

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022529Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022529

SUPPL #

HFD # 510

Trade Name Belviq

Generic Name lorcaserin hydrochloride

Applicant Name Arena Pharmaceuticals

Approval Date, If Known June 27, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# N/A

N/A

NDA# N/A N/A

NDA# N/A N/A

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Patricia Madara
Title: Regulatory Project Manager, DMEP
Date: June 28, 2012

Name of Office/Division Director signing form: Eric Colman, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

PATRICIA J MADARA
06/28/2012

ERIC C COLMAN
06/28/2012

Madara, Patricia

From: Greeley, George
nt: Monday, June 04, 2012 10:11 AM
: Madara, Patricia
: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Parks, Mary H
subject: NDA 22-529 Belviq

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Patricia,

The email serves as confirmation of the review for the Belviq (locaserin) product conducted by the PeRC PREA Subcommittee on May 16, 2012.

The Division presented a partial in patients birth through 6 years because studies are impossible or highly impracticable and a deferral in patients 7^{(b) (4)} years because the product is ready for approval in adults. Belviq was studied for weight management in obese patients with an initial body mass index ≥ 30 kg/m², and overweight patients with a body mass index ≥ 27 kg/m² in the presence of at least one weight-related comorbid condition as an adjunct to diet and exercise.

Belviq is a New Molecular Entity (NME). It is a 5HT_{2C} receptor antagonist indicated for the treatment of weight loss. This product was originally submitted in 2009. A Complete Response (CR) was issued after review by an Advisory Committee (AC) which voted to deny approval of the application. Data submitted in the submission resolved the earlier issues. The product was presented at a May 10, 2012 AC which resulted in the committee voting in favor of approving this product. Requiring pediatric studies for patients 7 years and older could be consistent with the PREA requirements for Qnexa (phentermine/topiramate)

The PeRC offers the following recommendations:

- *The PeRC recommended that prolactin serum levels and hemoglobin A1C be monitored in pediatric patients.*
- *The PeRC recommended that a standardized approach be adopted for tanner staging.*
- *The PeRC recommended that timelines be updated for the PREA PMRs.*
- *The PeRC recommended that the juvenile rat study include a post-nasal dose at day 14. The PeRC also recommended that reproductive performance be requested in the animal studies.*

The PeRC agreed with the Division to grant a partial waiver in patients birth through six years because the product does not represent a meaningful benefit and is not likely to be used in a substantial number of pediatric patients and to the deferral in patients 7 years though ^{(b) (4)} because the product is ready for approval in adults.

The pediatric record is attached for Belviq.



Pediatric_Record
pdf (57 KB)...

Thanks,

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

 Please consider the environment before printing this e-mail.

38 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

Debarment Certification Statement

Arena Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335a(k)) in connection with this drug product application.

Name Craig M. Audet	Title Vice President, Global Regulatory Affairs
Firm/Organization Arena Pharmaceuticals, Inc. 6166 Nancy Ridge Drive San Diego, CA 92121	
Signature <i>See appended electronic signature</i>	

Debarment Certification Statement

Arena Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335a(k)) in connection with this drug product application.

Name	Title
Mark Brunswick, PhD	Senior Director, Regulatory Affairs
Firm/Organization	
Arena Pharmaceuticals, Inc. 6166 Nancy Ridge Drive San Diego, CA 92121	
Signature	Date
<i>See appended electronic signature</i>	12/03/2009



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UserName: [REDACTED] (b) (4)
Title: Manager, Regulatory Affairs
Date: Thursday, 03 December 2009, 12:24 PM Pacific Standard Time
Meaning: Author Approval

UserName: Mark Brunswick
Title: Sr. Director, Regulatory Affairs
Date: Thursday, 03 December 2009, 12:27 PM Pacific Standard Time
Meaning: Approval

Madara, Patricia

From: Madara, Patricia
Sent: Monday, June 25, 2012 10:40 AM
To: 'Craig Audet'
Subject: Status of tcon for Belviq and request for clarification

Importance: High

Hi Craig;

I wanted to keep you updated on the Belviq status. At this point, the entire team is meeting at 3 PM for final review of the label. Unless something unexpected is brought up, Dr. Colman does not think we will need to have the scheduled tcon. However, I may not know for sure until close to 3:30 PM. Huge apologies for this awkward timing. I will email you or text you from my cell phone as soon as I have 100% confirmation. Unfortunately, it will mean having some Arena folks on standby. If there is a last minute request for discussion or clarification, we can plan to tcon at 3:30 - or as close to that time as possible.

Also, not for the label, I have a last minute request for information / clarification:

- **Please explain the imbalance in AEs of diabetes mellitus in BLOOM-DM (table 3) in the belviq vs placebo patients -- in other words, some context surrounding these adverse events, blood sugars, etc?**

You may submit this data informally, via email but also submit it officially to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
06/28/2012

Madara, Patricia

From: Madara, Patricia
Sent: Monday, June 25, 2012 10:01 PM
To: 'Craig Audet'
Subject: NDA 22529 - Information request for the NDA, not the label

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin HCl) Tablets, 10 mg.

We would like to have, for our records, the statistical results that support the following summaries in Part 14 (Clinical Studies) of the Belviq label:

- 1. Figure 2 ("Body Weight Changes during Study 1 in the Completers Population"): The LSM means and SEMs by treatment arm that are depicted in this figure.**
- 2. Table X ("Mean Changes in Cardiometabolic Parameters and Waist Circumference in Year 1 of Studies 1 and 2"): The summary statistics and analysis results that are reported for heart rate.**
- 3. Table X ("Mean Changes in Cardiometabolic Parameters and Waist Circumference in Patients with Type 2 Diabetes"): The summary statistics and analysis results that are reported for heart rate.**

This information should be officially submitted to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
06/28/2012

Madara, Patricia

From: Madara, Patricia
Sent: Friday, June 15, 2012 12:35 PM
To: 'Craig Audet'
Importance: High
Attachments: Belviq_PI only_FDA to arena_15June12.doc

Craig;

I have attached the draft PI for Belviq. The following additional information will be helpful during your review:

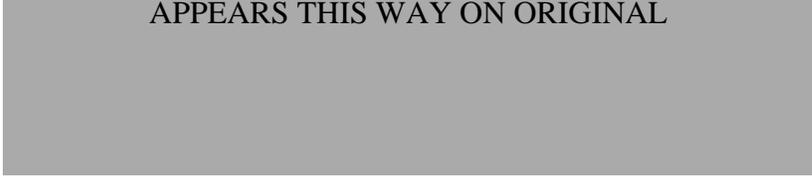
1. We have made many revisions but they are not in track changes. When we attempted to compare this version to the original (5/23/12) so FDA changes would be tracked, there were problems with WORD, possibly because you are using a newer WORD program. You will need to compare this label to the label sent to FDA on 23May12. Perhaps your WORD "compare documents" tool will work better. (The problems did not start until Section 5 of the full prescribing information.)
2. Please note requests for additional information (see comment balloons) and highlighted text such as (xx%)
3. Some formatting revisions have already been made and others are requested.
4. The PPI will follow.
5. FDA senior management must review and approve the label after you send it back. This is only the first of several rounds of negotiations.
6. We request you provide the label to FDA by 2 PM EDT on Wednesday of next week, at the latest.
7. For clarity, all the FDA revisions you find acceptable can remain in normal font. You can provide the additional requested data and any proposed changes to the FDA version in track changes. If you have a significant number of comments to include, consider a separate page that is referenced in the comment balloons.
8. Your PMRs and their timelines must be agreed upon and included in any approval letter.

Please contact me if you have any questions. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

APPEARS THIS WAY ON ORIGINAL



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/s/

PATRICIA J MADARA
06/28/2012

Madara, Patricia

From: Madara, Patricia
Sent: Friday, June 15, 2012 10:27 AM
To: 'Craig Audet'
Cc: Daniel Kim
Subject: RE: NDA 022529 PMR study timelines - request for revision
Importance: High

NDA 022529 **ADVICE / INFORMATION REQUEST**

Hi Craig:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin HCl) Tablets, 10 mg.

In addition, we reference your email below, requesting reconsideration of the originally proposed milestone dates for several of your postmarketing required studies. We have reviewed your rationale and have the following comments:

- **The clinical and safety review teams disagree with your request to maintain your proposed timelines for the PREA safety and efficacy studies and the cardiovascular outcome trial. They are inconsistent with our experience with other products developed for an obesity indication. An approval action on your application cannot be taken until we have reached agreement on PMR milestone dates. We suggest that you accelerate the processes you describe below to achieve our proposed timelines.**

As these PMRs and the timelines must be agreed upon and included in any approval letter, we request that you submit revised timelines at your earliest convenience.

Please submit these dates informally, via email. [Please confirm receipt of this email.](#)

Sincerely,

Pat Madara
 Regulatory Project Manager
 Division of Metabolism and Endocrinology Products
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research
 10903 New Hampshire Avenue
 Silver Spring, MD 20993-0002
 Phone: 301-796-1249

From: Craig Audet [mailto:CAudet@arenapharm.com]
Sent: Thursday, June 14, 2012 6:01 PM
To: Madara, Patricia
Cc: Daniel Kim
Subject: RE: NDA 022529 PMR study timelines - request for revision

Pat,

Please see the table below. We are asking that our original proposals be reconsidered and have provided some additional rationale for how we chose our dates. Additional detail is also included in the attached spreadsheet.

Thanks,

Craig

Juvenile animal study		
Final Protocol Submission	6/30/2013	Agreed
Study Completion	9/30/2014	Agreed
Final Report Submission	12/31/2014	Agreed
PREA PK study* (12-17)		
Final Protocol Submission	3/31/2013	Agreed
Study Completion	12/31/2013	Agreed
Final Report Submission	3/30/2014	Agreed
PREA Safety/Efficacy study(12-17)		(b) (4)
Final Protocol Submission	(b) (4)	
Study Completion	(b) (4) (9/30/2017)	
Final Report Submission	(b) (4) (3/30/2018)	
PREA PK study** (7-11)		
Final Protocol Submission	(b) (4) (9/30/2014)	Agreed
Study Completion	(b) (4) (6/30/2015)	Agreed

PREA Safety/Efficacy study(12-17)

Final Protocol Submission		6/30/2015
Study Completion	(b) (4)	(9/30/2017)
Final Report Submission	(b) (4)	(3/30/2018)
PREA PK study** (7-11)		
Final Protocol Submission	(b) (4)	(9/30/2014)
Study Completion	(b) (4)	(6/30/2015)
Final Report Submission	(b) (4)	(9/30/2015)
PREA Safety/Efficacy study### (7-11)		
Final Protocol Submission	(b) (4)	(6/30/2018)
Study Completion	(b) (4)	(10/31/2020)
Final Report Submission	(b) (4)	(4/30/2021)
CVOT		
Final Protocol Submission	(b) (4)	(12/31/2012)
Study Completion	(b) (4)	(12/31/2017)
Final Report Submission	(b) (4)	(12/31/2018)

As these PMRs and the timelines must be agreed upon and included in any approval letter, we request that you submit revised timelines at your earliest convenience.

Please submit these dates informally, via email. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
 Regulatory Project Manager
 Division of Metabolism and Endocrinology Products
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research
 10903 New Hampshire Avenue
 Silver Spring, MD 20993-0002
 Phone: 301-796-1249

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PATRICIA J MADARA
06/28/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, June 06, 2012 8:47 PM
To: 'Craig Audet'
Subject: NDA 022529 Belviq - Request for additional revisions to container label and carton
Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated June 5, 2012, containing **revised** draft mock-ups of the container label (100 tablets), professional sample blister cards, and cartons for the blister cards. We have reviewed these draft pieces of labeling and have the following additional request for revision.

Carton Labeling and Container Label:

- **Reduce the prominence of the net quantity statement (100 Tablets and 10 Tablets) and relocate to ensure that it is away from the strength presentation. As currently presented, the net quantity is more prominent than the strength and the net quantity statement can be misinterpreted as the strength of the drug.**

We suggest you submit the proposed labeling for review, unofficially only, via email. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
06/06/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, June 06, 2012 10:09 PM
To: 'Craig Audet'
Cc: Madara, Patricia
Subject: NDA 022529 - requests for additional analyses
Importance: High
Attachments: Belviq PI_FDA info req_6-6-12.pdf

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin HCl) Tablets, 10 mg.

In addition, reference your amendment dated May 23, 2012, containing a revised version of your package insert (PI) and patient package insert (PPI) for Belviq. We are currently reviewing your submission and have requests for additional information. These requests are explained in the attached PDF document.

Please submit your analyses informally, via email, but also submit them to your NDA. There is no need to submit revised labeling at this time. **Please confirm receipt of this email.**

Sincerely:

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Request for Information for Belviq label: Predicting Week 52 weight loss non-responders from Week 12 results

We would like to include the following statement in Part 2 (Dosage and Administration) of the label: “Response to therapy should be evaluated by week 12. If a patient has not lost at least (*criterion level %*) of baseline body weight, discontinue Belviq (*Table reference*).” The table reference will point to a table in Part 14, showing the sensitivity and specificity of the criterion level of weight loss at week 12, obtained from the combined Bloom and Blossom studies.

We identified a criterion level of 5% weight loss at week 12, based on a preliminary evaluation of sensitivity and specificity from the Bloom and Blossom studies (see Table 1 and Table 2 below). We request that you evaluate the sensitivity and specificity further, in order to select a criterion level for the label. We request that the evaluation include the following:

1. Combine the Bloom and Blossom databases
2. Use the 5% responder endpoint at week 52, with the MITT/LOCF database.
3. Use a Yes/No responder endpoint at week 12 for the predictor variable (MITT/LOCF).
4. Evaluate criterion levels of 3%, 4% and 5% for the Yes/No responder endpoint at week 12. Other criterion levels can also be included.
5. Calculate sensitivity and specificity, defined with reference to correctly identifying a 5% non-responder at week 52, based on being classified as a (*criterion-level %*) non-responder at week 12.

Table 1. Lorcaserin (10 mg bid), Study 009, based on a criterion of 5% at week 12 (MITT/LOCF):

		5% responder at week 52 (MITT/LOCF)		
		Correctly classified at week 52	Incorrectly classified at week 52	Total
Week 12 non-responder		686 (a non-responder at week 52)	145 (a responder at week 52)	831
Week 12 responder		587 (a responder at week 52)	120 (a non-responder at week 52)	707
Sensitivity:	(# non-responders at week 52 correctly predicted by being classified as a non-responder at week 12) (# week 12 non-responders)	686/ (686+120)	686/806	85.1%
Specificity:	(# responders at week 52 correctly predicted by being classified as a responder at week 12) (#week 12 responders)	587/ (587+145)	587/732	80.2%

Table 2. Lorcaserin (10 mg bid), Study 011, based on a criterion of 5% at week 12 (MITT/LOCF):

		5% responder at week 52 (MITT/LOCF)		
		Correctly classified at week 52	Incorrectly classified at week 52	Total
Week 12 non-responder		702 (a non-responder at week 52)	149 (a responder at week 52)	851
Week 12 responder		579 (a responder at week 52)	128 (a non-responder at week 52)	707
Sensitivity:	(# non-responders at week 52 correctly predicted by being classified as a non-responder at week 12) (# week 12 non-responders)	702/ (702+128)	702/830	84.5%
Specificity:	(# responders at week 52 correctly predicted by being classified as a responder at week 12) (#week 12 responders)	579/ (579+149)	579/728	79.5%

We also request that a similar evaluation be conducted for the Bloom-DM study.

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/s/

PATRICIA J MADARA
06/06/2012

Madara, Patricia

From: Madara, Patricia
Sent: Monday, June 04, 2012 3:14 PM
To: 'Craig Audet'
Subject: NDA 22529 - REQUEST FOR REVISED CONTAINER AND CARTON LABELING

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your email dated April 25, 2012, containing draft mock-ups of the container label (100 tablets), professional sample blister cards, and cartons for the blister cards. We have reviewed these draft pieces of labeling and have the following requests for revision.

A. Container Label (100-count)

- 1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).**
- 2. The finished dosage form (i.e. Tablets) is part of the established name. Therefore we request you include “Tablets” following (Lorcaserin HCl) on the principal display panel (PDP).**
- 3. Remove or reduce the prominence of the graphic located beside the proprietary name as it distracts from the most important information such as the proprietary name, established name, and strength statements.**
- 4. Relocate or reduce the prominence of the Manufacturers and Distributors logo located on the PDP and on the lower portion of the carton labeling as it distracts from the most important information such as the proprietary name, established name, and strength statements.**

B. Carton Labeling (10-count professional sample)

- 5. See Comments A1 though A4 and revise the carton labeling for the professional sample accordingly.**

C. Professional Sample Blister cards

- 6. Ensure that the sample blister cards incorporate the expiration date and lot number.**
- 7. Add the phrase “per tablet” after the strength as space permits (e.g., 10 mg per tablet).**

Please submit your revised full color mock-ups officially to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
06/04/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, June 27, 2012 10:55 AM
To: 'Craig Audet'
Subject: NDA 22529 BELVIQ (lorcaserin hydrochloride) 10 mg tablets

Importance: High

NDA 22529

Dear Craig,

We note your emails send June 26, 2012 at 10:30 PM and June 27, 2012 at 10:10 AM, stating Arena's agreement to the labeling sent to you via email on June 26, 2012 at 10:05 PM (PPI) and June 27, 2012 (PI) at 9:44 AM. No response to this email is required.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products Office of Drug Evaluation II Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

-----Original Message-----

From: Craig Audet [mailto:CAudet@arenapharm.com]
Sent: Wednesday, June 27, 2012 10:10 AM
To: Madara, Patricia
Subject: Re: From the top of the mountain - minor edit

Pat,

Arena accepts this revision.

Kind Regards,

Craig

Sent from my iPad

On Jun 27, 2012, at 6:44 AM, "Madara, Patricia" <Patricia.Madara@fda.hhs.gov> wrote:

> Craig;

>

> The highest levels of CDER have requested a very small edit in the indications section - see two words added to the Indications in the Highlights and FPI sections. Please let me know if you accept the revisions. If you accept, please do not send the label back.

>

- > Sorry about the lateness - many levels are involved here. (NME and
- > first approved in 13 yrs)
- >
- > Pat
- >
- > <27June12_Belviq_Pi only_FDA to arena.doc>

Madara, Patricia

From: Craig Audet [CAudet@arenapharm.com]
Sent: Wednesday, June 27, 2012 10:10 AM
To: Madara, Patricia
Subject: Re: From the top of the mountain - minor edit

Pat,

Arena accepts this revision.

Kind Regards,

Craig

Sent from my iPad

On Jun 27, 2012, at 6:44 AM, "Madara, Patricia" <Patricia.Madara@fda.hhs.gov> wrote:

> Craig;

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> The highest levels of CDER have requested a very small edit in the indications section - see two words added to the Indications in the Highlights and FPI sections. Please let me know if you accept the revisions. If you accept, please do not send the label back.

>

> Sorry about the lateness - many levels are involved here. (NME and first approved in 13 yrs)

>

> Pat

>

> <27June12_Belviq_PI only_FDA to arena.doc>

Madara, Patricia

From: Craig Audet [CAudet@arenapharm.com]
Sent: Tuesday, June 26, 2012 10:35 PM
To: Madara, Patricia
Cc: Daniel Kim
Subject: RE: NDA 22529 Belviq package insert and patient package insert

Pat,

Arena finds these documents acceptable.

Kind Regards,

Craig

Craig M. Audet
Vice President, Global Regulatory Affairs
Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, CA 92121

Tel: (858) 453-7200 ext. 1612
Fax: (858) 667-0065
caudet@arenapharm.com

=====
The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Tuesday, June 26, 2012 7:13 PM
To: Craig Audet
Subject: NDA 22529 Belviq package insert and patient package insert

NDA 022529 **Request for Labeling Agreement**

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin Hydrochloride) Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. Finally, we reference your revised package insert (PPI) and package insert (PI) submitted via email on June 22, 2012 (revised June 25, 2012) and June 25, 2012, respectively. We have reviewed your labeling and made minor language and formatting revisions.

I have attached the FDA approved versions of the PI and PPI. Please let us know, via email, if you find

these documents acceptable. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA J MADARA
06/27/2012

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, June 14, 2012 12:22 PM
To: 'Craig Audet'
Subject: NDA 022529 PMR study timelines - request for revision

Importance: High

NDA 022529

ADVICE / INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin HCl) Tablets, 10 mg.

In addition, reference our teleconference held on June 11, 2012, to discuss the post-marketing requirements (PMRs) for Belviq, and your email dated June 13, 2012, providing proposed milestone dates for your PMRs.

The Agency disagrees with your proposed timelines and has the following recommendations.

- **FDA has determined that the PREA pharmacokinetic studies should be done** (b) (4) **and has proposed alternative dates for the conduct of the PREA PK study in 7-11 year olds**
- **FDA is proposing alternative timelines for the PREA safety and efficacy studies that are consistent with PREA timelines we have reviewed for other products**
- **FDA is proposing alternative timelines for the cardiovascular outcome trial that are consistent with timelines we have reviewed for other products**

Please see FDA's proposed revised timelines - in red below

STUDY	sponsor proposed timelines (FDA proposed timelines)
Juvenile animal study	
Final Protocol Submission	6/30/2013
Study Completion	9/30/2014
Final Report Submission	12/31/2014
PREA PK study* (12-17)	
Final Protocol Submission	3/31/2013
Study Completion	12/31/2013
Final Report Submission	3/30/2014

PREA Safety/Efficacy study(12-17)	
Final Protocol Submission	6/30/2015
Study Completion	(b) (4) (9/30/2017)
Final Report Submission	(b) (4) (3/30/2018)
PREA PK study** (7-11)	
Final Protocol Submission	(b) (4) (9/30/2014)
Study Completion	(b) (4) (6/30/2015)
Final Report Submission	(b) (4) (9/30/2015)
PREA Safety/Efficacy study### (7-11)	
Final Protocol Submission	(b) (4) (6/30/2018)
Study Completion	(b) (4) (10/31/2020)
Final Report Submission	(b) (4) (4/30/2021)
CVOT	
Final Protocol Submission	(b) (4) (12/31/2012)
Study Completion	(b) (4) (12/31/2017)
Final Report Submission	(b) (4) (12/31/2018)

As these PMRs and the timelines must be agreed upon and included in any approval letter, we request that you submit revised timelines at your earliest convenience.

Please submit these dates informally, via email. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
06/14/2012

Madara, Patricia

From: Madara, Patricia
Sent: Monday, June 11, 2012 5:15 PM
To: 'Craig Audet'
Subject: NDA 22529 Belviq (lorcaserin HCl) Tablets - post marketing required studies.

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin HCl) Tablets, 10 mg.

In addition, reference our teleconference held today to discuss the post-marketing requirements (PMRs) for Belviq. As mentioned during the meeting, the studies are repeated below. Also, we reiterate the requirement to reach agreement regarding proposed timelines for submission of final protocols, study completion, and final report submission before an action letter for Belviq can issue.

1. **A clinical pharmacology study to assess pharmacokinetic parameters related to a BELVIQ dose of 10 mg in pediatric patients ages 12 to 17 years (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population.**
2. **A clinical pharmacology study to assess pharmacokinetic parameters related to a BELVIQ dose of 10 mg in pediatric patients ages 7 to 11 years (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population.**
3. **A 52-week randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of BELVIQ for the treatment of obesity in pediatric patients ages 12 to 17 years (inclusive). You may not initiate this study until the results of your juvenile animal study PMR have been submitted and reviewed.**
4. **A 52-week randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of BELVIQ for the treatment of obesity in pediatric patients ages 7 to 11 years (inclusive). You may not initiate this study until results from the BELVIQ adolescent safety and efficacy study (ages 12 to 17 years) have been submitted and reviewed by the Agency.**

5.  (b) (4)

- 6. A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with BELVIQ on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. Serial echocardiographic assessments should also be included.**

For each study/trial, please provide via e-mail correspondence, the following dates:

Final Protocol Submission: MM/DD/YY
Study/Trial Completion: MM/DD/YY
Final Report Submission: MM/DD/YY

Please be advised that a PMR protocol is deemed “final” when FDA and the applicant have reached agreement on the protocol. In your proposed timelines, you should allow sufficient time for FDA review and revision of your proposed protocol.

