of 80 mg), ezetimibe with simvastatin consistently provided greater LDL-C reductions than atorvastatin at all points in the treatment period.

Study patients underwent a four-week diet/placebo run-in period and were then randomized to three treatment groups, each of which underwent four sequential, six-week treatment periods: (1) atorvastatin 10 mg in Period One, titrated to A20 mg, A40 mg, and
A80 mg in Periods Two through Four (n=262); (2) ezetimibe with simvastatin 10 mg (10/10) in Period One, titrated to EZE/S20 mg (10/20), EZE/S40 mg (10/40), and EZE/S80 mg (10/80) in Periods Two through Four (n=263); and (3) ezetimibe with simvastatin 20 mg (10/20) in Period One, titrated to EZE/S40 (10/40) mg for Periods Two and Three, then EZE/S80 mg (10/80) in Period Four (n=263).

Results from this study also showed greater mean HDL-C increases across the treatment periods in patients taking ezetimibe with simvastatin (mean of 10 percent, range
8 to 12 percent) compared to patients taking atorvastatin alone (mean of 6 percent, range 5 to 8 percent).

Ezetimibe with simvastatin was well tolerated and had an overall safety profile similar to atorvastatin monotherapy in the study; there were no clinically or statistically significant

differences in the incidence of muscle enzyme elevations (5 to10 times or more than 10 times the upper limit of normal) or consecutive liver enzyme elevations (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] more than 3 times the upper limit of normal).

Ezetimibe with simvastatin provided greater LDL-C reductions compared to Zocor

In another study, patients taking ezetimibe with simvastatin experienced significantly greater LDL-C reductions across the doses tested compared to Zocor (simvastatin) alone.

- more -

Ezetimibe 10 mg with simvastatin 20 mg achieved a 51 percent LDL-C reduction compared to reductions of 35 percent and 42 percent, respectively, for simvastatin 20 mg and 40 mg
(typical starting doses for simvastatin) alone. In pooled results across the dosing ranges, patients taking ezetimibe with simvastatin experienced significantly greater LDL cholesterol reductions ranging from 46 to 61 percent compared to 31 to 46 percent reductions seen with simvastatin alone across the dosing ranges.

This multi-center, double-blind, randomized, placebo-controlled trial was conducted over 12 weeks. After a four-week placebo/diet run-in, 887 patients with LDL-C 145 mg/dL to
250 mg/dL and triglyceride levels at or below 350 mg/dL were randomized to one of 10 daily treatments: placebo (n=93); ezetimibe 10 mg (n=92); simvastatin 10, 20, 40, or 80 mg (n=349); ezetimibe 10 mg with simvastatin 10, 20, 40, or 80 mg (n=353).

Co-administration of ezetimibe with simvastatin was well tolerated and had an overall safety profile similar to that of simvastatin monotherapy in the study. There were more (6 vs. 0) cases of asymptomatic, consecutive elevations (more than 3 times the upper limit of normal) of aminotransferases with ezetimibe with simvastatin compared to simvastatin alone. In patients for whom follow-up testing could be obtained (five out of six), transaminase elevations remained asymptomatic and returned to baseline after treatment was discontinued as called for by study design.

VYTORIN (ezetimibe/simvastatin) provided greater reductions in remnant lipoproteins compared to Zocor

A similar, 12-week study compared the effects of the single tablet VYTORIN (ezetimibe/simvastatin) versus Zocor (simvastatin) pooled across the dosing ranges. After a four-week diet/placebo run-in period, 1,528 patients with LDL-C 145 mg/dL to 250 mg/dL and triglyceride levels at or below 350 mg/dL were randomized to one of ten treatment groups: placebo (n=141), ezetimibe 10 mg (n=144), simvastatin 10, 20, 40, or 80 mg (n=597), and VYTORIN (ezetimibe/simvastatin) 10/10, 10/20, 10/40, and 10/80 mg (n=570).

The objective of this analysis was to examine the effects of VYTORIN (ezetimibe/simvastatin) on remnant-like-particle cholesterol (RLP-C). The study's primary endpoint was percentage change from baseline LDL-C.

"Preliminary evidence suggests that the level of cholesterol-rich remnant lipoproteins or RLP-C may be an independent factor in assessing coronary risk," said Harold E. Bays, M.D., FACP, medical director/president of the Louisville Metabolic and Atherosclerosis Research Center Inc. "While the clinical significance of reducing RLP-C is unknown, this analysis showed that VYTORIN reduced RLP-C by 41 percent compared to 29 percent for simvastatin ($p<0.001$). In addition, VYTORIN provided significantly greater LDL-C reductions of 53 percent compared

- more -

to 39 percent for simvastatin alone ($p<0.001$), similar to LDL-C reductions seen in patients taking ezetimibe with simvastatin in other studies presented here at ACC."