As these PMRs and timelines must be agreed upon and included in any approval letter, we request that you submit your timelines at your earliest convenience.

Please submit these dates informally, via email. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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PATRICIA J MADARA
06/11/2012



NDA 022529

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, CA 92121

Attention: Craig M. Audet
Vice President, Global Regulatory Affairs

Dear Mr. Audet:

Please refer to your New Drug Application (NDA) dated December 18, 2009, received December 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorcaserin Tablets, 10 mg. Please also refer to your complete Class 2 resubmission to this NDA, dated December 23, 2011 and received December 27, 2011.

We also refer to your February 1, 2012, correspondence, received February 2, 2012, requesting review of your proposed proprietary name, Belviq. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Belviq, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If any of the proposed product characteristics as stated in your December 22, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0997. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Patricia Madara at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/02/2012

Madara, Patricia

From: Madara, Patricia
Sent: Friday, April 27, 2012 9:55 AM
To: 'Craig Audet'
Subject: NDA 022529 - Request for Information

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BELVIQ (lorcaserin HCl), tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, containing a complete response to our CR letter issued on October 22, 2010. We continue to review your submission and have a request for additional information. Please respond to the question below:

- **When did patient 181-S001 with prolactinoma in the BLOOM trial first start developing symptoms or signs that led to the diagnosis?**

You may submit this data informally, via email but also submit it officially to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
04/27/2012

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, April 12, 2012 10:50 AM
To: 'Craig Audet'
Cc: Madara, Patricia
Subject: NDA 022529 - Request for Information

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We continue to review your submission and have the following additional request for information:

- **Please clarify why the dissolution acceptance criterion listed in the CoA (Certificate of Analysis) of the NDA resubmission is not consistent with the acceptance criterion of Q = ^{(b) (4)} at 15 minutes previously agreed upon on 8/3/2010. Please revise the CoA and provide a copy of the updated specifications table for your product.**

You may submit this data informally, via email but also submit it officially to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
04/12/2012



NDA 022529

GENERAL ADVICE

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Vice President, Global Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Audet;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our complete response (CR) letter issued on October 22, 2010.

Controlled Substance Staff (CSS) has reviewed the referenced material and has the following comment:

1. CSS is recommending that lorcaserin hydrochloride be scheduled in Schedule IV of the Controlled Substances Act.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
04/10/2012

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, April 03, 2012 5:03 PM
To: 'Craig Audet'
Subject: NDA 022529 (lorcaserin) - requesting corrections to PLR format
Attachments: PLR format deficiencies.pdf

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011 and your email received on March 28, 2012, containing an unofficial WORD version of the PI in PLR format.

I have conducted a very brief review of the PI **format only**. The deficiencies found are listed in the attached PDF document. Please revise the label to correct the issues described and resubmit unofficially, via email, in WORD.

Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Physicians Labeling Rule Format Deficiencies

General

1. The symbols '<', '≤', '>', '≥' are utilized to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. Please revise the labeling to replace all symbols with corresponding text.
2. Any required section, subsection, or specific information that is clearly inapplicable may be omitted from the FPI. However, the numbering does not change. This is important to remember for the required subsections in Sections 8 (Use in Specific Populations), 12 (Clinical Pharmacology) and 13 (Nonclinical Toxicology). For example, subsection 8.2 is titled “Labor and Delivery.” Your label does not contain section 8.2 so the numbering would appear as 8.1, 8.3, 8.4, etc. in the table of contents and FPI and would be referenced appropriately in the Highlights section.
3. Each subheading that is used must be assigned a decimal number that corresponds to its placement and order in the FPI [e.g., (12.3 **Pharmacokinetics**)]. **Do not number headings within a subsection [e.g., (12.3.1 Metabolism)]**. Use headings within a subsection without numbering [e.g., *Metabolism*]. (i.e. There should be no more than one decimal point.) For other labeling information (headings within subheadings), use bold type sparingly. Use another method for emphasis such as italics or underline.
4. Per regulation 21 CFR 201.57(d)(8), the margins for HIGHLIGHTS must be ½ inch. Since the label is one document, all margins should be ½ inch. The margins should not differ.

Highlights

5. In the FPI, you refer to lorcaserin as a “selective serotonin 2C agonist.” If lorcaserin is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class as follows: “Lorcaserin is a (name of class) indicated for (indications(s)).” If the drug is not a member of an established pharmacologic class, the statement should be omitted. For the pharmacologic class web page see <http://elist/prpllr/ :Query/Substance and Pharmacologic Class/Active Moiety Name>.
6. The preferred presentation of referencing in Highlights is the numerical identifier in parentheses [e.g., (1)] **following** the summarized labeling information. This should be corrected in the INDICATIONS AND USAGE section.

7. You should include a concise statement of the drug's indications without the use of dashed lines. This should be corrected in the INDICATIONS AND USAGE section.
8. Patient Counseling Information is a REQUIRED section and must be included in the Highlights in bold type. If lorcaserin has (or will have) FDA-approved patient labeling, use the following verbatim statement: **“See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”**

Full Prescribing Information (FPI)

9. The purpose of the required **PATIENT COUNSELING INFORMATION** section is to draw the prescriber's attention to the presence and content of a PPI, MG or Instructions for Use at the end of the labeling. The statement “See FDA-approved patient labeling (Patient Information)” should appear at the beginning of Section 17 to give it prominence. The exact wording above should be used.

Include information for prescribers to convey to patients to use the drug safely and effectively (e.g., precautions concerning driving, concomitant use of other substances that may have harmful additive effects, adverse reactions reasonably associated with use of the drug, potential risks and benefits of use of the drug in pregnancy). The information, whether organized by subsection headings or bulleted items, should be listed in order of clinical importance. Do not insert a PPI or MG under the Patient Counseling Information section in lieu of developing this section.

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/s/

PATRICIA J MADARA
04/06/2012



NDA 022529

MEETING MINUTES

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Vice President, Global Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Audet;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Belviq (lorcaserin hydrochloride) Tablets, 10 mg.

We also refer to the informal teleconference between representatives of your firm and the FDA on March 26, 2012. The purpose of the meeting was to discuss topics of interest related to the upcoming Advisory Committee meeting.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 26, 2012
TIME: 3:45 – 4:30 PM
LOCATION: teleconference
APPLICATION: NDA 022529
DRUG NAME: Belviq (lorcaserin HCl)
TYPE OF MEETING: informal discussion of possible advisory committee issues
MEETING CHAIR: Eric Colman, M.D.; Deputy Director of DMEP
MEETING RECORDER: Patricia Madara

FDA Attendees:

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Patricia Madara, M.S.	Regulatory Project Manager

Industry Attendees:

Arena Participants

Hussien “Sunny” Al-Shamma, PhD	Pharmacology
Craig M. Audet	Regulatory Affairs
Dominic Behan, PhD	Receptor Pharmacology
William Shanahan, MD	Medical Affairs

Eisai Participants

Mark Taisey	Regulatory Affairs
Betsy Waldheim	Regulatory Affairs

Background:

On December 23, 2011, Arena Pharmaceuticals resubmitted new drug application (NDA) 022529 for Belviq (lorcaserin hydrochloride) tablets. Lorcaserin hydrochloride is a new molecular entity that targets activation of the serotonin 5HT_{2C} receptor and is intended to promote weight loss in an obese population.

An Advisory Committee meeting (AC) will be convened on May 10, 2012 to discuss new data submitted to the application. On March 26, 2012, in response to a request from the company, a brief, informal teleconference was held between the DMEP and Arena Pharmaceuticals to discuss topics of interest relevant to the upcoming AC. No formal meeting request or specific questions were submitted by Arena.

Discussion:

Arena (the company, the applicant), asked if the results of the pathology working group (PWG) would be a topic of discussion.

DMEP responded that they had no concerns with the new data. The results were comprehensive and answered the Division's questions. The PWG results were considered definitive.

The company asked if the increased aggressiveness of adenocarcinomas would be a focus of the Division's presentation at the AC.

DMEP responded that the PWG results had addressed the Division's concerns. Adenocarcinomas were only a concern at the high-dose multiple. Secondary metastases at the mid-dose were considered "equivocal."

DMEP noted that fibroadenomas were increased at all doses and the prolactin data submitted by Arena were not convincing. The prolactin response to lorcaserin was minimal and transitory, while the response to the positive control, perphenazine, was robust and persistent. The Division is not sure how the prolactin response to lorcaserin contributes to fibroadenoma development at low and mid-doses of drug. In addition, when prolactin data collected from 900 time points per treatment group are plotted, there were a handful of animals with increased prolactin levels. This does not explain the increases in numbers of fibroadenomas. Arena stated that a recent analysis of the prolactin data, not included in the CR response, more clearly demonstrated an increase in overall prolactin exposure in the low and mid doses of lorcaserin. The Division agreed that Arena should submit the recent analysis to the Agency for review.

The applicant asked about discussion of a REMS as related to the possible increased development of fibroadenomas in women.

The Division commented that it would be hard to imagine this would necessitate implementation of a REMS, since no women in the clinical trials developed fibroadenomas.

Arena asked if they should consider a postmarketing study to monitor for development of increased numbers of fibroadenoma in women taking lorcaserin.

DMEP responded that such a study might be of value if it was feasible. Arena should put together one or two reasonable protocol summaries and submit for review.

The Division asked the applicant if the mechanistic studies were conducted in a blinded manner by Dr. Russo's lab. In addition, it was noted that the treatment and animal ID numbers did not match in the table containing this data.

Arena commented that Dr. Russo's lab had been given blinded ID#s. The last data submitted to FDA had been QCd and were accurate. The company indicated they would respond to the Division's question.

DMEP commented that the CNS study results were surprising, noting that brain levels were lower than expected and increased the safety margin.

Arena agreed that the low partitioning was a surprise.

With respect to clinical data that would be presented at the AC meeting, DMEP stated that echo data would be discussed. Although DMEP noted that BLOOM-DM had more events of VHD in the lorcaserin group than placebo at week 52, they stated that results of the three trials would be pooled and that other echo analyses would be considered as well.

The company asked about FDA's interpretation of Arena's new analysis of the echo data that had recently been submitted to the NDA.

The Division stated that the statistical review team was currently reviewing the data and conducting their own analysis.

Arena asked if the recommendation by Controlled Substance Staff to schedule lorcaserin as a Schedule IV controlled substance remained the same.

DMEP noted this recommendation was unchanged.

Finally, the applicant asked about the make up of the advisory committee.

The Division stated the committee would include at least two toxicologists and several obesity experts.

The teleconference ended.

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/s/

PATRICIA J MADARA
04/28/2012

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, March 01, 2012 11:00 PM
To: 'Craig Audet'
Subject: NDA 022529 - Another request for information

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We continue to review your submission and have the following additional requests for information:

- 1. It is stated that receptor densities in all of the newly conducted functional assays were determined by radioligand binding. Please provide summary data describing the receptor densities achieved in the cell lines expressing the human 5HT2A, B, and C receptors.** Appears This Way On Original
- 2. It is stated that receptor densities in the newly conducted pharmacology studies were 'consistent with physiological levels', ranging from 30 to 300 fmol/mg membrane protein. Please clarify if this statement is based on data other than the publications cited previously in your advisory committee briefing book for mouse and human hypothalamus (Marazziti et al 1999; Li et al 1993).**
- 3. It is our understanding that the densities of 5HT2 receptors in the original 2002 functional assays ranged from 400-1100 fmol/mg membrane protein. Is this correct?**
- 4. Please clarify the approximate density of the human 5HT2 receptors and specifically the human 5HT2B receptor present in cell lines used for the 2009 functional assays.**

This information should be officially submitted to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
03/02/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, February 29, 2012 3:56 PM
To: 'Craig Audet'
Subject: NDA 022529 (lorcaserin HCl) - urgent request for information

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We continue to review your submission and have the following additional request for information:

- **Please submit the following NONMEM datasets:**
 1. **PopPK dataset: APD12911rINC10.csv**
 2. **Continuous PK/PD dataset: APD91011_CPKPD_ACTPL0.csv**
 3. **Categorical PK/PD dataset: PD091011L_LABS.CSV**

- **the NONMEM control streams (ctl) files for the final models.**

Please submit the requested files within seven days of receiving this communication, since they are needed to perform the analysis.

This information must be officially submitted to the NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
02/29/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, February 08, 2012 9:34 AM
To: 'Craig Audet'
Subject: NDA 22529 - REQUEST FOR INFORMATION

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We are reviewing your submission and have the following request for additional information:

- **Please provide individual animal data for plasma prolactin and mammary tissue morphology (b) (4) and Dr Russo's lab) and PCNA data for female rats in the DBR-11-002 study (Three Month Evaluation of Lorcaserin Effects on Prolactin Concentrations and Mammary Gland Histology in Female Sprague-Dawley Rats). The individual animal data in the format you have provided for the 3-month study in male rat study (DBR-11-004) will be adequate.**

You may provide responses unofficially, via email, but also submit them officially to your NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
02/08/2012

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, February 07, 2012 10:29 AM
To: 'Craig Audet'
Cc: Madara, Patricia
Subject: NDA 22529 (lorcaserin HCl) CLINICAL AND STATISTICAL REQUESTS FOR INFORMATION
Importance: High
Attachments: 07Feb12 Requests for Information.pdf

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We are reviewing your submission and have requests for additional information. Please see the attached PDF document ([2 pages](#)) containing our requests. Submit your responses as rapidly as possible so that we may continue our review process. Contact me if you have questions or require further clarification.

You may provide responses unofficially, via email, but also submit them officially to your NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Lorcaserin NDA 22-529

1. For the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), you only submitted 4 analysis datasets (DM, DS, Echo, and Prolactin). Please provide additional integrated datasets for vital sign.
2. With regard to the exploratory results submitted in “*Supplementary Analyses of Association of Weight (BMI) Change with Incidence of FDA-defined Valvulopathy in Pooled Phase 3 Studies*” (NDA 22-529/SN034, Section 5.3.5.3), please provide the following information in order to facilitate our review of the data and allow us to reproduce the results in your report.
 - 2.1 Please provide analysis data set(s) for these supplementary analyses.
 - 2.2 In all these supplementary analyses, the outcome variable was chosen to be ‘FDA-defined valvulopathy at Week 52’. Detailed definition of this variable should be provided. For example, whether subjects with FDA defined valvulopathy at baseline were included in the analyses? Whether EXAMPARM=’ FDA VALVULOPATHY’ or EXAMPARM=’ FDA VALVULOPATHY (LOCF)’ was used to identify records to be included in the analyses?
 - 2.3 For each Logistic Regression Model shown in Table 1 through Table 9, the number of subjects contributed to the model should be included in the tables.

1. Clarify the following discrepancies and provide the number and proportion of patients who *permanently discontinued the drug (regardless of whether they remained in the study)* due to an AE in the sample table, below. Describe what variable was used in the datasets to identify these adverse events.

In section 13.1.1 of the BLOOM-DM CSR, you state, “Adverse events accounted for treatment discontinuation in 6.3%, 8.6%, and 4.3% of the lorcaserin 10 mg QD, 10 mg BID, and placebo groups, respectively.”

However, Table 14.3.7 from BLOOM-DM reports the number (%) of patients reporting AEs leading to discontinuation of study drug as follows: lorcaserin 10 mg BID, 9 (3.5); lorcaserin 10 mg QD, 6 (6.3); and placebo, 8 (3.2).

Furthermore, Table 12 from the Summary of Clinical Safety reports that the number (%) of patients with “Discontinuation/Stop Study Drug due to AE” in the BLOOM-DM trial as lorcaserin 10 mg BID, 22 (8.6); lorcaserin 10 mg QD, 7 (7.4); and placebo, 14 (5.6).

	Lorcaserin 10 mg BID (N=256)	Lorcaserin 10 mg QD (N=95)	Placebo (N=252)
No (%) pts discontinued drug due to 1 or more AEs	n (%)	n (%)	n (%)
SOC 1	n (%)	n (%)	n (%)
PT 1	n (%)	n (%)	n (%)
PT 2	n (%)	n (%)	n (%)
SOC 2	n (%)	n (%)	n (%)
PT 3	n (%)	n (%)	n (%)

2. Provide a narrative for AE hepatitis for patient ID 1216-0548, including any work-up that was conducted.

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/s/

PATRICIA J MADARA
02/07/2012

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, January 31, 2012 8:50 AM
To: 'Craig Audet'
Subject: NDA 22529 (lorcaserin HCl) Tablets, 10 mg - REQUEST FOR INFORMATION

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We are reviewing your submission and have the following requests for additional information:

- 1. Describe the circumstances surrounding the closure of the 4 sites (sites 1102, 1186, 1199, and 1211) and the disposition of those patients.**
- 2. Please provide narratives for the following AEs:**
 - a. Subj ID 1105-0407: Agitation; also please state why Arena decided to discontinue the patient**
 - b. Subj ID 1273-0327: Confusional state**
 - c. Subj ID 1105-0278: Incoherent**
 - d. Subj ID 1130-0494: Dysarthria**
- 3. Please provide the most updated MedWatch forms for all SAEs**
- 4. In Table 30 of the summary of clinical safety, it is reported that 5 patients on lorcaserin had AEs of hyperprolactinemia in the BLOOM-DM trial, but those AEs could not be located in the BLOOM-DM AE dataset. Please provide patient IDs and describe the circumstances (prolactin levels, etc) surrounding those AEs.**
- 5. We note that there are 3 patients, all from site 1132 (-0154, -0158, -0223), with 59 events of PT 'blood glucose decreased' between them. (We note that that only 3 patients in the rest of the study had a total of 4 such events.) Please confirm and describe the circumstances.**
- 6. Patient 1158-S019 had elevated PASP (61 and 76 mmHg) by echo on weeks 24 and 52 and reportedly had a history of pulmonary hypertension, but PASP 25 mmHg on baseline echo. She followed up with the cardiologist who had seen her previously (and presumably made the diagnosis of PAH). How was PAH diagnosed in the past? What was PASP on previous echocardiograms?**

You may provide responses unofficially, via email, but also submit them officially to your NDA. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
01/31/2012

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, January 27, 2012 12:34 PM
To: 'caudet@arenapharm.com'
Subject: Re: NDA 022529 Information request-Jan.27, 2012

Dear Mr. Audet

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

We also refer to your resubmission dated Dec. 23, 2011.

Section 1.11.1 of your resubmission indicates that you intended to amend the protocol for annual commitment lots of the drug product. However, 3.2.P.8.2 (Table 2) remains unchanged. Please resolve this contradiction

Could you acknowledge the receipt of this email and provide timeline for a response.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
01/27/2012

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, January 04, 2012 3:21 PM
To: 'Craig Audet'
Subject: NDA 022529 - Request for Information

Importance: High

NDA 022529

INFORMATION REQUEST

Hi Craig;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

In addition, reference your amendment dated December 23, 2011, submitted in response to our CR letter issued on October 22, 2010. We are initiating a review of the information and have the following request for clarification:

- **The establishment information in Form 356h submitted on December 23, 2011, is different from the information submitted to FDA in the previous review cycle. Confirm that these manufacturing/testing facilities have been deleted from your NDA:** [REDACTED] (b) (4)
[REDACTED] **. And confirm that this new testing facility has been added to your NDA:** [REDACTED] (b) (4)

If the information submitted on the new 356h form is correct, a response via email will suffice. Please confirm receipt of this email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

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/s/

PATRICIA J MADARA
01/04/2012



NDA 022529

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Vice President, Global Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Audet;

We acknowledge receipt on December 27, 2011, of your December, 23, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride tablets, 10 mg.

We consider this a complete, class 2 response to our October 22, 2010, action letter. Therefore, the user fee goal date is June 27, 2012.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
01/03/2012



NDA 022529

MEETING PRELIMINARY COMMENTS

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

*meeting
cancelled*

11/3/11

Dear Mr. Audet;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride tablets, 10 mg.

We also refer to your August 25, 2011, correspondence, received August 26, 2011, requesting a meeting to discuss submission of your complete response for NDA 022529 and the format for presentation of the data.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 7, 2011, at 1:00 PM on the White Oak Campus (building 22), Silver Spring, MD, between Arena Pharmaceuticals and FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

Nonclinical Questions

Nonclinical Question #1

In the CRL, FDA requested a detailed accounting of all slides prepared from female rats that contributed to mammary tumor incidence data in each update to the FDA and in the final study report. Arena proposes to provide a tabulated listing that documents all changes in the diagnosis of female rat mammary tissues by animal number that details the diagnosis in the original study report and the Pathology Working Group's re-adjudication decision. This table will include the following headings: Animal ID, Blinded Animal Number, Tissue, Prior Microscopic Diagnosis, PWG Changes, and PWG Tissue Diagnosis. Is this acceptable to the Agency in order for the NDA review to move forward? (See Section 3.1.1.1.)

FDA Response

The proposed table listing diagnoses from the original study pathologists and the PWG is acceptable, though we request that the table be modified to list all diagnoses by individual slides from each animal. As stated at the End-of-Review meeting, FDA was making regulatory decisions regarding continuation of ongoing clinical studies based on the information provided by you in the interim updates. We acknowledge your explanation that documentation cannot be obtained from (b) (4) for changes in diagnoses made in the final study report from the interim reports submitted to FDA.

Nonclinical Question #2

The results of the Pathology Working Group's (PWG) re-evaluation of the relevant tissues from the rat carcinogenicity study indicate that 97% of fibroadenoma and 92.5% of adenocarcinoma initial diagnoses were unanimous. In addition, the re-adjudicated findings show that adenocarcinoma was increased only at the lorcaserin high dose of 100 mg/kg/day. There is thus a 24-fold margin between human lorcaserin exposures at the recommended dose and exposures in rats at the NOAEL of 30 mg/kg/day for mammary adenocarcinoma based on incidence and other measures of aggressiveness. If the Agency accepts the assertion that diagnostic certainty has been established and that conducting the analyses of tumor types separately is appropriate, are the margin and aggressiveness information related to rat mammary adenocarcinoma sufficient to permit re-assessment of clinical risk for lorcaserin for this issue? (See Section 3.1.1.2 and 3.1.2)

FDA Response

The difference in tumor incidence between the PWG and the original study report, particularly regarding adenocarcinoma, in our view highlights the difficulty in diagnosing these rodent tumors. Nevertheless, the results of the PWG will be viewed as the best estimate of actual mammary tumor incidence in the rat study. As stated in the End-of-Review meeting, the FDA is and has been aware of differences in the pathology and risk posed by mammary adenocarcinoma and fibroadenoma, and will take those differences into account in reviewing the PWG report in your resubmission. The contribution of the results regarding the aggressiveness and tumor latency data as re-interpreted by the PWG will be a review issue. In your resubmission, please include the historical incidence data and any relevant literature to support the claim that the imbalanced lung metastases are 'equivocal'.

Your background package states that a literature review will be provided to demonstrate that the pathogenesis of fibroadenoma in the rat differs from that in humans, and therefore the increase in fibroadenoma at all doses of lorcaserin would be of minimal significance to humans. The FDA risk assessment for the increase in fibroadenomas will be based on the mechanism by which lorcaserin increased this tumor type and whether key events of that mechanism are operative in human biology. To this end, the prolactin mechanistic studies will be pivotal to determining if lorcaserin is acting similarly to other pharmaceuticals known to increase mammary tumors in rodents via this pathway, as you have repeatedly proposed, or not.

Nonclinical Question #3

The results ADP356-022, “An Open Label Study to Assess the Pharmacokinetic Properties of Lorcaserin at Steady State in the Cerebrospinal Fluid of Healthy Volunteers” (the CSF Study) demonstrate that the lorcaserin brain exposure multiples at 10 mg/kg/day and at 30 mg/kg/day are 66 and 325, respectively (MPR-11-007). Is this margin information related to rodent astrocytoma sufficient to permit re-assessment of clinical risk for lorcaserin for this issue? (See Section 3.1.3.)

FDA Response

Yes, results of the completed study are adequate to permit re-assessment of clinical risk on this issue.

Administrative Questions

Administrative Question #1

Arena understands that the CRL response will not be considered complete until a package addressing all noted issues in the CRL is provided to the Agency. However, would the Agency allow Arena to submit the clinical study reports, datasets, and required case report prior to submission of the remainder of the response?

FDA Response

For ease of review we would prefer that the documents be submitted together. For example, it would be helpful for the ISE and ISS – as well as the table of contents you describe in administrative question #3 – to include hyperlinks to relevant clinical data.

Administrative Question #2

Arena plans to provide high level responses to specific issues raised in the CRL in module 1, which will be supported by and linked to reports and data included in modules 2, 4 and 5. Updates to integrated documents in modules 2 and 5 (i.e., ISS and ISE) will be provided, but original NDA documents will not be resubmitted. Does the Agency agree with this approach?

FDA Response

NDA documents do not need to be resubmitted, but updates should provide a comparison of what was shown previously in the original NDA and new data, with a discussion of how new data may modify or support those previous findings. Tables should include both the original NDA data and updated data - integrated when applicable. See the End of Review Meeting minutes for a list of some analyses of interest to the clinical team.

Administrative Question #3

For ease of review, Arena plans to include a table of contents in the cover letter for the CRL response that will be linked to each new document, and to sections of documents that specifically address the CRL questions. Does the Agency agree with this approach?

FDA Response

Yes.

Additional Clinical Information Requested

- 1. Please provide a variable in the BLOOM-DM datasets that indicates whether a particular patient was enrolled prior to or after Amendment 3.**
- 2. Please present the breast tumor data as in the *Breast Cancer Risk Report and Summary for Lorcaserin Phase 3 Trials* as time-to-event using Kaplan-Meier curves and as incidence per patient-year, summarized by treatment arm as well as by 'any lorcaserin dose' vs. placebo. If you have any follow-up information on breast tumor development in study subjects since the trials have been completed, include that as well.**

Additional Controlled Substance Staff Comment

You should submit the data and final study protocols for the two abuse-related nonclinical studies (overt behavior (Study DBR-11-001) and drug discrimination (Study TX11001)) when you submit your full response to the complete response letter (CRL).

Additional General Information

Prescribing Information

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
11/03/2011



NDA 22529

GENERAL ADVICE

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Vice President, Global Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Audet;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride tablets, 10 mg.

We also refer to your October 4, 2011, submission, containing a request for an extension until January 13, 2012, to resubmit the application, in the form of a response to the complete response letter dated October 22, 2010.

We agree with your request for the extension to resubmit this application. We remind you that per 21 CFR 314.110(c), an applicant's failure to resubmit the application within the extended time period or to request an additional extension may be considered a request by the applicant to withdraw the application.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
10/05/2011



NDA 022529

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Audet;

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride tablets, 10 mg.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK

09/06/2011

J. Marchick signing for M. Parks



NDA 022529

MEETING PRELIMINARY COMMENTS

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We also refer to your January 20, 2011, correspondence, requesting a teleconference to obtain guidance from the Controlled Substance Staff (CSS).

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 23, 2011, between Arena Pharmaceuticals and FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Questions

1. Is the proposal to test a range of DOM concentrations, with different doses possibly serving as positive controls for 2A and 2C behaviors, acceptable to the Agency?
2. A possible result of the proposed study is that lorcaserin will induce 2C but not 2A behaviors, and DOM will induce 2A but not 2C behaviors. If this result is observed, we propose performing additional experiments using dexfenfluramine as a positive control for 2C behaviors. Is this proposal to use dexfenfluramine as a positive control (if no 2C behaviors are observed with DOM) acceptable to the agency?

CSS Response (Questions #1 and #2)

Yes, both of these proposals are acceptable. But the Sponsor should bear in mind the caveats expressed below regarding the possible scientific limitations of the study.

CSS General Comments on the Overt Behavior Study Protocol:

The protocol for this study does not include an introduction that explains the purpose of the experiment. However, the protocol for a similar study (Study #DBR09-011) that was submitted in the original NDA states that the purpose of that study was:

- **“1) to determine whether [lorcaserin] produced behavioral signs in the rat which indicate agonist activity at 5-HT_{2C} receptors, and**
- **2) to assess whether the weak in vitro activity for [lorcaserin] at the 5-HT_{2A} receptor translated into any behavioral signs of 5-HT_{2A} activation in vivo.”**

It is unclear, though, to what degree the overt behavioral tests associated with 5-HT_{2A} and 5-HT_{2C} receptors can be used to differentially assess functional receptor activation. Evidence should be provided that the presence or absence of behaviors in response to 5-HT₂ agonist administration correlates: a) to the drugs' receptor binding affinity at the two 5-HT₂ receptor subtypes and b) to the drugs' functional activity at second messenger systems associated with 5-HT₂ receptor subtypes.

CSS also has comments on methodological issues for the overt behavioral study:

- **The doses of lorcaserin should produce plasma levels that are similar to, and greater than, those produced by the proposed therapeutic dose in humans (e.g., 20, (b) (4)).**
- **Administration of lorcaserin should occur via intraperitoneal injection, to match the proposed intraperitoneal administration of DOM and dexfenfluramine.**
- **Behavioral observations should be conducted at a timeframe that overlaps with the C_{max} for each drug.**

Questions (cont.)

3. Will the proposed revised study design satisfy the Agency's requirements for the drug discrimination study with lorcaserin?
4. Do these proposed protocol revisions address all of the procedural discrepancies noted by the CSS in the Complete Response Letter in reference to the original drug

discrimination study (TX08040)? If not, please advise us regarding additional revisions.

CSS Response (Questions #3 and #4)

In general, the protocol is well-designed to evaluate whether lorcaserin generalizes to the DOM discriminative cue.

However, CSS has the following comments regarding the design:

- **A published study investigating various pretreatment times for DOM in drug discrimination showed that a 75-minute pretreatment time was optimal for establishing generalization to LSD, another 5HT2 hallucinogen (Fiorella et al., Psychopharmacology 119(2):239-45, 1995). Thus, (b) (4) is unlikely to produce an appropriate interoceptive cue that is reflective of hallucinogenic effects.**
- **The doses of lorcaserin should produce plasma levels that are similar to, and greater than, those produced by the proposed therapeutic dose in humans (e.g., 20, (b) (4)).**

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

PATRICIA J MADARA
02/21/2011



M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 16, 2011

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
J.P. Gong, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: Type C meeting 2/23/11 regarding preclinical
abuse potential studies
Lorcaserin (Lorquess), NDA 22-529
Indication: Weight Management
Dose: 20 mg/day; 10 mg BID
Sponsor: Arena Pharmaceuticals

Materials Reviewed: Meeting Package

Background:

The Division of Metabolic and Endocrine Products consulted CSS regarding a Type C meeting with the Arena Pharmaceuticals on February 23, 2011. In the meeting package, the Sponsor posed four abuse-related questions for CSS regarding the design of two preclinical studies with lorcaserin (an overt behavioral study and a drug discrimination study).

Lorcaserin is a new molecular entity with 5HT_{2C} and 5HT_{2A} agonist properties, a mechanism of action identical to that of Schedule I hallucinogens. The proposed indication for lorcaserin is weight management, including weight loss and maintenance of weight loss, in conjunction with reduced-calorie diet and regular exercise. The proposed dose range is 20 mg/day (10 mg BID). The NDA for lorcaserin received a Complete Response letter on October 22, 2010.

CSS Comments on Sponsor Questions:

Overt Behavior Study (DBR-11-001):

Sponsor Question #1

Is the proposal to test a range of DOM concentrations, with different doses possibly serving as positive controls for 2A and 2C behaviors, acceptable to the Agency?

Sponsor Question #2:

A possible result of the proposed study is that lorcaserin will induce 2C but not 2A behaviors, and DOM will induce 2A but not 2C behaviors. If this result is observed, we propose performing additional experiments using dexfenfluramine as a positive control for 2C behaviors. Is this proposal to use dexfenfluramine as a positive control (if no 2C behaviors are observed with DOM) acceptable to the agency?

CSS Response to Questions #1 and #2:

Yes, both of these proposals are acceptable. But the Sponsor should bear in mind the caveats expressed below regarding the possible scientific limitations of the study.

CSS General Comments on the Overt Behavior Study Protocol:

The protocol for this study does not include an introduction that explains the purpose of the experiment. However, the protocol for a similar study (Study #DBR09-011) that was submitted in the original NDA states that the purpose of that study was:

“1) to determine whether [lorcaserin] produced behavioral signs in the rat which indicate agonist activity at 5-HT_{2C} receptors, and 2) to assess whether the weak *in vitro* activity for [lorcaserin] at the 5-HT_{2A} receptor translated into any behavioral signs of 5-HT_{2A} activation *in vivo*.”

It is unclear, though, to what degree the overt behavioral tests associated with 5-HT_{2A} and 5HT_{2C} receptors can be used to differentially assess functional receptor activation. Evidence should be provided that the presence or absence of behaviors in response to 5-HT₂ agonist administration correlates: a) to the drugs' receptor binding affinity at the two 5-HT₂ receptor subtypes and b) to the drugs' functional activity at second messenger systems associated with 5-HT₂ receptor subtypes.

CSS also has comments on methodological issues for the overt behavioral study:

- The doses of lorcaserin should produce plasma levels that are similar to, and greater than, those produced by the proposed therapeutic dose in humans (b) (4)
- Administration of lorcaserin should occur via intraperitoneal injection, to match the proposed intraperitoneal administration of DOM and dexfenfluramine.
- Behavioral observations should be conducted at a timeframe that overlaps with the Cmax for each drug.

Drug Discrimination Study (TX11001)

Sponsor Question #3:

Will the proposed revised study design satisfy the Agency's requirements for the drug discrimination study with lorcaserin?

Sponsor Question #4:

Do these proposed protocol revisions address all of the procedural discrepancies noted by the CSS in the Complete Response Letter in reference to the original drug discrimination study (TX08040)? If not, please advise us regarding additional revisions.

CSS Response to Questions #3 and #4:

In general, the protocol is well-designed to evaluate whether lorcaserin generalizes to the DOM discriminative cue.

However, CSS has the following comments regarding the design:

- A published study investigating various pretreatment times for DOM in drug discrimination showed that a 75-minute pretreatment time was optimal for establishing generalization to LSD, another 5HT2 hallucinogen (Fiorella et al., *Psychopharmacology* 119(2):239-45, 1995). Thus, (b) (4) is unlikely to produce an appropriate interoceptive cue that is reflective of hallucinogenic effects.
- The doses of lorcaserin should produce plasma levels that are similar to, and greater than, those produced by the proposed therapeutic dose in humans (e.g., 20, (b) (4))

Summary of Materials Submitted in the Meeting Package:

In addition to the four questions listed above, the Sponsor provided short protocols for two animal behavioral studies: an overt behavior study and a drug discrimination study.

Overt Behavior Study “Effect of lorcaserin and DOM on behavioral signs indicative of in vivo 5HT_{2A} and 5HT_{2C} activity” (DBR-11-001)

Male rats (number not provided) will receive administration of the test drugs or placebo, followed immediately by 60 minute observation for behaviors associated with agonist activity at 5-HT_{2A} receptors (wet dog shakes and back muscle fasciculations) and 5HT_{2C} receptors (penile grooming and decreased motor activity).

The proposed doses for lorcaserin are 4.5, 9, 18 and 36 mg/kg (p.o.).

The dose for the positive control drug, DOM has not been selected and will be based on a dose-finding study in which the doses 0.01, 0.1 and 1.0 mg/kg (i.p.) will be tested for their ability to induce 5HT_{2A}- and 5HT_{2C}-associated behaviors.

In the case that DOM is unable to induce both 5HT_{2A} and 5HT_{2C} behaviors, it is proposed that dexfenfluramine (a serotonin releasing agent that also has 5HT_{2A} and 5HT_{2C} agonist properties) be utilized as the positive control, since this drug is known to produce 5HT_{2A} and 5HT_{2C} behaviors. The proposed doses of dexfenfluramine are 1.0 and 10 mg/kg (i.p.).

Drug Discrimination Study “Evaluation of Lorcaserin in Rats Discriminating DOM” (TX11001)

Male rats (n = 12) will be trained to discriminate between intraperitoneal administration of DOM (0.56 mg/kg) and saline in a drug discrimination test. The schedule of reinforcement will be increased until rats respond on a fixed ratio (FR) value of 10. Rats will receive either treatment 15 minutes prior to placement in the test chamber, followed by an additional 15-minute time-out period in the chamber when the environment is dark. After this 30-minute total pretreatment time, rats will be allowed to respond on DOM-associated or saline-associated bars. Training will continue until rats respond appropriately to each treatment, with an 80% generalization rate. Test sessions will occur no more often than every third day.

After rats have satisfied the full generalization criteria with DOM, testing with lorcaserin will begin. Doses of lorcaserin to be tested include 0.1, 0.3, 1.0 and 3.0 mg/kg (i.p.), with a 30 minute total pretreatment time. During lorcaserin dose testing, rats will also periodically receive DOM or saline sessions in order to confirm continued accurate responses to these treatments.

REFERENCE

Fiorella D, Palumbo PA, Rabin RA, Winter JC. The time-dependent stimulus effects of R(-)-2,5-dimethoxy-4-methamphetamine (DOM): implications for drug-induced stimulus control as a method for the study of hallucinogenic agents. *Psychopharmacology (Berl)*. 1995 May;119(2):239-45.

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/s/

KATHERINE R BONSON
02/16/2011

Jianping P GONG
02/16/2011

MICHAEL KLEIN
02/16/2011



NDA 022529

MEETING MINUTES

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2010. The purpose of the meeting was to discuss the deficiencies to the Lorqess application described in our Complete Response letter, issued on October 22, 2010.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: meeting minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Review
Meeting Date and Time: December 15, 2010; 9:00 AM eastern time
Meeting Location: White Oak Campus, Silver Spring MD
Application Number: NDA 022529
Product Name: Lorqess (lorcaserin HCl) Tablets, 10 mg
Indication: An adjunct to diet and exercise for the treatment of obesity
Sponsor/Applicant Name: Arena Pharmaceuticals
Meeting Chair: Eric Colman, M.D.
Meeting Recorder: Pat Madara

CDER Attendees

Office of New Drugs

David Jacobson-Kram, Ph.D. Director for Pharmacology and Toxicology
Paul Brown, Ph.D. Associate Director for Pharmacology and Toxicology

Office of Drug Evaluation II

Curtis Rosebraugh, M.D., M.P.H. Director
Lee Ripper Associate Director for Regulatory Affairs

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D. Director
Eric Colman, M.D. Deputy Director
Amy Egan, M.D., MPH Deputy Director for Safety
Julie Golden, M.D. Medical Officer
Todd Bourcier, Ph.D. Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D. Pharmacology/Toxicology Reviewer
Patricia Madara, M.S. Regulatory Project Manager

Office of Biostatistics; Division of Biometrics II

Todd Sahlroot, Ph.D. Deputy Director
Janice Derr, Ph.D. Statistical Reviewer

CDER Office of the Center Director, Controlled Substance Staff (CSS)

Katherine Bonson, Ph.D. Pharmacology Reviewer
John Gong, M.D., Ph.D. Medical Officer Reviewer

Arena Pharmaceuticals Attendees

Jack Lief,	Chairman, President and CEO
Mark Brunswick, Ph.D.	Senior Director, Regulatory Affairs
William Shanahan, M.D.	Senior Vice President & Chief Medical Officer
Dominic Behan, Ph.D.	Senior Vice President & Chief Scientific Officer
Christen Anderson, M.D, Ph.D.	Vice President, Lorcaserin Development
Weichao Chen, Ph.D.	Senior Director, Drug Metabolism & Pharmacokinetics
Matilde Sanchez, Ph.D.	Senior Director, Biostatistics and Data Management
Michael Kim	Director, Regulatory Affairs
Hussien Al-Shamma, Ph.D.	Senior Director Pharmacology
K. A. Ajit Simh,	Vice President Quality & Regulatory Compliance

Eisai, Inc., Attendees

Mark Taisey,	President, Global Regulatory Affairs
Lynn Kramer, M.D.	President, Neuroscience Product Creation Unit
Paul Andrews, Ph.D.	Executive Director, Global Regulatory Affairs – Nonclinical

Consultants to Arena and Eisai

[REDACTED] (b) (4)

Jose Russo, MD,	Professor and Senior Member, Fox Chase Cancer Center, Philadelphia, Pennsylvania
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[REDACTED] (b) (4)

Background

On December 18, 2010, Arena Pharmaceuticals submitted new drug application (NDA) 022529 for Lorqess (lorcaserin hydrochloride) tablets. Lorcaserin hydrochloride is a new molecular entity that targets activation of the serotonin 5HT2C receptor and is intended to promote weight loss in an obese population.

On September 16, 2010, the application was discussed at an Advisory Committee meeting. The panel members voted 9 to 5 that the available data do not demonstrate that the potential benefits of lorcaserin hydrochloride outweigh the potential risks, when used long-term in a population of overweight and obese individuals.

On October 22, 2010, the Agency issued a complete response letter, describing our concerns and the deficiencies in the data provided with the application. It also provided, where possible, our recommendations to address the issues.

On October 28, 2010, Arena requested an End-of-Review meeting to discuss the Complete Response letter and obtain guidance from FDA. Pre-meeting draft minutes issued on December 14, 2010. Those minutes and the additional discussion from the meeting are described below.

Note: Arena's questions are in plain text. The FDA's pre-meeting responses are in **bold text**. Discussion at the meeting is in *italicized text*.

Discussion

Nonclinical

1. Diagnostic uncertainty in the classification of mammary masses in female rats

Q1a. Arena plans to convene a Pathology Working Group of 3 to 5 independent pathologists to re-adjudicate the female rat mammary and lung tumors in a blinded fashion as requested by the Agency. The slide blinding and un-blinding will be executed by (b) (4) Arena will provide a list of proposed pathologists, working group instructions, and reporting plans to the Agency for concurrence.

FDA Response:

The revised PWG protocol that incorporated the Division's recommendations is acceptable.

Arena can provide a list of all slides prepared for female rat mammary tissues presented in the updates and the final study report with tabulations of diagnoses that changed. Documentation of the discussions between the pathologists and their notes and reasons for these changes are not available, per standard pathology review practices in the industry. Although these tabulations can be provided, we believe the plans to re-adjudicate the mammary and lung tumors with an independent Pathology Working Group will more directly address the Agency's concern. Does the Agency agree that in view of our commitment to readjudicate these tumor findings this accounting is no longer necessary?

FDA Response:

We acknowledge your explanation that the reasons for the imbalanced change in diagnoses across dose groups were not documented and therefore cannot be provided. It would be acceptable to instead provide a spreadsheet documenting all changes in the diagnosis of female rat mammary tissues from the interim updates to the final study report, listed by animal number.

In addition, we request clarification regarding the pathology records for two high-dose female rats. The histopathology report for female #4202 describes mild atypic hyperplasia of the mammary tissue despite the presence of a large (2-3.9 cm) axillary mass present about 10 weeks prior to euthanasia. The report for female #4212 lists mammary tumors as the cause of death, yet no mammary tumor is described in the histology report for this animal.

Meeting Discussion:

Arena clarified that (b) (4) is unable to provide documentation of the change in diagnoses at the level of individual slides and animals; only the change in diagnoses as a group was documented. Arena explained that interim updates of carcinogenicity studies to the FDA is not standard practice, and therefore documentation of changes in diagnosis from 'preliminary' to 'final' assessments did not capture the information requested by the FDA. Arena restated that all the histology slides that contributed to the interim updates were also examined and contributed to

the final tally provided in the NDA, indicating that (b) (4) should have knowledge of the identity of slides evaluated for the interim updates. The FDA commented that regulatory decisions were being made based on the information provided by Arena in the interim updates, and that documentation that at least specified the subsequent changes to that information was of importance to FDA's review of the final data in the NDA. The FDA requested and Arena agreed to work further with (b) (4) in tracking the animal identification of the slides examined for the interim updates, noting that such information might be derived by examining the relevant histology/cutting notebooks. It was noted that the evaluation by FDA's Division of Scientific Investigations did not include examination of the histology notebooks and was unable to provide adequate clarification on this issue. The FDA remarked that if such documentation is unattainable after further consultation with (b) (4) review of Arena's NDA resubmission would necessarily move forward without the information.

Arena noted that clarification of the histopathology records for the two high-dose female rats would be addressed by the pathology working group.

Unresolved exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma

Q2a. The statistical analysis of the mammary tumor findings included combination of adenocarcinomas and fibroadenomas. This practice of combining the two tumor types is based on the publication by McConnell et al. However, there is now expert opinion based on current knowledge of mechanisms underlying mammary gland carcinogenesis that these tumor types should not be combined because fibroadenomas are known not to be a precursor to adenocarcinomas. Does the Agency agree that statistical analysis of mammary gland fibroadenomas and adenocarcinomas separately but not combined is appropriate?

FDA Response:

The FDA statistical analysis evaluated these two tumor types alone and in combination, as was done by the Sponsor (b) (4) and reported in NDA 22-529. The results of the FDA statistical analysis mirror those reported in the NDA. The FDA is aware that the human risk from these two tumor types may differ, and those differences in human risk can be taken into consideration when there is clarity of diagnosis as reflected in the pathology reports for carcinogenicity studies. Diagnostic uncertainty was evident in the classification of mammary masses in rats administered lorcaserin, for reasons summarized in the Complete Response Letter. Without confidence in the diagnoses, the more conservative approach to assessing human risk is most appropriate.

Some of the Division's recommendations for the PWG are directly targeted to clarify the degree of diagnostic certainty in distinguishing fibroadenoma from adenocarcinoma in the study conducted with lorcaserin. The Division will discuss the most appropriate approach of evaluating the mammary tumors after reviewing the PWG report and their comments on this issue.

Will establishment of a safety margin for the adenocarcinoma be sufficient to address the Agency's concerns?

FDA Response:

A ‘safety margin’ implies a dose range above therapeutic exposure within which adverse effects of a drug are not observed. As summarized in the Complete Response Letter, there is evidence of decreased latency and increased aggressiveness of adenocarcinoma at all doses of lorcaserin in female rats, and therefore, the exposure-response relationship remains unresolved. In addition to numerical increases in tumor incidence, evidence of decreased latency and increased aggressiveness of drug-induced malignancies in rodents contributes to the Division’s assessment of human risk, as does consideration of the risk/benefit associated with a given drug and clinical indication.

Q2b. If Arena provides acceptable evidence that the mammary tumors observed in the 2-year rat carcinogenicity study are due to increased prolactin either in blood or mammary gland, will the Agency consider the prolactin mechanism an adequate explanation for the tumors and their aggressiveness, and will this mechanism satisfy the Agency’s criterion that the tumors are reasonably irrelevant to human risk assessment?

Q2c. Does the weight of evidence introduced in this document provide sufficient evidence of a prolactin mechanism for rat mammary tumors? If not sufficient, would a demonstration of lorcaserin-mediated increases in serum prolactin in intact female rats or increases in prolactin in rat mammary gland be sufficient evidence for a mechanism irrelevant to human risk?

FDA Response to Q2b and 2c:

Experimental evidence with lorcaserin that demonstrably links its effects on mammary tissue in rodents to a prolactin-dependent mechanism will mitigate the Division’s level of concern for clinical risk.

As discussed in the Division’s briefing package to the Advisory Committee, the prolactin data submitted in NDA 22-529 does not provide persuasive evidence implicating this hormone in mammary tumors induced by lorcaserin. The information provided in your background package does not provide nor proposes a strategy to provide the experimental evidence with lorcaserin necessary for the Division to re-assess clinical risk.