VYTORIN (ezetimibe/simvastatin) was well tolerated and had an overall safety profile similar to simvastatin in the study; there were no clinically or statistically significant differences in the incidence of muscle enzyme elevations (five to10 times or more than 10 times the upper limit of normal) or consecutive liver enzyme elevations (ALT or AST more than three times the upper limit of normal).

Important information about ZETIA (ezetimibe)

The effects of ZETIA, either alone or in addition to a statin, on the risk of cardiovascular morbidity and mortality have not been established. ZETIA is a prescription medicine and should not be taken by people who are allergic to any of its ingredients. When ZETIA is used with a statin, liver function tests should be performed at the start of therapy and after that in accordance with the label for that statin. Liver function tests are not required when ZETIA is used alone.

Due to the unknown effects of increased exposure to ZETIA in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. In clinical trials, there was no increased incidence of myopathy or rhabdomyolysis associated with ZETIA; however myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. There are no adequate and well-controlled studies of ZETIA in pregnant women. ZETIA should not be used in pregnant or nursing women unless the benefit outweighs the potential risks. The safety and effectiveness of ZETIA with fibrates have not been established; therefore, co-administration with fibrates is not recommended.

When ZETIA was co-administered with a statin, consecutive elevations in liver enzymes, more than three times the upper limit of normal, were slightly higher than those with the statin

alone (1.3 percent vs. 0.4 percent). These elevations were generally asymptomatic and returned to baseline after discontinuation of therapy or with continued treatment. Because of significantly increased blood levels of ZETIA in one patient on multiple medications including cyclosporine, patients who take both ZETIA and cyclosporine should be carefully monitored.

For monotherapy, the most frequent adverse events reported with greater incidence than placebo, regardless of causality, were back pain (4.1 percent vs. 3.9 percent) and arthralgia
(3.8 percent vs. 3.4 percent). In co-administration with a statin, the most frequent adverse events reported with greater incidence for ZETIA plus statin versus statin or placebo alone, regardless of causality, were back pain (4.3 percent vs. 3.7 percent vs. 3.5 percent, respectively) and abdominal pain (3.5 percent vs. 3.1 percent vs. 2.3 percent, respectively).

ZETIA, marketed by Merck/Schering-Plough Pharmaceuticals, is the first in a class of cholesterol-lowering agents that inhibits the intestinal absorption of cholesterol through a unique

- more -

mechanism of action. ZETIA is complementary to the class of cholesterol-lowering agents known as statins, which work in the liver to reduce the production of cholesterol. ZETIA, along with diet, is indicated for use either by itself or together with statins in patients with high cholesterol to reduce LDL "bad" cholesterol and total cholesterol when the response to diet and exercise has been inadequate. ZETIA has been proven to significantly improve LDL cholesterol levels.

Important information about simvastatin

Simvastatin should not be used by anyone allergic to any of its components, with liver disease, or by women who are pregnant, breast-feeding or likely to become pregnant. Muscle pain or weakness in people taking simvastatin should be reported to a doctor because these could be signs of a serious side effect. Doctors may perform blood tests before and periodically during treatment with simvastatin to check for liver problems. People taking 80 mg of simvastatin should receive an additional liver function test at three months. To help avoid serious side effects, discuss with your doctor medicine or food you should avoid while taking simvastatin. In clinical trials, adverse reactions usually have been mild and transient. Most common side effects included headache (3.5 percent), abdominal pain (3.2 percent) and constipation (2.3 percent).

Simvastatin is marketed by Merck & Co., Inc. under the trade name Zocor and is in the class of cholesterol lowering agents known as statins. Zocor is used along with diet to improve cholesterol levels in people with high-cholesterol, when diet alone is not enough. Zocor has been proven to significantly improve LDL and HDL cholesterol levels, as well as triglyceride levels.

About Merck/Schering-Plough Pharmaceuticals

Merck/Schering-Plough Pharmaceuticals is a joint venture between Merck & Co., Inc. and Schering-Plough Corporation formed in May 2000 to develop and market in the United States new prescription medicines in cholesterol management. The collaboration was expanded in December 2001 to include worldwide markets (excluding Japan).

ZETIA, discovered by Schering-Plough scientists, is marketed by Merck/Schering-Plough Pharmaceuticals. Since its introduction in November 2002, more than six million prescriptions have been written for ZETIA in the U.S. and it is one of the fastest growing products in the lipid lowering market.1 The once-daily tablet of ZETIA 10 mg was approved in the United States in October 2002. Ezetimibe is also approved in several countries throughout the world. Following the successful completion of the European Union Mutual Recognition

1 IMS Health, NPA Plus (TM) and NPA Plus 7 (TM), TRXs Nov 02 - Jan 04, and weeks ending 2/6/04 and 2/13/04.

- more -

Procedure, EZETROL (the brand name for ZETIA outside of the United States) has now been launched in five European countries – Germany, the United Kingdom, Switzerland, Sweden and Holland.