The Division recommends that you propose experimental strategies evaluating lorcaserin which could be considered in support of prolactin as the mediating mode of tumorigenic action.

Your background document cites literature linking a 5HT_{2A/2C} pathway to negative regulation of dopamine and additional direct effects on prolactin release. These studies involved *in vitro* and *in vivo* approaches using mixed serotonergic receptor agonists, dopaminergic compounds, and pharmacological 5HT_R antagonists. Lorcaserin is a new molecular entity with a unique 5HT_R selectivity profile and tissue distribution characteristics. We recommend that you propose additional *in vitro* and *in vivo* studies to determine the potential for lorcaserin to alter release of pituitary/tissue prolactin and potentially its regulatory intermediaries such as dopamine and vasoactive intestinal polypeptide. Demonstration of a clear, persistent (<13 wks) increase in serum/tissue prolactin at doses of lorcaserin associated with mammary tumors would mitigate the Division’s concern of clinical risk for this target tissue. If a clear, persistent increase in prolactin is not demonstrable, the Division is interested in experimental designs that

intervene in the expression or activity of prolactin as an approach to implicate prolactin in lorcaserin's tumorigenic effect on mammary tissue.

The Division is not aware of an accepted threshold of prolactin elevation necessary for drug-induced induction or promotion of rodent mammary tumors. The Division disagrees that the data with aripiprazole provides evidence that a small elevation in prolactin may be sufficient for mammary tumor induction. Contrary to the argument presented in the briefing material, Aripiprazole did not increase mammary tumors in male mice (or rats), despite the small 2-4 fold increase in serum prolactin, as shown in Figures 2 & 4 of the background document. Also contrary to the assertion in the background document, aripiprazole increased fibroadenoma but not adenocarcinoma or metastases in female Fischer rats, unlike lorcaserin that increased the incidence and aggressiveness of both mammary tumor types. The increased incidence of adenocarcinoma in female mice with aripiprazole was associated with a 200- to 500-fold increase in serum prolactin within 4 hours after a single dose, and 8 to 9-fold increases (similar to haloperidol) after 1 week of dosing. Serum prolactin and persistent diestrus were documented after 13 weeks of dosing.

Meeting Discussion:

Arena commented that upon further evaluation and consultation with subject experts, an experimental approach has been identified that allows detection of prolactin elevation in response to lorcaserin in sexually intact female rats. Arena remarked that the failure of demonstrating such prolactin elevations in the studies provided in the NDA were due to sub-optimal experimental conditions including the timing of blood collection, animal handling (stress), and the use of isoflurane anesthesia.

The FDA inquired as to why the prior mechanistic studies were capable of detecting prolactin elevations in response to dexfenfluramine and haloperidol, but not to lorcaserin, if the prior studies were confounded by sub-optimal experimental conditions. Specifically, the FDA asked if the prolactin signal with lorcaserin was undetected due to a minimal elevation compared to that induced by haloperidol and dexfenfluramine. Arena remarked that the prolactin elevation with lorcaserin in the new studies is not necessarily minimal. Arena further explained that short-term elevations in prolactin, even minor elevations, could have a significant impact on mammary tumors over a 2-year period in rodents, citing the example involving bromocriptine. The FDA commented that the 6-month toxicology study in Sprague-Dawley rats did not result in histopathological changes in mammary tissue, despite receiving lorcaserin daily for 6 months which included the 'critical window' of exposure. Arena remarked that preneoplastic changes likely occurred in that study (though undetected), with detectable changes emerging at time points beyond six months of dosing.

The FDA specifically asked (b) (4), Arena's consultant on prolactin biology, if experimental approaches are available that would intervene in prolactin expression or activity as a method to more definitively implicate prolactin in the mechanism of lorcaserin's effect on mammary tissue. (b) (4) remarked that the current information in the field does not provide a consensus for how such an intervention could be done experimentally.

Arena remarked that lorcaserin induced changes in the pituitary of rats which are consistent with increased prolactin activity, citing the pathology data from the interim analysis of some rats after 12 months of dosing. The FDA commented that while lorcaserin indeed increased the

incidence of pituitary hyperplasia over the 2-year dosing period, the incidence of pituitary adenoma decreased with increasing doses, and that the incidence of mammary tumors exceeded the incidence of pituitary hyperplasia, suggesting that a relationship of the changes in pituitary to mammary tumors is not clear. (b) (4) added that local tissue expression of prolactin and negative feedback of hormones on the pituitary may confound associations of mammary tumors to changes in pituitary histopathology.

The FDA commented that the relationship of elevations in prolactin to promotion of mammary tumors in rodents is not being challenged; rather, the FDA is interested in determining the mechanism whereby lorcaserin results in mammary tumors, thereby providing a basis for risk assessment. The potential of lorcaserin to increase prolactin and how such increases, if observed, compare in magnitude and duration to other pharmaceuticals known to increase prolactin and mammary tumors in rats would be pivotal to adequately address this Complete Response deficiency. Additional experimental evidence that implicates prolactin in lorcaserin-induced changes in mammary tissue using experimental approaches that intervene in prolactin expression/activity would be particularly supportive.

2: Unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma

Q3a. Does the Agency accept that toxicity in high dose male rats, as evidenced in brain by gliosis and focal mineralization and systemically by pronounced weight loss and multiple histopathologic findings, contributed to the formation of astrocytoma?

- If so, does the Agency accept this toxicity as a mechanism that could contribute to development of astrocytoma, and that the finding of astrocytomas in male rats is reasonably unlikely to represent a relevant risk to humans?

FDA Response:

No, the Division does not agree that the weight loss or non-neoplastic findings contributed to the formation of astrocytoma at the mid and high doses of lorcaserin.

Weight loss in excess of 25% has been observed for investigational obesity compounds in 2-year carcinogenicity studies without compromising survival or inducing tumors. The FDA position is misstated in your background package. The weight loss in male rats is not viewed as secondary to tumor burden; rather, the weight loss is considered secondary to the intended pharmacodynamic effect of lorcaserin (evidenced by reduced food intake and weight loss in male but not female rats).

The brain gliosis and mild focal mineralization in high-dose males was not a pathological feature of mid-dose males that had astrocytoma, nor was it present in all high-dose males that had astrocytoma. Therefore, we do not agree that these histological findings are causally related to astrocytoma induced by lorcaserin.

The other non-neoplastic pathological findings in high-dose males listed in Table 4 do not constitute evidence that the maximum tolerated dose was exceeded, nor do they suggest a probable mechanism of tumorigenic action for the astrocytoma.

Q3b. We have been able to estimate lorcaserin brain concentrations in both monkey and human with calculations based on the minimum effective dose in the species and 5-HT_{2c} functional activity as determined by receptor EC₅₀.

- Will the Agency accept estimates of human brain exposure based on such a calculation to demonstrate exposure margin in the CNS of humans?
- Does the Agency agree that the calculated brain safety margin of approximately 30 provides an acceptable safety margin?

FDA Response:

The Division requires additional information and internal discussion before providing a definitive answer regarding the proposed predictive modeling of brain levels of lorcaserin. Please provide additional information on the assumptions and calculations used in your modeling, and on other methods that support the outcome of the model described. The Division has the following preliminary comments:

Predictability of *in vitro* EC₅₀ receptor activation data is questionable. Variable EC₅₀ values for 5HTR activation by lorcaserin was provided in the NDA. The variability was apparently due to uncontrolled degrees of receptor expression in the *in vitro* assays. The choice of the EC₅₀ value has a major impact on the prediction of brain drug concentrations in the proposed predictive model. To our knowledge, the monkey EC₅₀ of 36nM comes from a study (DBR-10-007) that the Division has not reviewed. The information in the NDA cites an EC₅₀ of 2nM for activation of monkey 5HT_{2c} and 1.8nM for human 5HT_{2c} (2009 studies). Given the sensitivity of the proposed model to changes in EC₅₀, it may be appropriate to reassess EC₅₀ for rat, monkey, and human 5HT_{2C} activation in the same series of assays that controls receptor reserve to a physiological range of receptor density.

As stated in your background information to the Advisory Committee, “the *in vitro* EC₅₀ at the 5HT_{2c} receptor (192nM, rat) significantly underestimates the *in vivo* effective concentration.” Differences in receptor density were cited as one possible explanation, which was proposed to account for the lack of 5HT_{2A} and 2B-associated effects in rodents despite high lorcaserin concentrations. Therefore, the relationship of the *in vitro* EC₅₀ for receptor activation to effective *in vivo* drug concentrations is not clear. The Division asks that you provide further justification for the use of EC₅₀s in the predictive model.

Pharmacological weight loss was observed in male rats but not in female rats. Please address how the proposed predictive model would work in this situation, as the minimally effective dose appears to be substantially higher in female compared to male rats. It may be instructive to compare a predicted versus an actual value of lorcaserin levels in brain tissue of female rats.

The Division has little information regarding the mechanisms by which lorcaserin partitions to the CNS. It is feasible that if mechanisms are identified, potential differences across species may inform prediction of brain partitioning in human subjects. It may also be informative to explore relationships of drug concentrations in the CSF, brain, and plasma that are potentially consistent across rats and monkeys, as a possible means to predict brain levels of lorcaserin in human subjects. The background material did not fully discuss this or other potential approaches to more directly measuring CNS levels of

lorcaserin in human subjects. Please address whether such approaches are feasible with lorcaserin.

Meeting Discussion:

Arena explained that the choice to use the EC50 values from studies conducted in 2004/5 instead of 2009 was based on the suspected overestimation of potency from the 2009 assays which reflected higher serotonin receptor density. The EC50 of 36nM for monkey 5HT2c was not submitted in the NDA, but Arena stated that these data were obtained in the 2004/5 series of assays. The FDA acknowledged that different receptor densities for this class of receptors can result in different estimates of EC50 without much change in binding affinity, as was observed with lorcaserin. Physiological receptor density should therefore be considered in a pharmacokinetic model that relies on estimates of in vitro EC50. The FDA reiterated that further internal discussion is required before accepting the proposed model, citing the issues of concern in the pre-meeting response to Arena's question. Arena remarked that they are open to further evaluating the EC50 for lorcaserin at the serotonin receptors, using a calcium response assay, over a range of receptor density expression levels, including designs that control receptor reserve by means of receptor cross-linking. The FDA agrees that further information on receptor pharmacology of lorcaserin would be helpful.

The FDA remarked that similar pharmacokinetic models are used in drug development to predict CNS penetration of drug candidates, with the predictions sometimes and sometimes not being correct from actual endpoints measured in subsequent early clinical trials of the investigational drug. The FDA inquired whether Arena has considered more direct methods of estimating brain levels of lorcaserin in human subjects, including collection of CSF samples at steady state. The FDA further noted that a consistent relationship between CSF and brain levels of lorcaserin across species (rats and monkeys), as opposed to the variable plasma:brain ratio in these species, might allow a more reliable estimation of brain levels in human subjects based on measured CSF levels of lorcaserin. Arena remarked that such an analysis would still require assumptions of a consistent relationship from rats and monkeys to human subjects, and therefore regarded this approach as providing only incremental data to the proposed pharmacokinetic modeling prediction. The FDA responded that estimating brain levels of lorcaserin based on actual (human) CSF concentrations of lorcaserin and an apparent consistent relationship of CSF:brain drug concentrations across species is preferable to relying on a variable plasma:brain relationship or a mathematical model that relies on less-than-definitive estimates of in vitro EC50s and weight loss across species.

Post-Meeting Comments

Arena inquired what the Division thought would be an appropriate study duration to demonstrate persistency of prolactin elevation in response to lorcaserin. The Division has the following recommendations for a possible study design:

- Dosing duration of no less than 3 months.
- Dose groups to include a control, a dose range of lorcaserin, and at least one relevant positive control (e.g., dexfenfluramine, mCPP, haloperidol).
- Measure serum prolactin at multiple time points (e.g., Days 1, 7, 30, 60, 90).

- Measure tissue prolactin (mammary & pituitary) at multiple time points (e.g., Day 1, 7, and 90).
- Changes in prolactin can be assessed by comparison to untreated control and to pre-study baseline prolactin in all groups.
- Include male and female rats.
- Consider monitoring other relevant endpoints (e.g., estrogens, progesterone, LH)

The Division requests that you submit protocols prior to initiating this and other mechanistic studies with lorcaserin. Comments and recommendations regarding these protocols will be provided within approximately one month of submission.

It is the Division's understanding of Arena's argument that the profile of lorcaserin-induced increases in prolactin is sufficient to activate cellular pathways in the short term that result in prolactin-dependent mammary tumors at later time points (≥ 1 year), without histological changes to mammary tissue over a 6-month dosing period. Consistent with this argument, it is expected that lorcaserin's effect on mammary tissue requires the intervening action of prolactin. In addition to providing evidence that lorcaserin increases prolactin robustly and persistently, we ask that you consider the following experimental approaches that would lend further support to this hypothesis. Please note that the Division requests explanations for why these or similar experimental strategies are either not feasible or would be unlikely to provide relevant information, as such explanations will be included in the review of the NDA resubmission. Submission of alternative mechanistic studies is encouraged.

- Consider experimental designs that demonstrate the necessity of prolactin in lorcaserin-induced changes to normal or neoplastic mammary tissue (in vivo, in vitro, or both). It is reasonable to expect that lorcaserin produces changes in mammary tissue over the short term (e.g., acute cellular signaling events, molecular changes, gene expression), before the hyperplastic/neoplastic changes are detected beyond 1 year of dosing. Identifying such lorcaserin-induced changes in mammary tissue over the short-term may allow the use of methods that intervene in prolactin expression or activity (e.g., pituitary ablation, PRLR antagonists, PRL/PRLR deficient tissues).
- Consider experimental approaches that address whether the tumorigenic effect of lorcaserin on mammary tissue resembles the tumorigenic profile proposed for prolactin, specifically that short-term exposure to elevated prolactin is sufficient to result in mammary tumors at much later time points. For example, consider a 12-month study that doses female rats for a short period (3-6 months) with lorcaserin, with one cohort remaining on drug and a second cohort withdrawn from drug for the remaining study duration, followed by histological evaluation of mammary tissue at 12 months.

The Division understands from the meeting discussion that you intend to perform further receptor transactivation studies with lorcaserin utilizing release of calcium in place of phosphoinositol as the reporter. Given the persistent imbalance in the development of FDA-defined valvulopathy in your clinical trials with patients treated with lorcaserin as compared to placebo, we strongly encourage you to consider expanding these studies to include multiple read-outs with comparison to one or more valvulopathogens with known (published) binding/activation kinetics for 5HT2B (e.g., pergolide, norfenfluramine) in order to more fully

characterize lorcaserin's activity at 5HT2B. Please refer to the publication by Huang et al. (Molec Pharm. 2009; 76:710-722) which describes an approach that would provide a more robust analysis than currently available for lorcaserin.

As stated in the pre-meeting minutes, the Division will consider further the proposed pharmacokinetic model as a method to estimating brain levels of lorcaserin in human subjects. The Division remains concerned regarding the adequacy of this approach for reasons stated in the pre-meeting minutes. In addition to the comments already provided, we ask that you attempt to apply the proposed model using EC50 values for 5HT2A or B and doses that have provoked responses associated with these receptors in animals and humans (please refer to comments by CSS). We strongly encourage Arena to reconsider strategies that provide more definitive information on brain levels of lorcaserin in human subjects, such as those raised by FDA (i.e., CSF sampling, imaging with radiolabeled lorcaserin).

Clinical

1. The weight-loss efficacy of lorcaserin 10 mg twice a day relative to placebo in overweight and obese individuals without type 2 diabetes is marginal.

Q4a. Does the Agency agree that the positive efficacy results, weight loss and blood glucose control demonstrated in the BLOOM-DM trial are sufficiently robust to increase the benefit profile of lorcaserin?

FDA Response

This is a review issue.

Meeting Discussion: *No additional discussion*

Q4b. Will the Agency consider submission of the BLOOM-DM study report prior to full submission of our complete response to alleviate concerns with regards to clinical benefit-to-risk ratio?

FDA Response

The BLOOM-DM CSR can be submitted at any time; however, we intend to review it as part of the complete response to the NDA.

Meeting Discussion: *No additional discussion*

Labeling

Q5. If Arena accepts the Schedule IV recommendation of the Agency, it is our understanding of the CRL that the animal studies would not have to be repeated. Is our understanding correct?

FDA Response

No, your understanding is not correct. Repeating the animal studies and submitting the data in your complete response will provide new information that will be reviewed and considered in CSS's abuse potential assessment of lorcaserin and final scheduling recommendation. CSS is available to review the protocols for the animal studies prior to their initiation.

Meeting Discussion:

Arena asked for clarification regarding scheduling for lorcaserin and CSS's recommendation to repeat the animal abuse liability studies.

CSS explained that there are two issues related to the assessment of the abuse potential of any drug: 1) acquiring sufficient safety data from preclinical and clinical studies so that an accurate drug label related to abuse potential, as required under the Food Drug and Cosmetic Act, can be written, and 2) determining whether the drug has abuse potential and needs to be recommended for scheduling under the Controlled Substances Act (CSA).

CSS noted that, at the present time, there are limited data that can be used to prepare the Drug Abuse and Dependence Section of the drug label and to determine to which schedule of the CSA lorcaserin should be recommended for placement.

The two animal-abuse studies that should be repeated are important to the understanding of whether lorcaserin functions behaviorally as a 5HT2 agonist, similar to 5HT2 agonist hallucinogens that are in Schedule I of the CSA. However, the overt behavioral study and the drug discrimination study submitted in the NDA for lorcaserin are invalid for numerous methodological reasons, as delineated in the CR letter. These reasons include use of a non-scheduled positive control drug (DOI) in the overt behavioral study and the inability of rats to continue to maintain recognition of the training drug, DOM, over the course of the drug discrimination study.

The animal studies are of particular importance because of limitations in the design of the human abuse potential study. Specifically, the ideal positive control drug for a human abuse potential study that evaluates a 5HT2 agonist like lorcaserin would have been a scheduled 5HT2 agonist hallucinogen. However, all such drugs are in Schedule I and would have been difficult to use in a clinical study. Instead, the positive control drugs selected were two drugs that produce hallucinogen-like responses through non-5HT2 mechanisms of action: ketamine (an NMDA antagonist in Schedule III) and zolpidem (a GABA agonist in Schedule IV). Since these two positive control drugs are mechanistically different from lorcaserin, they provided limited information regarding the relative abuse potential of lorcaserin.

Thus, directly assessing the similarity of lorcaserin to a scheduled 5HT2 agonist hallucinogen can only be accomplished in an animal study. Although our Complete Response letter did not require that the overt behavioral study and the drug discrimination study be repeated, CSS strongly encourages the Sponsor to do so in order to have appropriate safety information for labeling and scheduling decisions.

When the NDA for lorcaserin is re-submitted, CSS will evaluate all abuse-related data, including new clinical study data and any information available in the medical and scientific literature concerning 5HT2 agonists. Based on this re-assessment, CSS will prepare Section 9.0 Drug Abuse and Dependence for the drug label and will propose a CSA scheduling placement for lorcaserin.

Arena asserted that the incidence of hallucinations in the clinical trials was greater following administration of placebo compared to administration of lorcaserin. CSS refuted this assertion; while infrequent, more hallucinations occurred over the entire clinical program following administration of lorcaserin than placebo. Additionally, CSS is concerned about numerous case reports from the clinical studies conducted with lorcaserin in which subjects or patients experienced psychiatric adverse events that are similar to those produced by Schedule I 5HT2

agonist hallucinogens. One example is Subject #25 in the Phase 1 Study #001A, who experienced euphoria, hallucinations, disorientation, feeling abnormal and other hallucinogen-like responses. In the Phase 1 human abuse potential study (Study #013), three subjects experienced extended periods of euphoria (ranging from 8-20 hours) in response to the 60 mg dose of lorcaserin. The duration of euphoria from lorcaserin is consistent with the reported duration of euphoria resulting from abuse of the Schedule I 5HT2 agonist, DOM. Overall, these data indicate that lorcaserin produces responses similar to those of 5HT2 hallucinogens, which are indicative of abuse potential.

Safety

Q6. Does the Agency agree with our proposal (as described in the Safety section) to provide the new data from APD356-010 (BLOOM-DM) and the APD356-014 (TULIP) studies with no integration or pooling into the NDA ISS tables? The presentation of safety data will be similar to the 120-day update (Sequence Submission No. 0010 on April 20, 2010).

FDA Response

Echocardiography and prolactin data from BLOOM-DM should be provided separately as well as pooled (see comments below). If you choose not to pool other phase 3 data (e.g., adverse events, laboratory data, BDI-II, etc.), the results from BLOOM-DM should nevertheless be discussed in the safety update in the context of what is known about the safety profile of lorcaserin from the original NDA integrated summary of safety.

We have the following suggestions with regards to data and analyses (for BLOOM-DM, unless stated otherwise):

- 1. Provide an analysis of concomitant medications by treatment group. We are interested to see the breakdown by drug class (e.g., ACE inhibitors/ARBs, diuretics, nitrates, beta blockers, etc.).**
- 2. For concomitant diabetes drugs, indicate proportion of patients decreasing dose and discontinuing dose, as well as the average percent reduction in dose by treatment group and drug class.**
- 3. Provide an analysis of medical conditions (hypertension, coronary artery disease, sleep apnea, etc.) as well as years since diabetes diagnosis by treatment group.**
- 4. Provide a prolactin analysis evaluating BLOOM-DM separately and in combination with BLOSSOM. Mean and categorical (>2x, >5x, >10x) analyses should be conducted by visit and shift/quartile tables should also be presented.**
- 5. "Other" reasons for discontinuation should be listed by treatment group.**
- 6. Heart valve analyses should be presented as RR with 95% CI of development of FDA valvulopathy; these results should be presented for BLOOM-DM separately and for all phase 3 studies combined.**
- 7. Heart valve regurgitation changes should also be presented by valve, in the patients who developed FDA-valvulopathy (specific valve changes) and overall (proportion of patients who developed 1, 2, and 3 regurgitation score and any increase).**
- 8. Narratives should be provided for patients who developed FDA-valvulopathy.**

9. **For the hypoglycemia cases, provide a narrative, including blood sugar values, what intervention was needed, and whether another person was needed to resolve the hypoglycemic event.**
10. **Summarize mean weight loss and glycemc parameter efficacy by responder status, baseline blood sugar, and baseline HbA1c.**
11. **All datasets, CSR, and the safety update should use the same patient identifiers.**
12. **Analysis datasets should be provided for efficacy and safety parameters.**
13. **Integrate any data from BLOOM-DM into the NDA ISS datasets as is feasible.**
14. **Laboratory, vital sign, and ECG analyses should be presented as was done in response to the 74-day filing letter requests.**

Meeting Discussion: *No additional discussion*

The meeting ended.

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

/s/

PATRICIA J MADARA
01/11/2011



NDA 022529

MEETING PRELIMINARY COMMENTS

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We also refer to your October 28, 2010, correspondence, received October 29, 2010, requesting an End-of-Review meeting with the Agency to discuss the Complete Response Letter issued on October 22, 2010, regarding your NDA for Lorqess for the treatment of obesity.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 15, 2010 (10 – 11 AM; White Oak Campus), between Arena Pharmaceuticals and FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

Questions

Nonclinical

1. Diagnostic uncertainty in the classification of mammary masses in female rats

Q1a. Arena plans to convene a Pathology Working Group of 3 to 5 independent pathologists to re-adjudicate the female rat mammary and lung tumors in a blinded fashion as requested by the Agency. The slide blinding and un-blinding will be executed by [REDACTED] (b) (4) Arena will provide a list of proposed pathologists, working group instructions, and reporting plans to the Agency for concurrence.

FDA Response

The revised PWG protocol that incorporated the Division's recommendations is acceptable.

Arena can provide a list of all slides prepared for female rat mammary tissues presented in the updates and the final study report with tabulations of diagnoses that changed. Documentation of the discussions between the pathologists and their notes and reasons for these changes are not available, per standard pathology review practices in the industry. Although these tabulations can be provided, we believe the plans to re-adjudicate the mammary and lung tumors with an independent Pathology Working Group will more directly address the Agency's concern.

Does the Agency agree that in view of our commitment to readjudicate these tumor findings this accounting is no longer necessary?

FDA Response

We acknowledge your explanation that the reasons for the imbalanced change in diagnoses across dose groups were not documented and therefore cannot be provided. It would be acceptable to instead provide a spreadsheet documenting all changes in the diagnosis of female rat mammary tissues from the interim updates to the final study report, listed by animal number.

In addition, we request clarification regarding the pathology records for two high dose female rats. The histopathology report for female #4202 describes mild atypic hyperplasia of the mammary tissue despite the presence of a large (2-3.9cm) axillary mass present about 10 weeks prior to euthanasia. The report for female #4212 lists mammary tumors as the cause of death, yet no mammary tumor is described in the histology report for this animal.

2. Unresolved exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma

Q2a. The statistical analysis of the mammary tumor findings included combination of adenocarcinomas and fibroadenomas. This practice of combining the two tumor types is based on the publication by McConnell et al. However, there is now expert opinion based on current knowledge of mechanisms underlying mammary gland carcinogenesis that these tumor types should not be combined because fibroadenomas are known not to be a precursor to adenocarcinomas.

Does the Agency agree that statistical analysis of mammary gland fibroadenomas and adenocarcinomas separately but not combined is appropriate?

FDA Response:

The FDA statistical analysis evaluated these two tumor types alone and in combination, as was done by the Sponsor/^{(b) (4)} and reported in NDA 22-529. The results of the FDA statistical analysis mirror those reported in the NDA. The FDA is aware that the human risk from these two tumor types may differ, and those differences in human risk can be taken into consideration when there is clarity of diagnosis as reflected in the pathology reports for carcinogenicity studies. Diagnostic uncertainty was evident in the classification of mammary masses in rats administered lorcaserin, as summarized in the Complete Response Letter. Without confidence in the diagnoses, the more conservative approach to assessing human risk is most appropriate.

Some of the Division's recommendations for the PWG are directly targeted to clarify the degree of diagnostic certainty in distinguishing fibroadenoma from adenocarcinoma in the study conducted with lorcaserin. The Division will discuss the most appropriate approach of evaluating the mammary tumors after reviewing the PWG report and their comments on this issue.

Will establishment of a safety margin for the adenocarcinoma be sufficient to address the Agency's concerns?

FDA Response

A 'safety margin' implies a dose range above therapeutic exposure within which adverse effects of a drug are not observed. As summarized in the Complete Response Letter, there is evidence of decreased latency and increased aggressiveness of adenocarcinoma at all doses of lorcaserin in female rats, and therefore the exposure-response relationship remains unresolved. In addition to numerical increases in tumor incidence, evidence of decreased latency and increased aggressiveness of drug-induced malignancies in rodents contributes to the Division's assessment of human risk, as does consideration of the risk/benefit associated with a given drug and clinical indication.

Q2b. If Arena provides acceptable evidence that the mammary tumors observed in the 2-year rat carcinogenicity study are due to increased prolactin either in blood or mammary gland, will the Agency consider the prolactin mechanism an adequate explanation for the tumors and their aggressiveness, and will this mechanism satisfy the Agency's criterion that the tumors are reasonably irrelevant to human risk assessment?

Q2c. Does the weight of evidence introduced in this document provide sufficient evidence of a prolactin mechanism for rat mammary tumors? If not sufficient, would a demonstration of lorcaserin-mediated increases in serum prolactin in intact female rats or increases in prolactin in rat mammary gland be sufficient evidence for a mechanism irrelevant to human risk?

FDA Response to Q2b&c:

Experimental evidence with lorcaserin that demonstrably links its effects on mammary tissue in rodents to a prolactin-dependent mechanism will mitigate the Division's level of concern for clinical risk.

As discussed in the Division's briefing package to the Advisory Committee, the prolactin data submitted in NDA 22-529 does not provide persuasive evidence implicating this hormone in mammary tumors induced by lorcaserin. The information provided in your background package does not provide nor proposes a strategy to provide the experimental evidence with lorcaserin necessary for the Division to re-assess clinical risk.

The Division recommends that you propose experimental strategies evaluating lorcaserin which could be considered in support of prolactin as the mediating mode of tumorigenic action.

Your background document cites literature linking a 5HT_{2A/2C} pathway to negative regulation of dopamine and additional direct effects on prolactin release. These studies involved in vitro and in vivo approaches using mixed serotonergic receptor agonists, dopaminergic compounds, and pharmacological 5HT_{2A/2C} antagonists. Lorcaserin is a new molecular entity with a unique 5HT_{2A/2C} selectivity profile and tissue distribution characteristics. We recommend that you propose additional in vitro and in vivo studies to determine the potential for lorcaserin to alter release of pituitary/tissue prolactin and potentially its regulatory intermediaries such as dopamine and vasoactive intestinal polypeptide. Demonstration of a clear, persistent (<13 wks) increase in serum/tissue prolactin at doses of lorcaserin associated with mammary tumors would mitigate the Division's concern of clinical risk for this target tissue. If a clear, persistent increase in prolactin is not demonstrable, the Division is interested in experimental designs that intervene in the expression or activity of prolactin as an approach to implicate prolactin in lorcaserin's tumorigenic effect on mammary tissue.

The Division is not aware of an accepted threshold of prolactin elevation necessary for drug-induced induction or promotion of rodent mammary tumors. The Division disagrees that the data with aripiprazole provides evidence that a small elevation in prolactin may be sufficient for mammary tumor induction. Contrary to the argument presented in the briefing material, Aripiprazole did not increase mammary tumors in male mice (or rats), despite the small 2-4 fold increase in serum prolactin, as shown in Figures 2 & 4 of the background document. Also contrary to the assertion in the background document, aripiprazole increased fibroadenoma but not adenocarcinoma or metastases in female Fischer rats, unlike lorcaserin that increased the incidence and aggressiveness of both mammary tumor types. The increased incidence of adenocarcinoma in female mice with aripiprazole was associated with a 200- to 500-fold increase in serum prolactin within 4 hours after a single dose, and 8 to 9-fold increases (similar to haloperidol) after 1 week of dosing. Serum prolactin and persistent diestrus was documented after 13 weeks of dosing.

3. Unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma

Q3a. Does the Agency accept that toxicity in high dose male rats, as evidenced in brain by gliosis and focal mineralization and systemically by pronounced weight loss and multiple histopathologic findings, contributed to the formation of astrocytoma?

- If so, does the Agency accept this toxicity as a mechanism that could contribute to development of astrocytoma, and that the finding of astrocytomas in male rats is reasonably unlikely to represent a relevant risk to humans?

FDA Response

No, the Division does not agree that the weight loss or non-neoplastic findings contributed to the formation of astrocytoma at the mid and high doses of lorcaserin.

Weight loss in excess of 25% has been observed for investigational obesity compounds in 2 year carcinogenicity studies without compromising survival or inducing tumors. The FDA position is misstated in your background package. The weight loss in male rats is not viewed as secondary to tumor burden; rather, the weight loss is considered secondary to the intended pharmacodynamic effect of lorcaserin (evidenced by reduced food intake and weight loss in male but not female rats).

The brain gliosis and mild focal mineralization in high dose males was not a pathological feature of mid-dose males that had astrocytoma, nor was it present in all high dose males that had astrocytoma. Therefore, we do not agree that these histological findings are causally related to astrocytoma induced by lorcaserin.

The other non-neoplastic pathological findings in high dose males listed in Table 4 do not constitute evidence that the maximum tolerated dose was exceeded, nor do they suggest a probable mechanism of tumorigenic action for the astrocytoma.

Q3b. We have been able to estimate lorcaserin brain concentrations in both monkey and human with calculations based on the minimum effective dose in the species and 5-HT_{2c} functional activity as determined by receptor EC₅₀.

- Will the Agency accept estimates of human brain exposure based on such a calculation to demonstrate exposure margin in the CNS of humans?
- Does the Agency agree that the calculated brain safety margin of approximately 30 provides an acceptable safety margin?

FDA Response

The Division requires additional information and internal discussion before providing a definitive answer regarding the proposed predictive modeling of brain levels of lorcaserin. Please provide additional information on the assumptions and calculations used in your modeling, and on other methods that support the outcome of the model described. The Division has the following preliminary comments:

Predictability of *in vitro* EC₅₀ receptor activation data is questionable. Variable EC₅₀ values for 5HTR activation by lorcaserin were provided in the NDA, which apparently varied due to uncontrolled degrees of receptor expression in the *in vitro* assays. The choice of the EC₅₀ value has a major impact on the prediction of brain drug concentrations in the proposed predictive model. To our knowledge, the monkey EC₅₀ of 36nM comes from a study (DBR-10-007) that the Division has not reviewed. The information in the NDA cites an EC₅₀ of 2nM for activation of monkey 5HT_{2c} and 1.8nM for human 5HT_{2c} (2009 studies). Given the sensitivity of the proposed model to changes in EC₅₀, it may be appropriate to reassess EC₅₀ for rat, monkey, and human 5HT_{2C} activation in the same series of assays that controls receptor reserve to a physiological range of receptor density.

As stated in your background information to the Advisory Committee, “the *in vitro* EC50 at the 5HT2c receptor (192nM, rat) significantly underestimates the *in vivo* effective concentration.” Differences in receptor density were cited as one possible explanation, which was proposed to account for the lack of 5HT2A and 2B-associated effects in rodents despite high lorcaserin concentrations. Therefore, the relationship of the *in vitro* EC50 for receptor activation to effective *in vivo* drug concentrations is not clear. The Division asks that you provide further justification for the use of EC50s in the predictive model.

Pharmacological weight loss was observed in male rats but not in female rats. Please address how the proposed predictive model would work in this situation, as the minimally effective dose appears to be substantially higher in female compared to male rats. It may be instructive to compare a predicted vs. actual value of lorcaserin levels in brain tissue of female rats.

The Division has little information regarding the mechanisms by which lorcaserin partitions to the CNS. It is feasible that if mechanisms are identified, potential differences across species may inform prediction of brain partitioning in human subjects. It may also be informative to explore relationships of drug concentrations in the CSF, brain, and plasma that are potentially consistent across rats and monkeys, as a possible means to predict brain levels of lorcaserin in human subjects. The background material did not fully discuss this or other potential approaches to more directly measuring CNS levels of lorcaserin in human subjects. Please address whether such approaches are feasible with lorcaserin.

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FDA Response

This is a review issue.

Q4b. Will the Agency consider submission of the BLOOM-DM study report prior to full submission of our complete response to alleviate concerns with regards to clinical benefit-to-risk ratio?

FDA Response

The BLOOM-DM CSR can be submitted at any time; however, we intend to review it as part of the complete response to the NDA.

Labeling

Q5. If Arena accepts the Schedule IV recommendation of the Agency, it is our understanding of the CRL that the animal studies would not have to be repeated. Is our understanding correct?

FDA Response

No, your understanding is not correct. Repeating the animal studies and submitting the data in your complete response will provide new information that will be reviewed and considered in CSS's abuse potential assessment of lorcaserin and final scheduling recommendation. CSS is available to review the protocols for the animal studies prior to their initiation.

Safety

Q6. Does the Agency agree with our proposal (as described in the Safety section) to provide the new data from APD356-010 (BLOOM-DM) and the APD356-014 (TULIP) studies with no integration or pooling into the NDA ISS tables? The presentation of safety data will be similar to the 120-day update (Sequence Submission No. 0010 on April 20, 2010).

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Echocardiography and prolactin data from BLOOM-DM should be provided separately as well as pooled (see comments below). If you choose not to pool other phase 3 data (e.g., adverse events, laboratory data, BDI-II, etc.), the results from BLOOM-DM should nevertheless be discussed in the safety update in the context of what is known about the safety profile of lorcaserin from the original NDA integrated summary of safety.

We have the following suggestions with regards to data and analyses (for BLOOM-DM, unless stated otherwise):

- 1. Provide an analysis of concomitant medications by treatment group. We are interested to see the breakdown by drug class (e.g., ACE inhibitors/ARBs, diuretics, nitrates, beta blockers, etc.).**
- 2. For concomitant diabetes drugs, indicate proportion of patients decreasing dose and discontinuing dose, as well as the average percent reduction in dose by treatment group and drug class.**
- 3. Provide an analysis of medical conditions (hypertension, coronary artery disease, sleep apnea, etc.) as well as years since diabetes diagnosis by treatment group.**
- 4. Provide a prolactin analysis evaluating BLOOM-DM separately and in combination with BLOSSOM. Mean and categorical (>2x, >5x, >10x) analyses should be conducted by visit and shift/quartile tables should also be presented.**
- 5. "Other" reasons for discontinuation should be listed by treatment group.**
- 6. Heart valve analyses should be presented as RR with 95% CI of development of FDA valvulopathy; these results should be presented for BLOOM-DM separately and for all phase 3 studies combined.**
- 7. Heart valve regurgitation changes should also be presented by valve, in the patients who developed FDA-valvulopathy (specific valve changes) and overall (proportion of patients who developed 1, 2, and 3 regurgitation score and any increase).**
- 8. Narratives should be provided for patients who developed FDA-valvulopathy.**

9. **For the hypoglycemia cases, provide a narrative, including blood sugar values, what intervention was needed, and whether another person was needed to resolve the hypoglycemic event.**
10. **Summarize mean weight loss and glycemc parameter efficacy by responder status, baseline blood sugar, and baseline HbA1c.**
11. **All datasets, CSR, and the safety update should use the same patient identifiers.**
12. **Analysis datasets should be provided for efficacy and safety parameters.**
13. **Integrate any data from BLOOM-DM into the NDA ISS datasets as is feasible.**
14. **Laboratory, vital sign, and ECG analyses should be presented as was done in response to the 74-day filing letter requests.**

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

PATRICIA J MADARA
12/14/2010

MEMORANDUM

**RE: NDA 22529 End of Review Meeting
Arena Pharmaceuticals, Inc.
Complete Response letter sent October 22, 2010**

Clinical Information

Arena has submitted the top-line results of BLOOM-DM (APD356-010) in this briefing document; the results of this trial will make up the bulk of the responding to the clinical portion of the complete response letter.

The BLOOM-DM trial was conducted as a double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of lorcaserin hydrochloride for weight loss during 52 weeks of administration to 604 overweight and obese male and female patients with type 2 diabetes mellitus, aged 18 to 65 years. The primary efficacy endpoints were the proportion of patients achieving $\geq 5\%$ weight reduction, the change in body weight from baseline, and the proportion of patients achieving $\geq 10\%$ weight reduction.

After approximately 300 patients were enrolled, the lorcaserin 10 mg QD arm was discontinued in order to expedite enrollment.

At baseline, patients had an average Body Mass Index (BMI) of 36 kg/m^2 , weight of 103.6 kg, age of 53 years, and HbA1c of approximately 8%. Proportions of Caucasian, African American, and Hispanic patients were 61%, 21% and 14%, respectively, and 54% of patients were female. Approximately half of the patients were taking a sulfonylurea at baseline (50.2%), 91.7% were taking metformin, and 42.0% were taking both.

Efficacy

Primary Endpoints

Table 1. Number (%) of Patients Achieving $\geq 5\%$ Reduction in Body Weight after 52 Weeks of Treatment

Treatment	N	n (%)		
Lorcaserin 10 mg BID	251	94 (37.5)		
Lorcaserin 10 mg QD	94	42 (44.7)		
Placebo	248	40 (16.1)		
Between Treatment Comparison	Difference in Proportion (%) (95% CI) ¹	Odds-Ratio ² (95% CI)	p-Value ²	
Lorcaserin 10 mg BID vs. Placebo	21.32 (13.78, 28.86)	3.14 (2.05, 4.80)	<0.0001	
Lorcaserin 10 mg QD vs. Placebo	28.55 (17.51, 39.60)	4.19 (2.46, 7.13)	<0.0001	
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID	7.23 (-4.47, 18.93)	1.36 (0.84, 2.21)	0.2142	

¹ Confidence Interval computed using the normal approximation method
² From the logistic regression model, adjusting for baseline body weight, baseline HbA1c stratum, and baseline antihyperglycemic medication stratum

Table 2. Analysis of Change from Baseline in Body Weight (kg) at Week 52

Treatment	n	Mean (SD)		Change from Baseline			
		Baseline	Week 52	Mean (SE)	Median	Min	Max
Lorcaserin 10 mg BID	251	103.52 (17.18)	98.59 (17.71)	-4.93 (0.37)	-3.80	-36.1	4.3
Lorcaserin 10 mg QD	94	106.08 (19.61)	100.71 (20.41)	-5.37 (0.57)	-4.40	-23.7	7.2
Placebo	248	102.27 (17.99)	100.41 (18.02)	-1.86 (0.27)	-1.30	-24.3	16.5
Change from Baseline							
Treatment	LS Mean (SE)	95% CI for LS Mean		p-Value			
Lorcaserin 10 mg BID	-4.66 (0.37)	(-5.39, -3.93)		<0.0001			
Lorcaserin 10 mg QD	-5.02 (0.57)	(-6.13, -3.90)		<0.0001			
Placebo	-1.61 (0.37)	(-2.34, -0.87)		<0.0001			
Between Treatment Difference							
Between Treatment Difference	Difference in LS Means (95% CI)			p-Value			
Lorcaserin 10 mg BID vs. Placebo	-3.05 (-3.96, -2.15)			<0.0001			
Lorcaserin 10 mg QD vs. Placebo	-3.41 (-4.64, -2.18)			<0.0001			
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID	-0.36 (-1.58, 0.87)			0.5701			
p-Value for ANCOVA Effects							
Baseline Value				0.1021			
Baseline HbA1c Stratum				0.1278			
Baseline Antihyperglycemic Medication Stratum				0.2822			
Treatment				<0.0001			
Root Mean Square Error of Change = 5.16							
CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation; SE=Standard Error							
Source: Table 11.2							

Table 3. Proportion of Patients Achieving $\geq 10\%$ Reduction in Body Weight after 52 Weeks of Treatment

Treatment	N	n (%)	
Lorcaserin 10 mg BID	251	41 (16.3)	
Lorcaserin 10 mg QD	94	17 (18.1)	
Placebo	248	11 (4.4)	
Between Treatment Comparison			
Between Treatment Comparison	Difference in Proportion (%) (95% CI) [†]	Odds-Ratio [‡] (95% CI)	p-Value [‡]
Lorcaserin 10 mg BID vs. Placebo	11.90 (6.66, 17.14)	4.13 (2.10, 8.11)	<0.0001
Lorcaserin 10 mg QD vs. Placebo	13.65 (5.46, 21.84)	4.78 (2.18, 10.46)	<0.0001
Lorcaserin 10 mg QD vs. Lorcaserin 10 mg BID	1.75 (-7.27, 10.78)	1.16 (0.62, 2.15)	0.6483
[†] Confidence Interval computed using the normal approximation method [‡] From the logistic regression model, adjusting for baseline body weight, baseline HbA1c stratum, and Baseline antihyperglycemic medication stratum			

Secondary Endpoints

Table 4. Summary of Secondary Endpoints: Between Treatment Differences in Change from Baseline to Week 52

Between Treatment Difference	Baseline to Week 52					
	Lor 10 mg QD vs. Pbo	p-Value	Lor 10 mg BID vs. Pbo	p-Value	Lor 10 mg QD vs. Lor 10 mg BID	p-Value
Change in waist circumference (cm)	-1.62 (-3.26, 0.02)	0.0533	-2.17 (-3.40, -0.94)	0.0006	0.55 (-1.08, 2.19)	0.5072
Change in HbA1c (%)	-0.56 (-0.77, -0.34)	<0.0001	-0.49 (-0.65, -0.33)	<0.0001	-0.07 (-0.29, 0.14)	0.5156
Change in fasting plasma glucose (mg/dL)	-16.52 (-24.60, -8.44)	<0.0001	-15.50 (-21.51, -9.48)	<0.0001	-1.02 (-9.12, 7.07)	0.8039
Change in fasting insulin (μIU/mL)	-0.63 (-2.99, 1.74)	0.6032	-1.39 (-3.13, 0.36)	0.1203	0.76 (-1.60, 3.12)	0.5282
Change in systolic blood pressure (mm Hg)	1.51 (-1.28, 4.29)	0.2879	0.14 (-1.91, 2.20)	0.8905	1.36 (-1.42, 4.14)	0.3358
Change in diastolic blood pressure (mm Hg)	0.95 (-0.91, 2.81)	0.3168	-0.41 (-1.78, 0.97)	0.5633	1.36 (-0.50, 3.22)	0.1526
Change in total cholesterol (%)	1.53 (-2.22, 5.29)	0.4232	-0.52 (-3.29, 2.26)	0.7136	2.05 (-1.69, 5.80)	0.2824
Change in LDL cholesterol (%)	-0.86 (-9.55, 7.83)	0.8461	-0.81 (-7.11, 5.50)	0.8015	-0.05 (-8.73, 8.62)	0.9907
Change in HDL cholesterol (%)	2.80 (-0.62, 6.21)	0.1080	3.64 (1.12, 6.15)	0.0047	-0.84 (-4.24, 2.56)	0.6272
Change in triglycerides (%)	-0.70 (-8.84, 7.44)	0.8657	-5.90 (-11.91, 0.11)	0.0541	5.20 (-2.90, 13.30)	0.2082
Change in total body fat (%)	-2.04 (-3.30, -0.78)	0.0020	-1.75 (-3.10, -0.41)	0.0116	-0.29 (-1.65, -1.08)	0.6727
Change in lean body mass (kg)	0.343 (-1.14, 1.83)	0.6457	0.247 (-1.34, 1.83)	0.7569	0.096 (-1.52, 1.72)	0.9055

Lor=Lorcaserin; Pbo= Placebo

Data are reported as Difference in LS Means (95% CI)

Safety

Serious Adverse Events

No deaths occurred. A total of 50 SAEs occurred in 41 (6.8%) patients. Of these, 8 (8.4%) were in the lorcaserin 10 mg QD treatment group, 16 (6.3%) were in lorcaserin 10 mg BID treatment group, and 17 (6.7%) were in the placebo-treated group.