On Sept. 24, 2003, Merck/Schering-Plough Pharmaceuticals submitted to the U.S. Food and Drug Administration (FDA) for standard review a New Drug Application for VYTORIN, ezetimibe/simvastatin tablet, an investigational cholesterol-lowering medicine, as adjunctive to diet, for the reduction of elevated cholesterol levels (hypercholesterolemia). The application for filing was accepted for review on Nov. 23, 2003.

MERCK FORWARD-LOOKING STATEMENT:

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements include statements regarding product development. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. We undertake no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward- looking statements in this press release should be evaluated together with the many uncertainties that affect our businesses, particularly those mentioned in the cautionary statements in Item 1 of our Form 10-K for the year ended Dec. 31, 2002, and in our periodic reports on Form 10-Q and Form 8-K (if any) which we incorporate by reference.

SCHERING-PLOUGH FORWARD-LOOKING STATEMENT:

The information in this press release includes certain "forward-looking" information including the market potential for

VYTORIN and ZETIA. The reader of this release should understand that the extent that VYTORIN and ZETIA will be prescribed will be determined by market forces and the market viability of VYTORIN and ZETIA is subject to substantial risks and uncertainties. In addition, the forward-looking statements may also be adversely affected by general market and economic factors, competitive product development, product availability, the extent of market acceptance of new products, current and future branded, generic or over-the-counter competition, federal and state regulations and legislation, the

regulatory process for new products and indications, manufacturing issues, trade buying patterns, patent positions, litigation and investigations. For further details and a discussion of these and other risks and uncertainties, see the company's Securities and Exchange Commission filings, including the company's 10-K filed Feb. 26, 2004.

###

PAGE INTENTIONALLY LEFT BLANK

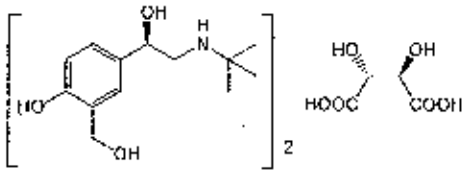
XOPENEX HFA™ (levalbuterol tartrate) Inhalation Aerosol

For Oral Inhalation Only

PRESCRIBING INFORMATION

DESCRIPTION

The active component of XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is levalbuterol tartrate, the (R)-enantiomer of albuterol. Levalbuterol tartrate is a relatively selective beta$_2$-adrenergic receptor agonist (see **CLINICAL PHARMACOLOGY**). Levalbuterol tartrate has the chemical name (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt), and it has the following chemical structure:



The molecular weight of levalbuterol tartrate is 628.71, and its empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot C_4H_6O_6$. It is a white to light-yellow solid, freely soluble in water and very slightly soluble in ethanol.

Levalbuterol tartrate is the generic name for (R)-albuterol tartrate in the United States. XOPENEX HFA Inhalation Aerosol is a pressurized metered-dose aerosol inhaler (MDI), which produces an aerosol for oral inhalation. It contains a suspension of micronized levalbuterol tartrate, propellant HFA-134a (1,1,1,2-tetrafluoroethane), Dehydrated Alcohol USP, and Oleic Acid NF.

The inhaler should be primed by releasing 4 sprays into the air, away from the face, before using it for the first time and when the inhaler has not been used for more than 3 days. After priming with 4 actuations, each actuation delivers 59 mcg of levalbuterol tartrate (equivalent to 45 mcg of levalbuterol free base) from the actuator (or mouthpiece). Each 15 g canister provides 200 actuations (or inhalations).

This product does not contain chlorofluorocarbons (CFCs).

CLINICAL PHARMACOLOGY

Mechanism of Action: Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations,

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol tartrate. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at, and above, dietary doses of 2 mg/kg/day (approximately 30 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis and approximately 15 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg/day (approximately 3800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis and approximately 1800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg/day (approximately 500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis and approximately 240 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Levalbuterol HCl was not clastogenic in the in vivo micronucleus test in mouse bone marrow. Racemic albuterol sulfate was negative in an in vitro chromosomal aberration assay in CHO cell cultures.

Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis).

Teratogenic Effects - Pregnancy Category C

A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis).

However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg/day (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a

10-Q 1 a2146207z10-q.htm FORM 10-Q

Use these links to rapidly review the document
INDEX

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Quarterly Period Ended September 30, 2004

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number 0-19410

Sepracor Inc.