Table 5. BLOOM-DM Serious Adverse Events by System Organ Class and Preferred Term

Screening Number	Patient ID Number	Gender	Preferred Term	System Organ Class	Outcome	Severity	Relationship
LORCASERIN 10 MG BID							
1105-S012	1105-0054	F	Uterine leiomyoma	Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Resolved	Severe	Not related
1130-S038	1130-0326	M	Thymoma	Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Resolved	Moderate	Not related
1130-S048	1130-0471	F	Abdominal abscess	Infections And Infestations	Resolved	Severe	Not related
1133-S004	1133-0084	F	Non-cardiac chest pain	General Disorders And Administration Site Conditions	Resolved	Mild	Not related
1145-S021	1145-0285	M	Non-cardiac chest pain	General Disorders And Administration Site Conditions	Resolved	Severe	Not related
1146-S018	1146-0423	M	Coronary artery occlusion	Cardiac Disorders	Resolved	Moderate	Not related
1149-S002	1149-0007	F	Hypotension	Vascular Disorders	Resolved	Severe	Unlikely
1158-S018	1158-0244	M	Osteoarthritis	Musculoskeletal And Connective Tissue Disorders	Resolved w/ Sequelae	Severe	Not related
1187-S019	1187-0307	F	Gastroenteritis	Infections And Infestations	Resolved	Moderate	Not related
1187-S021	1187-0359	M	Conversion disorder	Psychiatric Disorders	Resolved	Moderate	Unlikely
1218-S019	1218-0275	M	Back pain	Musculoskeletal And Connective Tissue Disorders	Resolved	Severe	Not related
1220-S026	1220-0549	F	Intervertebral disc protrusion	Musculoskeletal And Connective Tissue Disorders	Resolved	Severe	Not related
1222-S016	1222-0219	F	Gastroenteritis	Infections And Infestations	Resolved	Severe	Not related
1239-S054	1239-0576	M	Anaphylactic shock	Immune System Disorders	Resolved	Severe	Not related
1239-S057	1239-0590	M	Dehydration	Metabolism And Nutrition Disorders	Resolved	Severe	Not related
1251-S023	1251-0485	M	Adverse drug reaction	General Disorders And Administration Site Conditions	Resolved	Severe	Not related
1251-S023	1251-0485	M	Cholecystitis	Hepatobiliary Disorders	Resolved	Severe	Not related
LORCASERIN 10 MG QD							
1131-S002	1131-0061	M	Coronary artery disease	Cardiac Disorders	Resolved w/ Sequelae	Moderate	Not related
1158-S006	1158-0064	M	Infected skin ulcer	Infections And Infestations	Resolved	Severe	Not related
PLACED							
1158-S019	1158-0240	F	Anaemia	Blood And Lymphatic System Disorders	Resolved	Severe	Not related
1161-S052	1161-0242	M	Prostate cancer	Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Resolved w/ Sequelae	Severe	Not related
1174-S029	1174-0188	M	Angina pectoris	Cardiac Disorders	Resolved	Severe	Not related
1174-S040	1174-0200	F	Depression	Psychiatric Disorders	Resolved	Moderate	Unlikely
1227-S002	1227-0127	F	Cerebrovascular accident	Nervous System Disorders	Resolved	Moderate	Unlikely
1275-S005	1275-0276	M	Cerebrovascular accident	Nervous System Disorders	Resolved	Mild	Unlikely
PLACED							
1104-S014	1104-0408	F	Phlebitis	Vascular Disorders	Resolved	Moderate	Not related
1105-S028	1105-0238	F	Chest pain	General Disorders And Administration Site Conditions	Resolved	Severe	Not related
1105-S052	1105-0422	M	Nephrolithiasis	Renal And Urinary Disorders	Resolved	Severe	Not related
1105-S052	1105-0422	M	Nephrolithiasis	Renal And Urinary Disorders	Resolved w/ Sequelae	Severe	Not related
1130-S015	1130-0114	M	Convulsion	Nervous System Disorders	Resolved	Mild	Possible
1130-S015	1130-0114	M	Convulsion	Nervous System Disorders	Resolved	Mild	Possible
1130-S050	1130-0497	M	Myocardial infarction	Cardiac Disorders	Resolved	Moderate	Possible
1130-S050	1130-0497	M	Hypersensitivity	Immune System Disorders	Resolved	Severe	Not related
1145-S005	1145-0025	M	Cellulitis of male external genital organ	Infections And Infestations	Resolved	Severe	Not related
1145-S005	1145-0025	M	Urethral cancer	Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Resolved	Severe	Not related
1146-S037	1146-0536	M	Spinal column stenosis	Musculoskeletal And Connective Tissue Disorders	Resolved	Severe	Not related
1149-S033	1149-0174	F	Chest pain	General Disorders And Administration Site Conditions	Resolved	Severe	Unlikely
1174-S071	1174-0320	M	Atrial fibrillation	Cardiac Disorders	Resolved	Moderate	Not related
1174-S071	1174-0320	M	Cellulitis	Infections And Infestations	Resolved	Moderate	Not related
1180-S004	1180-0088	M	Gastrointestinal ulcer haemorrhage	Gastrointestinal Disorders	Resolved	Severe	Unlikely
1187-S023	1187-0463	M	Oesophageal carcinoma	Neoplasms Benign, Malignant And	Ongoing	Severe	Not related

Screening Number	Patient ID Number	Gender	Preferred Term	System Organ Class	Outcome	Severity	Relationship
1222-S050	1222-0578	F	Endometrial cancer	Unspecified (incl Cysts And Polyps) Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Resolved	Severe	Not related
1236-S006	1236-0262	F	Colitis	Gastrointestinal Disorders	Resolved	Moderate	Possible
1239-S020	1239-0266	F	Asthma	Respiratory, Thoracic And Mediastinal Disorders	Resolved	Severe	Not related
1243-S011	1243-0304	M	Myocardial infarction	Cardiac Disorders	Resolved w/ Sequelae	Severe	Not related
1250-S007	1250-0227	M	Pancreatitis acute	Gastrointestinal Disorders	Resolved	Mild	Unlikely
1250-S007	1250-0227	M	Non-cardiac chest pain	General Disorders And Administration Site Conditions	Resolved	Mild	Unlikely
1250-S007	1250-0227	M	Acute prerenal failure	Renal And Urinary Disorders	Resolved	Mild	Unlikely
1274-S009	1274-0309	M	Bursitis infective	Infections And Infestations	Resolved	Severe	Not related
1274-S009	1274-0309	M	Cellulitis	Infections And Infestations	Resolved	Severe	Not related

Note: At each level of summarization, patients reporting more than one event were only counted once. MedDRA version 10.1 is used as the adverse event coding dictionary.

Adverse Events Leading to Discontinuation

- A total of 39 patients reported adverse events that led to study withdrawal or to permanent discontinuation of study drug.

Table 6. Summary of Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by System Organ Class

System Organ Class	Lorcaserin 10 mg BID n (%)	Lorcaserin 10 mg QD n (%)	Placebo n (%)
Number (%) of Patients Reporting AEs	22 (8.6)	6 (6.3)	11 (4.4)
Ear And Labyrinth Disorders	0 (0.0)	1 (1.1)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	1 (1.1)	2 (0.8)
General Disorders And Administration Site Conditions	3 (1.2)	0 (0.0)	0 (0.0)
Hepatobiliary Disorders	2 (0.8)	0 (0.0)	0 (0.0)
Infections And Infestations	1 (0.4)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	0 (0.0)	0 (0.0)	1 (0.4)
Investigations	1 (0.4)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	1 (0.4)	0 (0.0)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders	3 (1.2)	0 (0.0)	0 (0.0)
Neoplasms Benign, Malignant And Unspecified (includes Cysts and Polyps)	1 (0.4)	1 (1.1)	2 (0.8)
Nervous System Disorders	5 (2.0)	2 (2.1)	2 (0.8)
Psychiatric Disorders	2 (0.8)	1 (1.1)	1 (0.4)
Skin And Subcutaneous Tissue Disorders	2 (0.8)	0 (0.0)	1 (0.4)
Vascular Disorders	1 (0.4)	0 (0.0)	2 (0.8)

At each level of summarization, patients reporting more than one event were only counted once.

Other Adverse Events

During the study, 89 (93.7%) patients in the lorcaserin 10 mg QD group, 236 (92.2%) patients in the lorcaserin 10 mg BID group, and 213 (84.5%) patients in the placebo group reported at least 1 adverse event. The most frequent adverse events occurring in greater than or equal to 10% of patients (excluding hypoglycemia) and the proportion of patients affected for lorcaserin 10 mg BID and placebo, respectively, were as follows: headache (14.5%, 7.1%), upper respiratory infection (13.7%, 14.7%), back pain (11.7%, 7.9%) and nasopharyngitis (11.3%, 9.9%).

Adverse events of "hypoglycemia," which included asymptomatic low blood glucose measurements (glucose < 70 mg/dL) and symptomatic events, were reported by 29.3% and 21.0% of lorcaserin 10 mg BID and placebo patients, respectively. No events of severe hypoglycemia were reported in either treatment group. Specifically, no patient experienced confusion, loss of consciousness or seizure associated with hypoglycemia.

Other Safety Data

Echocardiograms were performed at baseline and at Weeks 24 and 52. At Week 24, 2.5% of lorcaserin 10 mg BID patients and 1.9% of placebo patients had new FDA valvulopathy, and at Week 52, 2.9% of lorcaserin 10 mg BID patients and 0.5% of placebo patients had new FDA valvulopathy. All of the new valvulopathy was based on moderate mitral regurgitation and/or mild aortic regurgitation.

Results for laboratory, ECG, depression and suicidal ideation evaluations, and other assessments are not available.

Clinical Questions and Draft Responses

CLINICAL

Q4a. Does the Agency agree that the positive efficacy results, weight loss and blood glucose control demonstrated in the BLOOM-DM trial are sufficiently robust to increase the benefit profile of lorcaserin?

Draft Response: This is a review issue.

Q4b. Will the Agency consider submission of the BLOOM-DM study report prior to full submission of our complete response to alleviate concerns with regards to clinical benefit-to-risk ratio?

Draft Response: The BLOOM-DM CSR can be submitted at any time; however, we intend to review it as part of the complete response to the NDA.

SAFETY

Q6. Does the Agency agree with our proposal (as described in the Safety section) to provide the new data from APD356-010 (BLOOM-DM) and the APD356-014 (TULIP) studies with no integration or pooling into the NDA ISS tables? The presentation of

safety data will be similar to the 120-day update (Sequence Submission No. 0010 on April 20, 2010).

Draft Response: Echocardiography and prolactin data from BLOOM-DM should be provided separately as well as pooled (see comments below). If you choose not to pool other phase 3 data (e.g., adverse events, laboratory data, BDI-II, etc.), the results from BLOOM-DM should nevertheless be discussed in the safety update in the context of what is known about the safety profile of lorcaserin from the original NDA integrated summary of safety.

We have the following suggestions with regards to data and analyses (for BLOOM-DM, unless stated otherwise):

- Provide an analysis of concomitant medications by treatment group. We are interested to see the breakdown by drug class (e.g., ACE inhibitors/ARBs, diuretics, nitrates, beta blockers, etc.).
- For concomitant diabetes drugs, indicate proportion of patients decreasing dose and discontinuing dose, as well as the average percent reduction in dose by treatment group and drug class.
- Provide an analysis of medical conditions (hypertension, coronary artery disease, sleep apnea, etc.) as well as years since diabetes diagnosis by treatment group.
- Provide a prolactin analysis evaluating BLOOM-DM separately and in combination with BLOSSOM. Mean and categorical (>2x, >5x, >10x) analyses should be conducted by visit and shift/quartile tables should also be presented.
- “Other” reasons for discontinuation should be listed by treatment group.
- Heart valve analyses should be presented as RR with 95% CI of development of FDA valvulopathy; these results should be presented for BLOOM-DM separately and for all phase 3 studies combined.
- Heart valve changes should also be analyzed by valve, in the cohort who developed FDA-valvulopathy and overall.
- Narratives should be provided for patients who developed FDA-valvulopathy.
- For the hypoglycemia cases, provide a narrative, including blood sugar values, what intervention was needed, and whether another person was needed to resolve the hypoglycemic event.
- Conduct mean weight loss and glycemic parameter efficacy analyses by responder status, baseline blood sugar, and baseline HbA1c.
- All datasets, CSR, and the safety update should use the same patient identifiers.
- Analysis datasets should be provided for efficacy and safety parameters.
- Integrate any data from BLOOM-DM into the NDA ISS datasets as is feasible.
- Laboratory, vital sign, and ECG analyses should be presented as was done in response to the 74-day filing letter requests.

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/s/

JULIE K GOLDEN
12/08/2010

ERIC C COLMAN
12/14/2010

Madara, Patricia

From: Madara, Patricia
Sent: Monday, August 02, 2010 2:19 PM
To: Terri Heyward; 'Mark Brunswick'
Subject: NDA 22529 (lorcaserin HCl) - containers and cartons - advice

Importance: High

NDA 22529

ADVICE

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

We also reference your container and carton labels submitted with the original NDA. The Division of Medication Error Prevention and Analysis evaluated the proposed labels for Lorqess (NDA 022529) and identified areas of vulnerabilities that could lead to medication errors. We are providing their recommendations with the aim of reducing the risk of medication errors with regards to the proposed product containers and cartons.

A. Container Label (10 mg 100 tablets)

1. The proprietary name and established name are separated by intervening graphics. In accordance with 21CFR 201.10(a), the proprietary name and established name should appear together without any intervening written, printed or graphic matter. Revise this label to remove the green graphic separating the proprietary name and the established name.
2. The product strength and net quantity are located next to each other on the principal display panel and are of equal prominence. The size of the product strength should be increased to appear more prominently on the label. In addition the net quantity statement should be relocated to a less prominent area of the label to minimize the potential for confusion with the product strength.
3. The Principal display panel (PDP) appears crowded as it contains the “each tablet contains” statement in addition to the “made in”, manufactured and distributed by information. Relocate the “each tablet contains.” statement to the side panel to minimize the clutter and allow for more important information to be provided on the PDP.

B. Sample Pack Carton Labeling (10 mg 10 tablets)

1. See comment A1.
2. The product strength and net quantity are located next to each other on the principal display panel and

are of equal prominence. The size of the product strength should be increased to appear more prominently on the label. In addition the net quantity statement should be relocated to a less prominent area of the label.

C. Blister Sample Pack Label (10 mg 10 tablets)

1. The proprietary name, established name and strength are present only on the back panel. Thus when tablets are removed this information may be destroyed and unreadable. This label should be revised so that the proprietary name, established name and strength presentation are also located on the front panel or at a minimum ensure that the information remains on the blister pack label after each tablet is removed.

Please submit the revised container and carton labels for Lorqess officially to the NDA **and title the cover letter "amendment to proposed tradename."** Also, cite this email in your submission.

Please confirm receipt of the email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
08/03/2010



NDA 22-529

INFORMATION REQUEST

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick:

Please refer to your December 18, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorcaserin Hydrochloride tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Based on the solubility, dissolution, and permeability data provided, the BCS Class I designation was granted. However, based on the dissolution data submitted, we recommend the following dissolution methodology and acceptance criteria.

Apparatus:	USP <711> apparatus 2 (paddles)
Agitation speed:	50 rpm
Medium:	0.1 N HCl
Volume:	900 mL
Temperature:	37°C ± 0.5°C.
Acceptance criteria:	Q = ^{(b) (4)} at 15 min

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

ALI H AL HAKIM
07/23/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, July 23, 2010 10:07 AM
To: 'Mark Brunswick'
Subject: NDA 22529 - Information request

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following request for additional information:

- **Please provide your rationale for using the 90% CI (vs the more standard 95%) for the primary safety endpoint for FDA valvulopathy.**

You may submit your response informally, via email but all information must also be submitted officially to the NDA and the appropriate email cited. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
07/23/2010



NDA 22529

GENERAL ADVICE

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your new drug application (NDA) dated December 18, 2009, received December 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lorqess (lorcaserin HCl) Tablets, 10 mg.

After a review of the materials submitted in the NDA, the Controlled Substance Staff (CSS) concludes that lorcaserin has abuse potential and will be recommended for placement in Schedule IV of the Controlled Substances Act.

We recommend that:

1. **You report to FDA all cases of abuse, misuse, overdose and addiction associated with lorcaserin after its introduction on the market.**
2. **You provide draft text for the label for Sections 9.2 and 9.3 of the Drug Abuse and Dependence section (Section 9.0), with language that captures the specific safety risks associated with lorcaserin (such as euphoria and hallucinations).**

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

ERIC C COLMAN
09/07/2010

Madara, Patricia

From: Madara, Patricia
Sent: Monday, September 06, 2010 11:48 PM
To: 'Mark Brunswick'
Subject: NDA 22529 (Lorqess) INFORMATION REQUEST

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your application and have the following requests for additional information:

- **Please submit the method validation titled "Medeval Method No. 147/001: Method for the Determination of APD356 and 7-Hydroxy APD356 in Human plasma by LC-MS/MS."**
- **Additionally, please submit the data for the validation of the Caco-2 cell monolayer model using 20 recommended model compounds and GI stability data for BCS class 1 classification.**
- **In case you submitted the data, please direct us to its location in the submission. If this data is not included in the original submission, please submit this data within one week from receiving this request.**

Please submit this information officially to the NDA and cite this email. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
09/06/2010

Madara, Patricia

From: Madara, Patricia
Sent: Monday, August 09, 2010 2:30 PM
To: 'Mark Brunswick'
Subject: NDA 22529 (Lorqess) - Chemistry Information Request

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lorcaserin HCl Tablets, 10 mg.

We continue to review your application and have the following request:

- **Change the drug substance specification for [REDACTED] (b) (4) to NMT [REDACTED] (b) (4) to limit the exposure of [REDACTED] (b) (4) from a 10 mg BID dose of lorcaserin to NMT [REDACTED] (b) (4) micrograms/day.**

Please submit this information officially to the NDA and cite this email. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA

08/09/2010

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, July 20, 2010 9:06 AM
To: 'Mark Brunswick'
Subject: NDA 22529 (lorcaserin) Additional carcinogenicity Information Required.

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review the carcinogenicity data submitted with your NDA. In addition to those requests sent on Friday, July 16, 2010 (via email), we have the following requests:

- **Resubmit the rat carcinogenicity dataset, listing only neoplastic tumors (the dataset should not contain entries for atrophy, inflammation, bacterial colonies, etc).**

In addition, please make the following revisions to the rat AND mouse datasets and resubmit for review.

- **It is not appropriate to distinguish between benign and malignant forms of the same tumor in the TUMORNAM field. The MALIGNST field exists to record this information. MALIGNST should take the value 1 when the tumor is deemed to be malignant, and 2 when it is deemed to be benign. The value 3 is to be used when it is not possible to determine whether the tumor is malignant or benign. This field should be left blank when the organ has not been examined.**
- **The data should still conform to the required standards, so each animal should still have an entry, even if no neoplastic tumor is detected. In this case, the SEX, SPECIES, ANIMLNUM, DTHSACTM and other "animal specific" fields should still be completed, but ORGANNAM, ORGANCOD, TUMORNAM, TUMORCOD, DETECTTM, MALIGNST and other "tumor specific" codes should be left missing (i.e. blank).**
- **If an organ is unexamined, this information is captured by setting ORGANEXM to 3 (or 2, if the organ is unexamined due to autolysis). In such cases the TUMORCOD and TUMORNAM should be left missing.**
- **Again, we refer you to the carci data format and stats guidance information sheets sent previously.**

If you have any questions, please contact me via email. All information should be submitted officially to the NDA and the appropriate emails cited. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
07/20/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, July 16, 2010 10:20 PM
To: 'Mark Brunswick'
Subject: NDA 22529 Information request (#2 on 7/16/10)
Importance: High
Attachments: Carci Data Format and Stat Guidance Info Sheets 07-16-09.pdf

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We are reviewing the carcinogenicity data submitted with your NDA and have the following requests for information:

- **The rat data are missing fields DTHSACTM and DETECTTM for both the male and female rat studies. Please submit this information. In addition, please submit an official summary document.**
- **Consult the attached Guidance document for details.**

If you have any questions, please contact me via email. All information should be submitted officially to the NDA.
Please confirm receipt of the email.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

7/16/2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
07/16/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, July 16, 2010 8:41 AM
To: 'Mark Brunswick'
Subject: NDA 22529 (lorcaserin HCl) - Information Request

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following requests for additional information.

1. Please recheck the results in table E28.0 (wk 52 PASP) -- are these numbers and/or treatment assignments correct?

- Pooled Placebo mean -0.33; Pooled Lorcaserin 10 mg BID mean -0.43
- Pooled Placebo LS means -0.46; Pooled Lorcaserin 10 mg BID LS means -0.30

2. Please identify where we can find the list of patients who discontinued the study but were brought back for a week 52 echo (or provide the list). Are these the same patients who were brought back for a weight measurement at week 52?

3. Table 64 in the ISS -- broad depression SMQ -- is missing the PT 'substance abuse' (comparing with the table S09.1 in the statistical ISS). Please recalculate the total narrow + broad depression SMQ including this PT, since the narrow and broad SMQs were not combined in the statistical report.

4. In several tables in the prolactin analysis, explain why the numbers for pre, peri, and post menopausal women don't add up to the total number of women.

5. Do we know any more details about the 12/13 subjects who discontinued en masse from study -008?

6. Please explain more fully how the 2 question depression instrument was used in the BLOSSOM study -- were any data collected from it?

7. There appears to be a discrepancy in the treatment assignments for study 007 in table 71 from the ISS as compared to the adverse events reported in the 007 dataset/AE listings. Please clarify and/or update.

8. In table 81 in the ISS the n's don't add up. Please clarify and/or update.

9. Table 2 from the echo notifications document and table 55 from the BLOSSOM CSR misclassify patient 2202-S042 as a MR alert, rather than AR. This discrepancy appears to affect table 58 of the ISS. Please confirm that this misclassification did not impact other analyses.

10. Please confirm that Figure 4 in the ISS has a plot that is mislabeled: depression, narrow SMQ (should be broad?)

If you require any clarification, please submit your questions via email. All information should be submitted officially to the NDA. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
07/16/2010



NDA 22-529

INFORMATION REQUEST

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick:

Please refer to your December 18, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorcaserin Hydrochloride tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Clarify the standard batch sizes (in terms of kg) for [REDACTED] (b) (4)
2. Clarify the commercial scale for a batch of drug substance manufactured at the [REDACTED] (b) (4)
3. We note that the particle size [REDACTED] (b) (4)
[REDACTED]
Include a specification for the particle size for the drug substance.
4. Include optical rotation in the reference standard specifications for [REDACTED] (b) (4) and drug substance.
5. The following passage in the application regarding the control strategy should be removed. [REDACTED] (b) (4)
[REDACTED] Such deviations should be managed through the quality system under cGMPs.

Drug Product

6. We appreciate your detailed work to characterize the [REDACTED] (b) (4)
[REDACTED] there are additional details needed to complete the description:
 - i. Indicate whether the [REDACTED] (b) (4)
 - ii. [REDACTED] (b) (4)
 - iii. [REDACTED]

7. Provide stratified sampling data across an (b) (4) run evaluating content uniformity as an indication of potential for product segregation.
8. In section 3.2.P.2.2.1, a (b) (4) study is discussed. Submit the raw and processed data from the (b) (4) that were used to generate the data in Table 16. Also, provide your justification for the variation in (b) (4) potential (based upon (b) (4)) as batch sizes changed.
9. Currently, you do not have a (b) (4) for the manufacture of lorcaserin HCl 10-mg tablets. Note that an addition of a (b) (4) step would require a prior approval supplement.
10. For your commercial scale in-process testing of the (b) (4) tablet weight and hardness, discuss how frequently samples are taken for testing and how many tablets are tested to ensure consistent quality throughout the run.
11. Because microbial growth was observed during stability testing of some batches, you should add microbial limits testing to the drug product specification. A prior approval supplement may be submitted to delete this test when sufficient supporting data are available.
12. Your manufacturing process description does not provide sufficient process details (e.g. equipment type and size, batch size, process parameters). Submit a master batch record or revise section 3.2.P.3.3 to provide a comparably detailed process description.
13. Clarify whether you are proposing a design space for drug product. If so, include the proposed design space in section 3.2.P.3.3. In addition, comment on the following:
 - i. Clarify whether there is a scale or equipment dependence in your design space? Clarify how your design space, which was defined at developmental scale, was scaled up to the commercial scale? Provide supporting data for both cases.
 - ii. Clarify how you model the scale up of the final blend step?

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

ERIC P DUFFY
07/07/2010

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, May 25, 2010 2:37 PM
To: 'Mark Brunswick'
Subject: NDA 22529 - Information Request

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following request for information.

- We notice that there is a 'withdrawal from study' and a 'discontinuation from study drug' action option for the investigator to check when a patient has an AE. Please describe the distinction, whether investigators were given instructions to determine which action to take, why some AEs are 'yes' for w/d but 'no' for drug discontinuation (and vice versa or both 'yes'), and what implications to study procedures it had if a patient discontinued drug but not study (i.e., did that person still undergo all testing?).

All information should be submitted officially to the NDA. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA

05/25/2010

Madara, Patricia

From: Madara, Patricia
Sent: Thursday, May 20, 2010 9:58 AM
To: 'Mark Brunswick'
Cc: Tran, Paul
Subject: NDA 22529 - Advisory Committee Meeting Notification

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

I am writing to inform you that an Advisory Committee meeting has been TENTATIVELY scheduled for Thursday, September 16, 2010, to discuss your NDA for Lorqess. A notice will be published in the Federal Register 6-8 weeks prior to the scheduled meeting date.

Please note that your contact person at the Advisors and Consultants Staff is Paul Tran. Paul will be able to provide timelines and additional information related to the AC as it becomes available.

Paul Tran, R.Ph
Health Science Administrator
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Advisors and Consultants Staff
Office of Executive Programs
5600 Fishers Lane (Bldg 5630, Rm.1086)
Rockville, MD 20857-0001
Phone: 301-827-6760
Fax: 301-827-6776
Email: paul.tran@fda.hhs.gov

Please feel free to contact Paul or me if you have any questions or concerns.

Please confirm receipt of the email. Also, can you please confirm receipt of the Information Request sent yesterday, via email.

Sincerely;

Pat Madara

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
05/20/2010

Madara, Patricia

From: Madara, Patricia
Sent: Wednesday, May 19, 2010 4:05 PM
To: 'Mark Brunswick'
Subject: NDA 22529 - Request for Information

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following requests for information.

Clinical

- **Please provide a CRF/narrative for subject 25 in study 001a that fully describes the hallucination, along with descriptions of subject 25's other simultaneous AEs and their timing, duration, etc. The current CRF doesn't provide this information.**
- **In "batch 2" where you provided laboratory values exceeding predefined limits of change, it appears that creatinine clearance (actual and IBW) cannot be calculated for <LLN-60 mL/min because the LLN is defined as 52 mL/min for females and 55 mL/min for males. Please recalculate using 90 mL/min instead of LLN.**

All information should be submitted officially to the NDA. Thank you for your help with this matter. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
05/19/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, May 07, 2010 10:53 AM
To: 'Mark Brunswick'
Subject: NDA 22259 - Request for Information

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following requests for information and clarification.

Clinical

In your response (dated March 10, 2010 and described as "batch 1") to our request 2d: *Present a similar analysis as in Table S14 for vital signs and ECG parameters, with a separate presentation for BLOOM (through year 2) and justification for outlier cutoffs.*

Your comment was: **The analyses of ECG and vital sign parameters will be provided in Batch 2.**

However in your amendment dated April 5, 2010 (and described as "batch 2"), your response to our request 2d was: **Submitted to the agency on March 10, 2010, sequence 0007.**

Thus, it appears that this information has not been submitted since batch 1 states it will be submitted in batch 2 but batch 2 states it was already submitted in batch 1. This is very confusing. Please provide a clarification and submit the information requested as soon as possible.

Biometrics

We would like to be able analyze the disposition data for all randomized patients in Studies 009 and 011. We would like to be able to develop Kaplan-Meier plots of disposition, and a summary of the average time on study for patients categorized by the reason for their early withdrawal. We also plan additional sensitivity analyses of the efficacy data, based on patients' time on study. In order to accomplish this, we need to have data for the "time on study" for each randomized patient in Study 009 and Study 011. To date, we have been unable to obtain complete information from all randomized patients in the databases that have been submitted.

We request electronic data files for Studies 009 and 011 that would enable us to analyze the disposition data from all randomized subjects. These files should include, at a minimum, the following variables: (a) the unique

subject ID which would enable these files to be merged with already existing files; (b) the treatment code; (c) the status of the subject with regard to completing the study (for study 009 we refer to the 52-week part of the study); (d) the reason for early discontinuation; (e) the subject's time on study: For subjects who did not complete the study, we suggest that time on study can be calculated from the last clinic visit before the subject discontinued. However, if you have a preferred algorithm, please use it and provide the documentation for how this time on study was calculated.

We would be glad to discuss this request further in a telephone conference.

All information should be submitted officially to the NDA. Thank you for your help with this matter. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Madara, Patricia

From: Madara, Patricia
Sent: Friday, May 07, 2010 11:09 AM
To: 'Mark Brunswick'
Subject: RE: NDA 22259 - Request for Information
Importance: High

Thanks, Mark;

A correction - we reference your amendment dated April 5, 2010. This is incorrect, it should read, "your submission dated April 2, 2010 and received April 5, 2010. Apologies for the confusion.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

From: Mark Brunswick [mailto:MBrunswick@arenapharm.com]
Sent: Friday, May 07, 2010 10:58 AM
To: Madara, Patricia
Subject: RE: NDA 22259 - Request for Information

Pat,

I got the e-mail.

Mark Brunswick PhD

Senior Director Regulatory Affairs

Arena Pharmaceuticals

6166 Nancy Ridge Drive

San Diego, CA 92121

Ph (858)-453-7200

Fax (858)-677-0222

mbrunswick@arenapharm.com

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5/7/2010

From: Madara, Patricia [mailto:Patricia.Madara@fda.hhs.gov]
Sent: Friday, May 07, 2010 7:53 AM
To: Mark Brunswick
Subject: NDA 22259 - Request for Information
Importance: High

NDA 22529 **INFORMATION REQUEST**

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following requests for information and clarification.

Clinical

In your response (dated March 10, 2010 and described as "batch 1") to our request 2d: *Present a similar analysis as in Table S14 for vital signs and ECG parameters, with a separate presentation for BLOOM (through year 2) and justification for outlier cutoffs.*

Your comment was: **The analyses of ECG and vital sign parameters will be provided in Batch 2.**

However in your amendment dated April 5, 2010 (and described as "batch 2"), your response to our request 2d was: **Submitted to the agency on March 10, 2010, sequence 0007.**

Thus, it appears that this information has not been submitted since batch 1 states it will be submitted in batch 2 but batch 2 states it was already submitted in batch 1. This is very confusing. Please provide a clarification and submit the information requested as soon as possible.

Biometrics

We would like to be able analyze the disposition data for all randomized patients in Studies 009 and 011. We would like to be able to develop Kaplan-Meier plots of disposition, and a summary of the average time on study for patients categorized by the reason for their early withdrawal. We also plan additional sensitivity analyses of the efficacy data, based on patients' time on study. In order to accomplish this, we need to have data for the "time on study" for each randomized patient in Study 009 and Study 011. To date, we have been unable to obtain complete information from all randomized patients in the databases that have been submitted.

We request electronic data files for Studies 009 and 011 that would enable us to analyze the disposition data from all randomized subjects. These files should include, at a minimum, the following variables: (a) the unique subject ID which would enable these files to be merged with already existing files; (b) the treatment code; (c) the status of the

5/7/2010

subject with regard to completing the study (for study 009 we refer to the 52-week part of the study); (d) the reason for early discontinuation; (e) the subject's time on study: For subjects who did not complete the study, we suggest that time on study can be calculated from the last clinic visit before the subject discontinued. However, if you have a preferred algorithm, please use it and provide the documentation for how this time on study was calculated.

We would be glad to discuss this request further in a telephone conference.

All information should be submitted officially to the NDA. Thank you for your help with this matter. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
05/07/2010

Madara, Patricia

From: Madara, Patricia
Sent: Friday, April 30, 2010 8:06 PM
To: 'Mark Brunswick'
Subject: NDA 22529 Request for clarification

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We continue to review your NDA and have the following request for clarification.

- In the adverse event listings dataset for study 001a, the data in variable TREATMEN differs in the ADV vs. ADV_ datasets. Please explain the discrepancy and any other important differences between the 2 datasets.

Your explanation should be submitted officially to the NDA. Thank you for your help with this matter. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
04/30/2010

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, April 20, 2010 4:38 PM
To: 'Mark Brunswick'
Subject: NDA 22529 (Lorqess) - INFORMATION REQUEST

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg. We also refer to your submission dated March 10, 2010, containing responses to our previous requests for information.

We are reviewing your amendment and have the following request for additional information.

- For the studies APD-356-016 and APD-356-017, you submitted the individual subject concentration data on 03/10/2010 for the parent drug only. Please submit the individual subject concentration data for the measured metabolites including the renal impairment and hepatic impairment classification information from the studies APD-356-016 and APD-356-017, respectively. Additionally, for study APD-356-016, please also include demographics data, such as subject age and serum creatinine level. Please submit the data within 2 weeks of receiving this request.

Submit this additional information officially to the NDA. Thank you for your help with this matter. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA

04/20/2010

Madara, Patricia

From: Madara, Patricia
Sent: Monday, April 05, 2010 4:08 PM
To: 'Mark Brunswick'
Subject: NDA 22529: Amendment dated April 2, 2010 - request for clarification.

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mark;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg. We also refer to your submission dated April 2, 2010, containing responses to our previous requests for information.

We are beginning to review your amendment and have the following request for clarification.

- Please explain where we can find the “raw” compiled initial ratings for the 3 Arena physicians, which are supposed to be provided in the introductory pages within Supporting Documents for Suicidality Assessments: APD356-009 (a 463 page document: page 1 is a cover page, pages 2-4 provide final ratings, page 5 is a listing of extra patients of interest, and pages 6-463 are source documents).

Please respond via email. Any additional information should be submitted officially to the NDA. Thank you for your help with this matter. **Please confirm receipt of the email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
04/05/2010

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, March 23, 2010 11:44 AM
To: 'Mark Brunswick'
Subject: NDA 22529 - Request for Information

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We are continuing to review your NDA and have the following information request. Please submit all information officially to your NDA and cite this email request.

With respect to the suicidality assessment for studies -009 and -011, please provide:

- A list of cases flagged for review and the method by which each case was selected (AE term, BDI-II question 9, etc)
- Any supplementary information that was gathered on those cases
- Each evaluator's individual ratings for each case and documentation regarding how any differences were resolved in determining the final scored value
- Beyond the work document, was any training provided to the evaluators regarding how to rate a particular case?

You state that PASP was estimated from the echocardiographic tricuspid regurgitant jet velocity and that because this method requires that the jet be adequately visualized the sonographers and cardiologists were unable to report PASP in some patients. Confirm that this is the reason for a relatively large proportion of missing PASP data and describe, if known, the reason(s) for the lack of tricuspid regurgitant jet velocity visualization in some patients.

Please contact me if you have any questions. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue

Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
03/23/2010



NDA 22529

FILING COMMUNICATION

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your new drug application (NDA) dated December 18, 2009, received December 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We also refer to your submissions dated December 30, 2009, and January 12 and 13, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 22, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 1, 2010.

During our filing review of your application, we have identified the following deficiencies and request submission of the information described below. Please submit the requested materials as rapidly as possible so that we may continue our review of your NDA.

Clinical: Please respond to the request in bold font (1.h.) within one week. Provide an estimated timeline for your responses to the other requests.

1. Adverse Events of Special Interest

- a. In the note under table S09.1, you state that AESI categories were defined by the Sponsor using existing SMQs or a customized list. Please clarify whether those AESIs that used existing SMQs were customized. For those AESIs that were generated by Arena (e.g., Cardiac Valve Disorder), describe the process used to select the MedDRA preferred terms.
- b. All AESIs as presented in section 6.1.2 of the ISS statistical report should be also conducted for the two phase 2 studies, and BLOOM (through year 2) and BLOSSOM studies, separately.
- c. An analysis using PTs related to male and female priapism should be conducted (as asked for at the preNDA meeting); see suggested search terms, below. These data should be presented as with other AESIs in Table S09.1, for phase 2 and phase 3 studies separately and phase 3 studies pooled.

MedDRA Search Terms for Priapism

<u>LLT</u>	<u>PT</u>	<u>HLT</u>	<u>SOC</u>
Priapism	Priapism	Erection and ejaculation disorders	Reproductive system and breast disorders
Priapism aggravated			
Clitoral engorgement	Clitoral engorgement	Vulvovaginal signs and symptoms	
Clitorimegaly	Enlarged clitoris	Female gonadal function disorders	Endocrine disorders
Clitoris engorgement			
Clitoris enlarged			
Hypertrophy of clitoris			
Vulvodinia	Vulvovaginal pain		
Erection increased	Erection increased	Sexual arousal disorders	Psychiatric disorders
Penile edema	Penile oedema	Penile disorders NEC	
Penile vascular disorder	Penile vascular disorder		
Penile pain	Penile pain		
Spontaneous penile erection	Spontaneous penile erection		

- d. ‘Hyperprolactinemia’, ‘blood prolactin abnormal’, and ‘blood prolactin increased’ were not included in the PTs searched for the AEs related to prolactin and should be added to the analysis. These data should be presented as with other AESIs in Table S09.1, for phase 2 and phase 3 studies separately and phase 3 studies pooled.
- e. ‘Serotonin syndrome’ was not included in the PTs searched for AEs related to serotonin syndrome and should be added to the analysis. These data should be

- presented as with other AESIs in Table S09.1, for phase 2 and phase 3 studies separately and phase 3 studies pooled. Additionally, please perform analyses using the *neuroleptic malignant syndrome SMQ* and *dystonia SMQ*. Narrow and broad SMQs should be presented.
- f. Update Table 60 in ISS (breast cancers) to include any baseline or on-study prolactin concentrations that are available for these patients.
 - g. An additional AESI analysis that we are requesting is: *acute renal failure SMQ*. Please present this analysis for phase 2 and phase 3 studies separately and phase 3 studies pooled.
 - h. Suicidality analysis: detail how your implementation of C-CASA was different from the Posner 2007 publication and justify the rationale for those modifications.**
 - i. Provide the literature references (actual articles) that describe the validation of the BDI-II and the procedure for scoring, or describe their location in the NDA.
2. Laboratory and vital sign data
 - a. All laboratory data as presented in Table S14 of the ISS statistical report should be also be presented through year 2 of the BLOOM study (i.e., present the BLOOM study separately).
 - b. Please conduct similar outlier analyses for all safety laboratory values (not just selected).
 - c. Provide the criteria used to identify safety laboratory outliers.
 - d. Present a similar analysis as in Table S14 for vital signs and ECG parameters, with a separate presentation for BLOOM (through year 2) and justification for outlier cutoffs.
 - e. Identify the prolactin assay that was used in your program, or state where in the NDA this information is located.
 3. Echocardiograms
 - a. Please provide the 90% CI for the proportion of patients who developed FDA valvulopathy for each study individually.
 - b. Additional information/analyses related to echocardiogram inter- and intrareader variability not included in the 6-month EDSMB report were supposed to be included in the final study reports. Please state the location of these analyses in the NDA, or provide them.
 - c. As discussed in the preNDA meeting, source documents (written interpretations) were supposed to be provided for all cases of FDA-defined valvulopathy and in those situations that required third reader adjudication for AR and MR readings with ≥ 2 grades discordance. Please describe their location in the NDA or provide them.
 4. Concomitant medications
 - a. In BLOSSOM, Tables 32 and 33 (patients who changed or initiated selected medications) are helpful. Similar analyses were conducted in BLOOM, although only in the PP1 population (see request (b)). Please generate these tables for the Safety population for BLOOM (through year 2) and for the phase 3 studies, pooled.

- b. In BLOOM, please clarify why the numerators in Table 14.2.140 add up to the denominator and yet there are still patients counted as “yes” in the respective medication category for Table 14.2.141. These groups should be mutually exclusive.
 - c. Similar tables to those in request (a) should be generated for concomitant psychiatric medications, and then further separated by antidepressants, anxiolytics, and antipsychotics.
 - d. In the preNDA meeting, you alluded to approximately 50 – 100 patients who had broken protocol and been exposed to SSRIs for up to six months during the clinical trials. Please present a treatment exposure and safety analysis (SAEs, withdrawals, AESIs, and common AEs) by treatment group for these patients (phase 3 studies individually and pooled).
5. Comorbid conditions
- a. Provide an analysis of efficacy (weight loss) and safety (common AEs) by the presence or absence of comorbid condition: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.
6. CRFs and investigators
- a. Please describe how eCRFs were filled out, or where in the application this is described (i.e., were they entered electronically by the investigator or filled out by hand and entered electronically by the CRO).
 - b. Please describe where on the CRF the investigator made narrative comments about a particular adverse event.
 - e. It appears that there are CRFs included for patients who did not experience death, SAEs, or AEs leading to dropout. Describe the selection process for the inclusion of additional CRFs in the NDA.
 - f. In study 003, it appears that there was a patient who was discontinued for pregnancy, but that CRF was not located.
 - g. In study 004, there are links to CRFs for subjects 08-012 and 40-031, but the links do not work and the CRFs are not included in the separate listings.
 - h. Please clarify:
 1. whether Larry Dee Stonesifer (site 173, BLOOM) enrolled any patients.
 2. why, in the BLOSSOM trial, there were a number of sites with an investigator formerly another investigator (e.g., Douglas Denham, formerly Mark Kipnes).
 3. the name and address for site 2165 in the BLOSSOM trial.
7. Miscellaneous
- a. Provide a table of overall drug exposure by days of treatment including year 2 of BLOOM (i.e., extend Table 7 in the ISS), or, enumerate how many patients have been exposed to lorcaserin for 18 months and 2 years.
 - b. Please provide an analysis of lorcaserin overdose experience in the clinical trials (intentional or accidental), and a discussion of any theoretical or observed risk from lorcaserin overdose.

Biometrics

1. At the pre-NDA meeting on August 12, 2009, we requested additional statistical analyses of certain efficacy endpoints from Study 009 and Study 011. While we did locate the results of the completers analysis for the two studies combined, we did not locate results of the other analyses that we requested. For this reason, we request that you conduct the following analyses separately for Study 009 and Study 011: a) for the co-primary endpoints, use the completers population and the primary efficacy analysis models; and b) for the percent change in body weight from baseline, use the MITT1 and PP1 populations and a mixed-model-repeated measures (MMRM) analysis model. If you have already conducted and reported these analyses, please indicate their location in the submitted materials.

Clinical Pharmacology

1. Submit the bioanalytical method validation for study APD-356-001C.
2. Submit individual subject concentration data including their renal impairment and hepatic impairment classification information from the studies APD-356-016 and APD-356-017, respectively.
3. Submit the actual names of the analytes that are reported in individual subject concentration datasets for studies APD-356-012 and APD-356-002.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Metabolism and Endocrinology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies [REDACTED] (b) (4) for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies [REDACTED] (b) (4) (yrs) for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

ERIC C COLMAN
02/24/2010

Madara, Patricia

From: Madara, Patricia
Sent: Monday, February 22, 2010 5:28 PM
To: 'Mark Brunswick'
Subject: NDA 22529 (Lorqess) - Information Request

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We are beginning our preliminary review of your application and have been unable to find any tables or charts listing each investigator site (site #, investigator name and address) that also includes the number of subjects screened and enrolled for each site. Please submit this information for all phase 2 and 3 trials or tell us where the information is located within the NDA.

The 60-day filing date for Lorqess has passed and it will be filed. The next official communication will be our 74-day letter containing additional requests for information and possible review issues.

Please contact me if you have any questions. **Please confirm receipt of this email.**

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA
02/22/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22529

DENY FAST TRACK

2/19/10

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We note that your original application, dated December 18, 2010, contained a request for Fast Track designation for treatment of obesity.

We reviewed your request for fast-track designation and conclude that the lorcaserin development program does not qualify for this designation. Although the Division acknowledges that obesity is a serious condition, based on preliminary review of your efficacy data, we do not agree that lorcaserin has the potential to address an unmet medical need (e.g., significantly reduce the risk for morbidity or premature death in obese individuals). Secondly, the lorcaserin development program was not designed to demonstrate the drug's potential to address an unmet medical need, as outlined in section B(1) of the Fast Track guidance, and it is arguable as to whether the lorcaserin development program was designed to demonstrate lorcaserin's effect on a serious aspect of obesity.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review". This document is available on the internet at <http://www.fda.gov/cder/guidance/index.htm> or may be requested from the Office of Training and Communications, Division of Drug Information at (301) 827-4570.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	GI-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

ERIC C COLMAN
02/19/2010

Madara, Patricia

From: Madara, Patricia
Sent: Tuesday, February 02, 2010 9:28 AM
To: 'Mark Brunswick'
Subject: NDA 22529 (Lorqess) Urgent Request for Information

Importance: High

NDA 22529

INFORMATION REQUEST

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We are beginning a preliminary review of your NDA and have the following information request. **We request a prompt written response before February 19, 2010, in order to continue our evaluation of your NDA.** Please note, submission of this information is required for review of your NDA and its omission is considered a possible refuse-to-file issue.

The analysis files from Study 009 are not adequate to support a statistical review of the primary efficacy results. The analysis files from Study 009 do not include the following information: (1) the status of each patient with respect to each of the key analysis populations; (2) key baseline clinical characteristics; (3) the co-primary efficacy endpoints in their final state; (4) sufficient intermediate data so that it is possible to follow the derivation of the primary efficacy endpoints and (5) the status of each value with respect to whether it is a measured value or an imputed value.

We request an analysis file from Study 009 that addresses our statistical review concerns. This file should have the same format as the file VSN.xpt for Study 011. The file should also be well annotated in a define.pdf file. If the file we are requesting is already available in the current submission, please describe its location. The analysis file from Study 009 that we are requesting should have the following characteristics (obtained from the characteristics of the file VSN.xpt from Study 011):

- A) Analysis populations: the status of each patient should be clearly coded with respect to the analysis population (i.e., MITT1, PP1, W52, MITT2, PP2 and Safety).
- B) Key baseline clinical characteristics: The file should include key baseline clinical characteristics for each patient, such as the status with respect to BMI group, hypertension comorbid condition and hyperlipidemic comorbid condition.
- C) Primary efficacy endpoints: The file should include the co-primary efficacy endpoints and other weight-related endpoints (such as BMI) that are used in sensitivity analyses of the primary endpoints. For endpoints that are derived, such as "change from baseline," "% change from baseline," and "5% weight loss responder (y/n)," the analysis data files should include sufficient intermediate data so that it is possible to follow the derivation. Endpoint levels that are imputed should be coded to indicate the imputation. The file should provide values for each patient at

each clinic visit.

Please contact me if you have any questions. I will call later today to confirm receipt.

Sincerely;

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 301-796-1249

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
02/02/2010



NDA 22529

NDA ACKNOWLEDGMENT

Arena Pharmaceutical, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Lorqess (lorcaserin HCl) Tablets, 10 mg

Date of Application: December 18, 2009

Date of Receipt: December 22, 2009

Our Reference Number: NDA 22529

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 20, 2010, in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the

certification requirement. The form may be found at
<http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at:
<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at:
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website
<http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFileSDFs/ucm073080.htm>

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22529

ORIG-1

ARENA
PHARMACEUTICA
LS INC

LORQUESS (lorcaserin
hydrochloride) Tablets

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/s/

PATRICIA J MADARA

01/06/2010



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 12, 2009; 1:30 PM Eastern time
Meeting Location: Building 22, White Oak Campus, Silver Spring, MD

Application Number: 69888
Product Name: lorcaserin hydrochloride (ADP356)
Indication: treatment of obesity
Sponsor/Applicant Name: Arena Pharmaceuticals, Inc

Meeting Chair: Eric Colman, M.D.; Deputy Director
Meeting Recorder: Patricia Madara

FDA ATTENDEES

Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Eric Colman, M.D.	Deputy Director
Amy Egan, M.D., MPH	Deputy Director for Safety
Julie Golden, M.D.	Medical Officer
Todd Bourcier, Ph.D.	Preclinical Pharmacology/Toxicology Team Leader
Fred Alavi, Ph.D.	Preclinical Pharmacology/Toxicology Reviewer
Patricia Madara, M.S.	Regulatory Project Manager

Office of Biostatistics; Division of Biometrics II

Todd Sahlroot, Ph.D.	Deputy Director
Lee Ping Pian, Ph.D.	Statistical Reviewer @ DMEP

Office of Biostatistics; Division of Biostatistics VI (Quantitative Safety and Pharmacoeconomics Division)

George Rochester, Ph.D.	Statistical Reviewer for Safety, Team Leader
Janelle Charles, Ph.D.	Statistical Reviewer for Safety

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Immo Zdrojewski, Ph.D.	Clinical Pharmacology Reviewer



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 69888

MEETING MINUTES

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lorcaserin hydrochloride (APD356).