(Exact name of registrant as specified in its charter)

Delaware	**22-2536587**
(State or Other Jurisdiction of Incorporation or Organization)	(IRS Employer Identification No.)
84 Waterford Drive Marlborough, Massachusetts	**01752**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **(508) 481-6700**

Indicate by check mark whether the registrant: (1) has filed all repors required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Exchange

During September 2004, certain holders of our 0% Series A convertible senior subordinated notes due 2008, or 0% Series A notes due 2008, and 0% Series B convertible senior subordinated notes due 2010, or 0% Series B notes due 2010, agreed, in separately negotiated transactions, to convert $177,200,000 and $351,980,000 in aggregate principal amount of their 0% Series A notes due 2008 and 0% Series B notes due 2010, respectively, into an aggregate of 5,556,104 and 11,797,483 shares of our common stock, respectively. As an inducement to convert their notes, we paid the holders of the 0% Series A notes due 2008 and 0% Series B notes due 2010 aggregate cash payments of $23,868,250 and $45,899,900, respectively.

On July 15, 2004, we announced that the United States Food and Drug Administration, or FDA, had accepted our resubmission of our New Drug Application, or NDA, for ESTORRA™ brand eszopiclone for the treatment of insomnia characterized by difficulty falling asleep, and/or difficulty maintaining sleep during the night and early morning. We received an "approvable" letter from the FDA on February 27, 2004 for the original NDA for ESTORRA. The FDA has classified our resubmission as a Class 2 resubmission. Under the Prescription Drug User Fee Act, or PDUFA, the FDA is expected to complete its review of this Class 2 resubmission within a six-month period beginning on the date that the resubmission was received. As a result of this Class 2 designation, the PDUFA date, or the date by which the FDA is expected to review and act on the NDA submission for our ESTORRA NDA, is December 15, 2004. We are currently planning for a January 2005 product launch, contingent upon approval from the FDA. We have expanded our sales force in anticipation of marketing ESTORRA to primary care physicians and psychiatrists, the principal prescribers of sleep medications. Contingent upon approval from the FDA, we expect the recommended dosing to achieve sleep onset and maintenance to be 2 mg or 3 mg for adult patients, 2 mg for elderly patients with sleep maintenance difficulties, and 1 mg for sleep onset in elderly patients whose primary complaint is difficulty falling asleep. The FDA has not requested additional clinical or preclinical trials for final approval. If the FDA delays or denies final approval of our NDA for eszopiclone, or the trademark we propose to use in connection with the product, then our plans for commercialization of ESTORRA would be delayed or terminated, which would have a material adverse effect on our business.

On July 15, 2004, we announced that the FDA had accepted for formal review our NDA for XOPENEX HFA™ (levalbuterol tartrate HFA) Inhalation Aerosol, a hydrofluoroalkane, or HFA, metered-dose inhaler, or MDI. The FDA has notified us that the PDUFA date for our NDA for XOPENEX HFA MDI is March 12, 2005. On May 12, 2004, we submitted our NDA to the FDA for XOPENEX HFA MDI for the treatment or prevention of bronchospasm in adults, adolescents and children 4 years of age and older with reversible obstructive airway disease, such as asthma and chronic obstructive pulmonary disease, or COPD. MDIs are hand-held, pressurized canisters that deliver inhaled medications directly to the lungs. Our MDI development program included approximately 1,870 pediatric and adult subjects and 54 studies (preclinical and clinical). In 2003, we completed our Phase III studies of XOPENEX HFA. In each of the three, large-scale, pivotal Phase III trials that we conducted, the XOPENEX HFA MDI was well tolerated and met the targeted efficacy endpoints in both adults and children with asthma. In the primary airway function measure, FEV1 (a test of lung function that measures the amount of air forcefully exhaled in one second), the XOPENEX HFA MDI produced statistically and clinically significant improvements relative to placebo ($p<0.001$). If the FDA delays or denies approval of our NDA for XOPENEX HFA MDI, then commercialization of this product candidate could be delayed or terminated, which would have a material adverse effect on our business.

On July 13, 2004, we announced a conditional amendment to our agreement with Aventis relating to eszopiclone. The amendment became effective upon the completion of the business combination between Aventis and Sanofi-Synthelabo. Under the amended agreement, we have the right to read and reference Aventis' regulatory filings related to zopiclone outside of the United States for the purpose of development and regulatory registration of eszopiclone outside of the U.S., and Aventis will assign to

EXHIBIT X

Summary of Individual Defendants' Holdings of Arena Pharmaceuticals, Inc. Stock

NAME	HOLDINGS AS OF 3/21/2008[1]	HOLDINGS AS OF 3/31/2011[2]	INCREASE IN HOLDINGS
Jack Lief	1,143,285	1,441,670	+ 298,385
Robert Hoffman	190,294	243,981	+ 53,687
Dominic Behan	681,948	784,448	+ 102,500
William Shanahan, Jr.	141,250	245,000	+ 93,750
Christy Anderson	N/A[3]	N/A	N/A
TOTAL	2,156,777	2,715,099	+ 558,322 (+ 25.9%)

[1] *See* p. 259.
[2] *See* p. 265.
[3] Individual defendant Christy Anderson was not a Section 16 reporting officer during the Class Period.

EXH. X
P. 255

PAGE INTENTIONALLY LEFT BLANK

Morningstar® Document Research℠

FORM DEF 14A

ARENA PHARMACEUTICALS INC - ARNA

Filed: April 24, 2008 (period: June 11, 2008)

Official notification to shareholders of matters to be brought to a vote (Proxy)

QuickLinks -- Click here to rapidly navigate through this document

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of
the Securities Exchange Act of 1934 (Amendment No.)

Filed by the Registrant ☒

Filed by a Party other than the Registrant ☐

Check the appropriate box:

☐ Preliminary Proxy Statement

☐ **Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**

☒ Definitive Proxy Statement

☐ Definitive Additional Materials

☐ Soliciting Material Pursuant to §240.14a-12

Arena Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

☒ No fee required.

☐ Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11

(1) Title of each class of securities to which transaction applies:

(2) Aggregate number of securities to which transaction applies:

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined):

(4) Proposed maximum aggregate value of transaction

(5) Total fee paid.

☐ Fee paid previously with preliminary materials.

☐ Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(1) Amount Previously Paid:

(2) Form, Schedule or Registration Statement No.:

(3) Filing Party:

Compensation and Other Information
Concerning Executive Officers, Directors and Certain Stockholders

Security Ownership of Certain Beneficial Owners and Management

The following table sets forth certain information known to us with respect to the beneficial ownership of our common stock as of March 21, 2008 by:

- Each person, group or entity who is the beneficial owner of 5% or more of our common stock,
- Each director and nominee for director,
- Our Named Executive Officers; and
- All current directors and executive officers as a group.

Unless otherwise indicated in the footnotes below, the address for the beneficial owners listed in this table is in care of Corporate Secretary, Arena Pharmaceuticals, Inc., 6166 Nancy Ridge Drive, San Diego, California 92121. This table is based on information supplied by executive officers, directors and principal stockholders and Schedules 13D, 13G and other filings made with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that the stockholders named in this table have sole voting and investment power with respect to the shares indicated as beneficially owned. Applicable percentages are based on 73,759,776 shares of common stock outstanding on March 21, 2008, including 31,000 restricted shares of common stock, and as adjusted as required by the rules promulgated by the SEC. This table includes shares issuable pursuant to stock options and other rights to purchase shares of our common stock exercisable within 60 days of March 21, 2008.

Name and Address of Beneficial Owner	Shares Beneficially Owned	Percentage of Total
Wellington Management Company, LLP(1)	9,758,683	13.2%
The Bank of New York Mellon Corporation(2)	7,517,844	10.2%
Entities affiliated with Deerfield Capital, L.P.(3)	5,950,643	8.1%
Mainfield Enterprises, Inc.(4)(5)	5,284,202	6.8%
Federated Investors, Inc.(6)	4,137,500	5.6%
TCW Business Unit(7)	3,907,696	5.1%
Sectoral Fiduciary LLC(5)(8)	3,062,647	4.2%
Jack Lief(9)	1,143,285	1.5%
Dominic P. Behan, Ph.D.(10)	683,948	*
Steven W. Spector, J.D.(11)	241,500	*
Robert E. Hoffman, C.P.A.(12)	190,297	*
J. Clayburn La Force, Jr., Ph.D.(13)	152,502	*
William R. Shanahan, Jr., M.D., J.D.(14)	141,250	*
Harry F. Hixson, Jr., Ph.D.(15)	104,916	*
Donald D. Belcher(16)	99,906	*
Scott H. Bice(17)	61,568	*
Tina Nova, Ph.D.(18)	59,000	*
Christine A. White, M.D.(19)	32,374	*
Phillip M. Schneider(20)	1,896	*
Randall E. Woods(21)	1,596	*
All directors and executive officers as a group (13 persons)(22)	3,096,299	4.1%

* Less than one percent

(1) The principal business office of Wellington Management Company, LLP is 75 State Street, Boston, Massachusetts 02109.

(2) The principal business office of The Bank of New York Mellon Corporation is One Wall Street, 31st Floor, New York, New York 10286.

(3) Represents shares held by Deerfield Capital, L.P., Deerfield Partners, L.P., Deerfield International Limited, Deerfield Management Company, L.P., and James E. Flynn. The principal business address of Deerfield Capital, L.P., Deerfield Partners, L.P., Deerfield Management Company, L.P., and James E. Flynn is 780 Third Avenue, 37th Floor, New York, New York 10017. The principal business address of Deerfield International Limited is c/o Bisys Management, Bison Court, Columbus Centre, P.O. Box 3460, Road Town, Tortola, British Virgin Islands.

(4) Pursuant to an investment management agreement, Avi Vigder has voting discretion and investment control over the shares held by Mainfield Enterprises, Inc. Avi Vigder disclaims beneficial ownership of such shares. The principal business office of Mainfield Enterprises, Inc. is in care of Sage Capital Growth, Inc., 660 Madison Avenue, New York, New York 10022.

(5) The holder disclaims beneficial ownership of our common stock that exceeds 4.999% of our outstanding common stock. Under the terms of our Preferred Stock, the number of shares of our common stock that may be acquired by the holder upon any conversion of our Preferred Stock is limited to the extent necessary to ensure that, following such conversion, the total number of shares of our common stock then beneficially owned by such holder and its affiliates and any other persons whose beneficial ownership of our common stock would be aggregated with the holders for purposes of Section 13(d) of the Securities Exchange of 1934 does not exceed 4.999% of our common stock (including shares of our common stock issuable upon such conversion). The holder can waive this provision or increase (but not to more than 9.999%) or decrease this percentage by giving us written notice, but (i) any such waiver or increase will not be effective until the 61st day after such notice is delivered to the us, and (ii) any such waiver or increase or decrease will apply only to such holder. The 4.999% limitation is disregarded for purposes of this table. This table includes the shares of our common stock that the holder may acquire by exercising warrants that they hold. The warrants provide that the number of shares of our common stock that may be acquired by the holder upon any exercise of the warrant is limited to the extent necessary to ensure that, following such exercise, the total number of shares of our common stock then beneficially owned by such holder and its affiliates and any other persons whose beneficial ownership of our common stock would be aggregated with the holders for purposes of Section 13(d) of the Securities Exchange of 1934 does not exceed 4.999% of our common stock (including shares of our common stock issuable upon such exercise). The holder can waive this limitation on exercise or increase or decrease the 4.999% by giving us written notice, but (i) any such waiver or increase will not be effective until the 61st day after such notice is delivered to us and (ii) any such waiver or increase or decrease will apply only to such holder and not to any other holder of warrants. This does not include any common shares of which the holder may have beneficial ownership.

(6) The principal business office of Federated Investors, Inc. is Federated Investors Tower, 1001 Liberty Avenue, Pittsburgh, Pennsylvania 15222

(7) The principal business office of TCW Business Unit is The TCW Group, Inc, on behalf of the TCW Business Unit, 865 South Figueroa Street, Los Angeles, California 90017

(8) Highbridge Capital Management, LLC, is the trading manager of Smithfield Fiduciary LLC and consequently has voting control and investment discretion over securities held by Smithfield Fiduciary LLC. Glenn Dubin and Henry Swieca control Highbridge Capital Management, LLC. Each of Highbridge Capital Management, LLC, Glenn Dubin and Henry Swieca disclaims beneficial ownership of the securities held by Smithfield Fiduciary LLC. The principal business office of Smithfield Fiduciary LLC is in care of Highbridge Capital Management, LLC, 9 West 57th Street, 27th Floor, New York, New York 10019.

(9) Includes 603,600 shares issuable to Mr. Lief upon the exercise of stock options that are exercisable within 60 days of March 21, 2008. Also includes 12,000 restricted shares of our common stock which are scheduled to vest on January 20, 2009

(10) Includes 346,448 shares issuable to Dr. Behan upon the exercise of stock options that are exercisable within 60 days of March 21, 2008. Also includes 5,000 restricted shares of our common stock which are scheduled to vest on January 20, 2009

(11) Includes 187,500 shares issuable to Mr. Spector upon the exercise of stock options that are exercisable within 60 days of March 21, 2008. Also includes 5,000 restricted shares of our common stock which are scheduled to vest on January 20, 2009.

(12) Includes 123,750 shares issuable to Mr. Hoffman upon the exercise of stock options that are exercisable within 60 days of March 21, 2008. Also includes 5,000 restricted shares of our common stock which are scheduled to vest on January 20, 2009.

(13) Includes 152,502 shares issuable to Dr. La Force upon the exercise of stock options that are exercisable within 60 days of March 21, 2008

(14) Includes 141,250 shares issuable to Dr. Shanahan upon the exercise of stock options that are exercisable within 60 days of March 21, 2008.

(15) Includes 94,916 shares issuable to Dr. Hixson upon the exercise of stock options that are exercisable within 60 days of March 21, 2008.

(16) Includes 94,906 shares issuable to Mr. Belcher upon the exercise of stock options that are exercisable within 60 days of March 21, 2008.

(17) Includes 60,468 shares issuable to Mr. Rice upon the exercise of stock options that are exercisable within 60 days of March 21, 2008.

(18) Includes 59,000 shares issuable to Dr. Nova Bennett upon the exercise of stock options that are exercisable within 60 days of March 21, 2008

(19) Includes 32,374 shares issuable to Dr. White upon the exercise of stock options that are exercisable within 60 days of March 21, 2008.

(20) Includes 1,596 shares issuable to Mr. Schneider upon the exercise of stock options that are exercisable within 60 days of March 21, 2008

(21) Includes 1,596 shares issuable to Mr. Woods upon the exercise of stock options that are exercisable within 60 days of March 21, 2008.

(22) Includes 2,053,656 shares issuable upon the exercise of stock options held by our directors and executive officers that are exercisable within 60 days of March 21, 2008. Also includes 27,000 restricted shares of our common stock that we granted our executive officers.

PAGE INTENTIONALLY LEFT BLANK

FORM DEF 14A

ARENA PHARMACEUTICALS INC - ARNA

Filed: April 27, 2011 (period: June 13, 2011)

Official notification to shareholders of matters to be brought to a vote (Proxy)

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934 (Amendment No.)

Filed by the Registrant ☒

Filed by a Party other than the Registrant ☐

Check the appropriate box:

☐ Preliminary Proxy Statement

☐ **Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**

☒ Definitive Proxy Statement

☐ Definitive Additional Materials

☐ Soliciting Material Pursuant to §240.14a-12

Arena Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

☒ No fee required.

☐ Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.

(1) Title of each class of securities to which transaction applies:

(2) Aggregate number of securities to which transaction applies:

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined):

(4) Proposed maximum aggregate value of transaction:

(5) Total fee paid:

☐ Fee paid previously with preliminary materials.

☐ Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(1) Amount Previously Paid:

(2) Form, Schedule or Registration Statement No.:

(3) Filing Party:

(4) Date Filed:

Table of Contents

Unless otherwise indicated in the footnotes below, the address for the beneficial owners listed in this table is in care of Corporate Secretary, Arena Pharmaceuticals, Inc., 6166 Nancy Ridge Drive, San Diego, California 92121. This table is based on information supplied by executive officers, directors and principal stockholders and Schedules 13D, 13G and other filings made with the SEC on or before March 31, 2011. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that the stockholders named in this table have sole voting and investment power with respect to the shares indicated as beneficially owned. Applicable percentages are based on 136,744,281 shares of common stock outstanding on March 31, 2011, as adjusted as required by the rules promulgated by the SEC. This table includes shares issuable pursuant to warrants, Series C Convertible Preferred Stock, or Series C Stock, stock options and other rights to purchase shares of our common stock exercisable within 60 days of March 31, 2011.

Name and Address of Beneficial Owner	Shares Beneficially Owned	Percentage of Total
Wellington Management Company, LLP (1)	14,847,142	10.80%
Deerfield Capital, L.P. and affiliates (2)	13,581,275	9.98%
BlackRock Inc. (3)	7,548,298	5.64%
Jack Lief (4)	1,441,670	1.07%
Dominic P. Behan, Ph.D. (5)	394,448	*
Steven W. Spector, J.D. (6)	399,233	*
Mary Ann Gray, Ph.D. (7)	268,204	*
William R. Shanahan, Jr., M.D., J.D. (8)	245,000	*
Robert E. Hoffman (9)	241,981	*
Donald D. Belcher (10)	228,196	*
Christine A. White, M.D. (11)	148,154	*
Scott H. Bice (12)	118,190	*
Phillip M. Schneider (13)	103,750	*
Tina S. Nova, Ph.D. (14)	95,000	*
Randall E. Woods (15)	84,720	*
All directors and executive officers as a group (13 persons) (16)	4,283,404	3.13%

* Less than one percent

(1) The principal business office of Wellington Management Company, LLP is 75 State Street, Boston, Massachusetts 02109.

(2) As of March 31, 2011, subject to the limitation set forth in the below paragraph, Deerfield Capital, L.P. and affiliates own, or have rights to purchase within 60 days of March 31, 2011, shares of our common stock, as follows: (a) for Deerfield Private Design Fund, L.P., 2,297,166 shares of common stock underlying warrants that are exercisable within 60 days of March 31, 2011, 2,047,518 shares of common stock underlying shares of Series C Stock that are convertible within 60 days of March 31, 2011, and 1,894,272 shares of outstanding common stock; (b) for Deerfield Private Design International, L.P., 3,700,655 shares of common stock underlying warrants that are exercisable within 60 days of March 31, 2011, 3,298,482 shares of common stock underlying shares of Series C Stock that are convertible within 60 days of March 31, 2011, and 3,051,605 shares of outstanding common stock; (c) for Deerfield Partners, L.P., 2,699,019 shares of common stock underlying warrants that are exercisable within 60 days of March 31, 2011, 2,405,700 shares of common stock underlying shares of Series C Stock that are convertible within 60 days of March 31, 2011, and 2,223,096 shares of outstanding common stock; (d) for Deerfield International Limited, 4,116,686 shares of common stock underlying warrants that are exercisable within 60 days of March 31, 2011, 3,669,300 shares of common stock underlying shares of Series C Stock that are convertible within 60 days of March 31, 2011, and 3,397,219 shares of outstanding common stock; (e) for Deerfield Special Situations Fund, L.P. 287,895 shares of common stock underlying warrants that are exercisable within 60 days of March 31, 2011, 256,608 shares of common stock underlying shares of Series C Stock that are convertible within 60 days of March 31, 2011, and 237,883 shares of outstanding common stock; and (f) for Deerfield Special Situations Fund International Limited, 529,989 shares of common stock

underlying warrants that are exercisable within 60 days of March 31, 2011, 472,392 shares of common stock underlying shares of Series C Stock that are convertible within 60 days of March 31, 2011, and 436,555 shares of outstanding common stock.

James E. Flynn has the power to vote or dispose of the shares held by these entities, and, therefore, may be deemed to beneficially own these shares. Mr. Flynn and these entities disclaim beneficial ownership of our common stock that exceeds 9.98% of our outstanding common stock. Under the terms of the warrants held by these entities, as well as the provisions of our Series C Stock, the number of shares of our common stock that may be acquired upon any exercise of the warrants or conversion of our Series C Stock is limited so that, following such exercise or conversion, the total number of shares of our common stock then beneficially owned by the applicable stockholder, together with its affiliates and any other persons or entities whose beneficial ownership of our common stock would be aggregated with such stockholder for purposes of Section 13(d) of the Exchange Act and the applicable regulations of the SEC, cannot exceed 9.98% of the total number of shares of our common stock then issued and outstanding. The number of shares included in the table as being beneficially owned by all such persons, and the related percentage ownership, reflects the foregoing limitation. The principal business office of Deerfield Capital, L.P., Deerfield Partners, L.P., Deerfield Special Situations Fund, L.P., Deerfield Management Company, L.P., Deerfield Private Design Fund, L.P. and James E. Flynn is 780 Third Avenue, 37th Floor, New York, New York 10017. The principal business office of Deerfield International Limited, Deerfield Private Design International, L.P. and Deerfield Special Situations Fund International Limited is c/o Citi Hedge Fund Services (B.V.I.), Bison Court, P.O. Box 3460, Road Town, Tortola, British Virgin Islands.

(3) The principal business office of BlackRock Inc. is 40 East 52nd Street, New York, NY 10022.

(4) Includes 945,538 shares issuable to Mr. Lief upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(5) Includes 361,448 shares issuable to Dr. Behun upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(6) Includes 340,000 shares issuable to Mr. Spector upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(7) Includes 178,206 shares issuable to Dr. Hixson upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(8) Includes 245,000 shares issuable to Dr. Shanahan upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(9) Includes 185,000 shares issuable to Mr. Hoffman upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(10) Includes 178,196 shares issuable to Mr. Belcher upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(11) Includes 128,164 shares issuable to Dr. White upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(12) Includes 108,290 shares issuable to Mr. Bice upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(13) Includes 93,720 shares issuable to Mr. Schneider upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(14) Includes 95,000 shares issuable to Dr. Nova upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(15) Includes 93,720 shares issuable to Mr. Woods upon the exercise of stock options that are exercisable within 60 days of March 31, 2011.

(16) Includes 3,066,032 shares issuable upon the exercise of stock options held by our current directors and executive officers and Mr. Hoffman that are exercisable within 60 days of March 31, 2011.

CERTIFICATE OF SERVICE

I hereby certify that, on October 24, 2014, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit using the appellate CM/ECF system. Participants in the case who are registered CM/ECF users will be served by the appellate CM/ECF users. Upon acceptance by the Clerk of the Court of the electronically filed document, one copy of the following will be served, via U.S. Mail, postage prepaid on:

Eirk D. Peterson
Kessler Topaz Meltzer & Check LLP
One Sansome Street
Suite 1850
San Francisco, CA 94104

Dated: October 24, 2014

/s/William E. Grauer
William E. Grauer