We also refer to the meeting between representatives of your firm and the FDA on August 12, 2009, to discuss issues related to submission of a new drug application (NDA) for lorcaserin hydrochloride (APD356).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: meeting minutes

Meeting Minutes
PreNDA, type B
August 12, 2009

Office of New Drug Quality Assessment; Division of Pre-Marketing Assessment I

Suong Tran, Ph.D.

CMC Lead, Branch 2

Office of the Center Director; Controlled Substance Staff (CSS)

Katherine Bonson, Ph.D.

Pharmacology Reviewer

Lori Love, M.D.

Medical Officer

John Gong, Ph.D.

Pharmacology Reviewer

ARENA PHARMACEUTICALS ATTENDEES

Mark Brunswick, Ph.D.

Senior Director, Regulatory Affairs

William Shanahan, M.D.

Chief Medical Officer

Christen Anderson, M.D., Ph.D.

Vice President, Clinical Development

Marianne Mancini, M.B.A, MA

Senior Director, Clinical Operations and Project
Management

Matilde Sanchez, Ph.D.

Senior Director, Biostatistics and Data Management

Daniel Kim

Director, Regulatory Operations

BACKGROUND

Lorcaserin hydrochloride is a serotonin 5HT_{2c} receptor agonist being developed as a treatment for obesity. Arena Pharmaceuticals is currently completing the phase 3 clinical trials for lorcaserin and plans to submit an NDA by December 2009. The purpose of this meeting was to obtain guidance from FDA on the overall format, structure and content of the NDA. On July 6, 2009, Arena submitted a briefing document containing specific questions related to their NDA submission. FDA issued pre-meeting minutes on August 10, 2009. Based on the FDA responses to Arena's questions, and additional comments provided by the Agency, the company requested further discussion on:

- question #4
- question #5a and d
- question #6
- question #9
- additional nonclinical comments provided

For convenience, all the questions and pre-meeting comments are repeated below in regular font while the meeting discussion is in **bolded** font.

Clinical Questions

Question #1

The primary efficacy data for the APD356-009 (BLOOM) clinical trial are summarized above. *Provided that the data from the APD356-011 (BLOSSOM) trial are consistent with these results,* does the Agency agree that the efficacy data meet criteria for approvability for the following proposed indication: weight management in patients with obesity and in overweight patients (BMI 27.0-29.9) with at least one comorbidity, including weight loss and maintenance of weight loss, used in conjunction with a reduced calorie diet?

FDA PreMeeting Response

The drug's approvability is a review issue, as is any proposed labeling language, although you should note that we may not entertain a ^{(b) (4)} indication. In determining approvability, we will take into consideration not only the primary efficacy results, but also improvements in markers of co-morbidity and how the safety profile balances the efficacy findings. We consider the valvulopathy endpoint as critical for approvability as the primary weight loss endpoint.

Please note that statistical tests for both the 5% responder and body weight change from baseline endpoints have to be significant in order to declare the study is positive.

Question #2

Phase 2 and phase 3 trials generated a large amount of echocardiographic data. These data consist of (1) sonographic images [video tapes for phase 2 trials, digital images in AVI format for phase 3]; (2) source documents from the echo core lab comprising written interpretation of

each echocardiogram; (3) SAS datasets that include all parameters reported in the written interpretations; (4) listings and tabular summaries for each clinical trial.

Arena proposes that we provide echocardiographic data to the Agency in the formats described below. Is this acceptable to the Agency?

- a. Listings and tabular summaries provided as part of each clinical study report
- b. SAS dataset for each clinical trial

FDA PreMeeting Response

Source documents (written interpretations) should be provided for all cases of FDA-defined valvulopathy and in those situations that required third reader adjudication for AR and MR readings with ≥ 2 grades discordance. Otherwise, source documents should be available upon request. The sonographic images do not have to be included in the NDA, although we cannot guarantee that some subset of these images will not be requested during the course of the review.

Question #3

The Agency has previously requested that we evaluate variability of echocardiographic assessments, prolactin levels in clinical trial participants, and breast cancer risk, as indicated by the NCI Breast Cancer Risk Assessment Tool. In response to these requests, we have provided interim reports for the first two. Arena proposes that we submit final reports for these three requests in the NDA without additional interim reports. Is this acceptable to the Agency?

FDA PreMeeting Response

Yes. We note that you have not described in the ISS SAP how you plan to analyze and present the prolactin data.

Question #4

The primary safety analysis of echocardiographic data from the BLOOM (APD356-009) trial will be provided in the Briefing Package. Does the Agency agree that a pooled analysis of the APD356-009 echo data (2472 evaluable patients at Week 52) and the APD356-011 echo data (predicted 2240 evaluable patients in the placebo and lorcaserin 10 mg BID groups) will adequately address the risk of developing FDA-defined valvulopathy?

FDA PreMeeting Response

This is a review issue. As we have previously conveyed to you, at a minimum your echocardiographic data must be robust enough to rule out a relative risk of 1.5 for FDA-defined valvulopathy.

Please provide both separate and combined analysis results. Please propose in advance the analysis model in combining the 2 studies. The analysis should present the confidence intervals for the risk ratio for the primary safety analysis on FDA-defined valvulopathy.

Meeting Discussion

The sponsor proposed to combine the 2 studies using study as a stratification factor in the model. The Division replied this is acceptable.

Additional Clinical Comments

1. The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf>. To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template (see Appendix A, below).
2. We note that your attrition in the BLOOM study was quite high (55% placebo, 45% lorcaserin). A total of 22% of placebo-treated patients and 18% of lorcaserin-treated patients were discontinued due to "other" reasons. These reasons will need to be identified. In situations where patients were discontinued due to patient request or investigator discretion, any recent adverse events should be described and considered in light of the discontinuation. Reasons for sponsor-requested discontinuation will also need to be described.
3. Additional analyses for the 2-year data we are interested in seeing include: 1) the proportion of placebo responders (pla/pla group) who maintained $\geq 5\%$ weight loss over 2 years (Figure 2), and 2) body weight change by study week using the modified intent-to-treat population (Figure 3).
4. Table 10 from your Briefing Document (Proportion of Patients with FDA-defined Valvulopathy at Each Scheduled Time Point) should include the following: 1) completers at each time point; 2) for weeks 24 and 52: a) include discontinued patients who were brought back for echos with any drug/placebo exposure, b) include discontinued patients who were brought back for echos with ≥ 3 months drug/placebo exposure; 3) for weeks 76 and 104: include analysis of patients who ever had any exposure to lorcaserin. Similar analyses should be done for the BLOSSOM trial (as applicable) and for the trials combined (as applicable).
5. You should identify adverse events of special interest (AESI) to evaluate as separate analyses in the ISS. They can be based on existing MedDRA SMQs or you can create your own, but inclusion or exclusion of selected preferred terms should be justified. Some examples of AESI for this NDA might be: cardiac valve disorders, pulmonary hypertension, depression and suicide, psychosis, serotonin syndrome, breast neoplasms, and priapism (male and female).
6. Lorcaserin is the last centrally-acting obesity treatment in development that was not required to incorporate specific psychiatric screening and monitoring guidelines. We nevertheless acknowledge that you have undertaken an evaluation for suicidality and depression with alternate instruments. Because the C-SSRS, which is an important part of FDA's recommendations for prospective monitoring of suicidality, was not included in the

obesity program, you should employ a retrospective analysis of your data for suicidality [i.e., Columbia Classification Algorithm for Suicide Assessment (C-CASA)].

Meeting Discussion

The sponsor noted that they had used a “modified” version of the Columbia Classification Algorithm for Suicide Assessment (C-CASA). Since the published version of C-CASA has a large number of choices, Arena narrowed the possible responses down to six choices.

[Post-Meeting Comment: It appears that the key difference between your suicidality assessment scoring and C-CASA is the assessment of self-injurious behavior. Please clarify what assessment should have been made by the raters if there was self-injurious behavior and no intent to die (either with intent to harm or no intent to harm). The NDA should include the work process for blinded adjudication and any written interpretation of suicidality by the raters.]

7. We note that you have referred to the Draft Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation for discussion of liver laboratory testing in section 5.5.1 of your SAP. To expand on your proposal, please conduct analysis of liver laboratories based on the following cut-points of interest (if not already proposed):
 - >3x-, 5x-, 10x-, and 20xULN elevations of AST and ALT
 - Bilirubin >1.5xULN and >2xULN
 - ALP >1.5xULN
 - Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN)Please refer to the Draft DILI 2007 guidance for a full discussion of the recommended evaluation of potential DILI in a NDA submission.
8. Key ISS tables (deaths, SAEs, and AEs leading to discontinuation) should hyperlink to the relevant CRFs.
9. Narratives should be provided for deaths and SAEs.
10. Consider returning to demonstrate the electronic submission for the primary reviewers. Ideally, this would occur once the NDA is complete and ready for review, but prior to application. Clarifications, and if necessary, corrections, could be made before the “review clock” starts.
11. Please discuss the projected status of BLOOM-DM at the proposed time of filing.

Meeting Discussion

The sponsor noted that BLOOM DM had finished enrollment and they expected the study report to be available by December 2010.

Additional Clinical Pharmacology Comments

1. Since the metabolism pathway of lorcaserin is unclear, we can not comment whether the evaluations performed during the clinical pharmacology development program (e.g. drug-drug interaction studies) are sufficient.
2. During your development program you requested feedback on a phase 3 lorcaserin-SSRI drug interaction study (APD356-019) and a population PK analysis plan. These studies were not included in the summary table of studies to be submitted in this NDA. Please confirm that these studies will be submitted with your NDA.

Meeting Discussion

Arena noted that although a protocol had been submitted for a lorcaserin – SSRI drug interaction study, the study had never been initiated. However, Arena did point out that 50 – 100 patients had broken protocol and been exposed to SSRIs for up to six months during the clinical trials. Arena stated that a separate analysis will be performed on patients exposed to SSRIs.

Regarding the population PK analysis plan, the Division confirmed that they had located the SAP document.

Statistical and Data Management Questions

Question #5

An overview of the clinical data and key analyses to be included with the NDA in support of the efficacy and safety of lorcaserin is provided in the briefing package. The Statistical Analysis Plan (SAP) for the pooled analyses for efficacy and safety and sample tables is also included as an Appendix.

- a. Does the Agency concur with the proposed efficacy analyses of the pooled study results for the Phase 3 studies (APD356-009 and APD356-011) with respect to time-points, weight efficacy-related endpoints and subgroups?

FDA PreMeeting Response

We are interested in the test of mean *percent* change from baseline body weight in addition to mean *absolute* change. Additional subgroups of interest would be individual baseline co-morbidities. We are not sure why “responder status” is included as a subgroup.

The 3 analysis populations are MITT1, W52 population and PPI. Please perform a completers analysis in place of PPI.

The W52 population should include all patients in the MITT1 population (that is, patients who completed, patients who did not complete (using LOCF), and withdrawals who returned for a Week 52 weight measurement).

Please perform a mixed-model-repeated-measure (MMRM) analysis at year 1 for the MITT1 population and the W52 population.

- b. Does the Agency concur with the proposed durability analysis of the lorcaserin treatment effect on body weight during Year 1 from the pooled APD356 Phase 3 studies?

FDA PreMeeting Response

You are free to conduct any analysis you wish. [REDACTED] (b) (4)

- c. Does the Agency concur with the patient populations and subgroups proposed for the lorcaserin integrated analyses for safety?

FDA PreMeeting Response

See Additional Clinical Comments for populations to be included in the echocardiography analyses. Subgroup analyses (same subgroups as for efficacy) should be conducted for adverse events, particularly for SAEs, AEs leading to discontinuation, and AESI.

- d. Does the Agency concur with the format of the sample tables provided?

FDA PreMeeting Response

1. Clinical finds the single dose phase 1 tables acceptable.
2. We note that no examples were provided for adverse events from the phase 3 trials. See Appendix B for a standard table to be used for AEs and SAEs.
3. We assume that the tables presented are meant to serve as examples (e.g., serum uric acid will not be the only laboratory parameter presented as mean change).
4. It would be more informative in the ISS to include mean change in laboratory data from baseline to final visit, rather than at each visit. Tables in the ISS can refer to appendices that include all time points.
5. It would be more informative to see cut-offs for laboratory data presented as, for example, the proportion meeting $> 3x$ ULN, $> 5x$ ULN, $> 20x$ ULN etc., rather than proportion meeting $> 3x$ ULN and $\leq 5x$ ULN, $> 5x$ ULN and $\leq 20x$ ULN, etc.
6. It is not clear what the distinction is between those cut-offs that use "one value" (e.g., bilirubin) vs. "any value" (e.g., neutrophil count).
7. Similar tables and formatting should be used for the clinical study reports for BLOOM and BLOSSOM that are used in the ISS.

- e. Does the Agency have any further comments on the SAP for the integrated analyses for efficacy and safety?

FDA PreMeeting Response

This is addressed in responses and comments above.

Question #6

Are the clinical study data specifications that are delineated in the following section acceptable to the Agency for Arena's NDA submission?

For each clinical study and integrated analysis, Arena will provide the following data components:

- Listing (raw) data sets (xpt v.5 format)
- Analysis data sets (xpt v.5 format)
- Data definitions (pdf format)
- Annotated CRF (pdf format)
- Blank CRF (pdf format)
- SAS program codes for the key endpoints in PDF format

FDA PreMeeting Response

Please provide analysis datasets which conform to the CDISC ADaM convention.

<http://www.cdisc.org/models/adam/V2.0/index.html>

Meeting Discussion

Arena noted that the datasets had been analyzed using the 1999 Guidance to Industry. The sponsor had submitted a request for concurrence from the Agency regarding this proposal on September 18, 2008. A response was not received and they had assumed acceptability.

The Division noted datasets conforming to CDISC ADaM convention were preferred but not mandatory.

Formatting and Submission Questions

Question #7

Given the safety profile, efficacy and novel mechanism of action of lorcaserin, we intend to request Priority Review for the NDA. Does the Agency agree that this application will meet the criteria for Priority Review?

FDA PreMeeting Response

This will be determined at the time of filing.

Question #8

Given the safety profile seen in the lorcaserin clinical trials, Arena does not plan to submit a Risk Evaluation and Mitigation Strategies (REMS) as part of the NDA. Is this acceptable to the Agency? If not, please provide guidance.

FDA PreMeeting Response

This is a review issue. If during the course of our review of the NDA, we find that a REMS is necessary to ensure that the benefits of the drug outweigh the risks, you will be so notified.

Question #9

Arena is preparing an 8-Factor Analysis of the abuse liability of lorcaserin, which we propose to submit as part of the ISS of the NDA. Is this acceptable to the Agency?

FDA PreMeeting Response

- A. The Eight Factor Analysis is a scientific and medical evaluation that forms the basis for a drug scheduling recommendation from the Department of Health and Human Services to the Drug Enforcement Administration. The Sponsor is not required to prepare and submit this document in the NDA.

Meeting Discussion

The Controlled Substance Staff (CSS) reiterated that the Eight Factor Analysis is a legal document that HHS submits to DEA. Thus, it is not the responsibility of the sponsor to prepare this document. Instead, CSS referred the sponsor to the requirements for information in the Abuse Potential Section of the NDA, which includes a proposal for scheduling and all of the primary data that support that proposal.

- B. However, an NDA should contain an Abuse Potential Section that contains all data and necessary elements for fully assessing the abuse potential of a drug (21 CFR § 314.50 (d) (5) (vii)).

The Abuse Potential Section of the NDA includes a proposal for scheduling the drug and all scientific information (including primary data) that forms the basis of the proposal as described below:

1. Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug from the preparation for possible administration by alternative routes)
2. Pharmacokinetics and pharmacodynamics (including full data on receptor binding)
3. Abuse potential studies in animals and humans (including studies evaluating physical dependence), if conducted
4. Assessment of adverse events in clinical studies related to abuse potential, with an emphasis on MedDRA terms that report incidents related to behaviors associated with euphoria; impaired attention, cognition, mood, and psychomotor events; and dissociative or psychotic behaviors (see additional information below). Complete case report forms (CRF) should be provided for any individual who experiences overdose, psychiatric or neurological adverse events during a Phase 1, 2 or 3 study conducted with lorcaserin.

Meeting Discussion

Regarding submission of adverse events related to abuse potential, the sponsor noted that there were a large number of headaches reported by study subjects. They asked if it would be acceptable to delete "headache" from the assessment of adverse events related to abuse potential.

Arena questioned the timeframe for scheduling. CSS noted that they attempted to complete their abuse potential assessment during the NDA review cycle. However, they cautioned that scheduling actions involve analysis and decisionmaking by FDA, HHS and DEA, so it is not possible to predict when final scheduling might occur relative to the PDUFA date.

[Post-Meeting Comment: CSS policy is to try to finalize the scheduling action as close as possible to the PDUFA date, so that marketing is not delayed. However, CSS can not prevent delays that occur by other groups involved in the drug scheduling process.]

5. Assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, and diversion during clinical studies.
 6. Integrated summaries of safety and efficacy (ISS and ISE) in clinical studies.
 7. Information related to overdose in clinical studies.
 8. Epidemiological information on abuse potential, if available
 9. Foreign experience with the drug (including adverse events, abuse potential, marketing and labeling), if available
- C. As noted above, all clinical studies should be evaluated for indicators of abuse potential. The Sponsor should ensure that investigators are trained to recognize the adverse events that are indicators of abuse and that they are consistently reported across study sites. The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA dictionary and frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes is a key observation that may influence a recommendation for scheduling. However, the overall behavioral profile and pharmacologic similarity to a scheduled drug is critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-Related Terms

- * **Euphoric mood**: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high*, high*, high feeling*, laughter (* Terms that clearly are not pertinent or relevant such as "high blood pressure," "respiratory depression," etc. should be excluded).
- * **Elevated mood**: mood elevated, elation
- * **Feeling abnormal**: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey
- * **Feeling drunk**: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged
- * **Feeling of relaxation**: Feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness
- * **Dizziness**: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy
- * **Thinking abnormal**: abnormal thinking, thinking irrational, wandering thoughts
- * **Hallucination**: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted

Terms Related to Impaired Attention, Psychomotor Event, Cognition, and Mood:

- * Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor
- * Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional lability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability
- * Mental impairment disorders: memory loss (excl dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders
- * Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative and Psychotic Terms:

- * Psychosis: psychotic episode or disorder
 - * Aggressive: hostility, anger, paranoia
 - * Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity
- D. The Abuse Potential section of the NDA is submitted in the eCTD as follows below. Links to the following sections should be compiled in the Abuse Potential section for ease of review.

Module 1: Administrative Information and Prescribing Information
1.11.4 Multiple Module Information Amendment

This section should contain:

- * A summary, interpretation and discussion of abuse potential data provided in the NDA.
- * A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.
- * A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the non-clinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- * A complete discussion of the non-clinical data related to abuse potential.
- * Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product.

Question #10

Since we have converted the IND to an eCTD format and have or will have submitted final Clinical Study reports and Toxicological reports to the IND, is it acceptable to the Agency to electronically link the aforementioned reports to the NDA in the eCTD?

FDA PreMeeting Response

This is acceptable assuming it conforms to eCTD regulations and the navigation of the application is seamless (meaning that the reviewer cannot tell whether a particular document is being accessed through the IND or NDA).

CMC Question

Question #11

At the time of NDA submission, Arena will have stability studies that are ongoing for Drug Substance and Drug Product. Arena intends to update the stability sections of the NDA as new data become available throughout the review, to support the proposed dating of the Drug Substance and Product. The final update will be submitted at least one month prior to the PDUFA date to allow for adequate review. Is this acceptable to the Agency?

FDA PreMeeting Response

No. You should submit a complete NDA with a complete stability data package, including at least 12-month long-term data. While we may attempt to review amendments submitted during the review cycle, the review of such amendments will depend on the timeliness of the submission, extent of the submitted data, and available resources. Therefore, in accordance with Good Review Management Principles and Practices (GRMPPs) timelines, we cannot guarantee that we will review unsolicited amendments.

Additional Nonclinical Comments

1. If not done already, please submit tumor dataset files suitable for FDA Biometrics review (Guidance for Industry; Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals). Note that we are unable to complete review of the carcinogenicity studies without an internal statistical analysis of mortality and tumor data by the FDA Biometrics group.
2. Please resubmit the final study report for the rat carcinogenicity assay to the IND as soon as is feasible.

Meeting Discussion

The Division noted that the rat carcinogenicity study report and rat tumor dataset had been lost from the electronic record and asked for this information to be resubmitted. The sponsor assured that they could resubmit all of these data.

3. We request that the integrated non-clinical section of the NDA include a thorough discussion of the positive tumor findings with lorcaserin in rodents that clearly conveys your analysis of the drug-relatedness of the tumors, the underlying mechanism, the relevance to human risk, and how the rodent tumor findings contribute to the overall risk/benefit profile for the treatment of obesity.
4. If you plan to include tabulated summary toxicology tables, we request that the data be separated by species and accompanied by summary of drug-related acute, subchronic, and chronic study findings, clinical observations, pathophysiology, clinical pathology, and histopathology.
5. Please ensure that all final study reports of the non-clinical studies are included in the initial NDA submission. Draft audited reports are not acceptable.

6. Histopathology data should include individual animal reports as well as tabulated data listed by incidence and severity score.
7. Include a Table that specifies the drug batches used in non-clinical and clinical studies, including links to impurity profiles.

Meeting Discussion (miscellaneous)

The firm asked if the FDA field offices had access to the EDR so that a paper copy of the NDA would not need to be sent to them separately. The Division agreed to check on this and let Arena know as soon as possible.

[Post Meeting Comment: Paper copies of electronic documents do not need to be sent to the field office.]

The statistical reviewers for safety requested the firm resubmit the electronic datasets already sent to the Office of Business Process Support (OBPS) as a sample submission. While the dataset had “passed” OBPS inspection, the reviewers wanted to double-check that all the information needed was present in the appropriate format.

The sponsor commented that this would not be a problem.

[Post Meeting Comment: Arena submitted the datasets to the IND on August 14, 2009.]

APPENDIX A. Recommended Analyses to Address Items in the Clinical Template

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Section 7.4.2 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.4.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.4.2 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.4.3 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.4.3 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.4.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.4.4 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.4.4. – Standard analyses and explorations of ECG data.
12. Section 7.6.4 – Overdose experience.
13. Section 7.5.1 - Explorations for dose dependency for adverse findings.
14. Section 7.5.2 - Explorations for time dependency for adverse findings.
15. Section 7.5.3 - Explorations for drug-demographic interactions.
16. Section 7.5.4 - Explorations for drug-disease interactions.
17. Section 7.5.5 - Explorations for drug-drug interactions.
18. Section 7.5.5 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

APPENDIX B. Sample Table Shell for Submission of Adverse Events

This is a standard table not designed specifically for the lorcaserin development program, and therefore includes columns not appropriate to lorcaserin analyses (e.g., active comparator). Modify the table to conform to the lorcaserin NDA.

You should construct one table for all AEs and an identical table for serious adverse events. This table is for the number and percentage of patients who had an event; it could also be done for the rate of events, e.g., the number of events per 1000 patient-years.

Table X: Incidence of All Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	Pooled Placebo	Pooled Active Comparator	All Pooled Comparator	All Pooled Study Drug Doses	Pooled Study Drug Dose A	Pooled Study Drug Dose B	Pooled Study Drug Dose C	Pooled Study Drug Dose D	etc (column for each Study Drug dose studied)
		N= n (%)	N= n (%)	N= n (%)	N= n (%)	N= n (%)	N= n (%)	N= n (%)	N= n (%)	

N = number of patients in dose group
n = number of patients who experienced a given event
 Source: (link to dataset)

APPENDIX Z

CDISC Data Requests to Sponsors Quantitative Safety and Pharmacoepidemiology Group Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please provide a Quantitative Safety Analysis Plan (QSAP). The QSAP generally states the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

- Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf>).
- Safety endpoints for Adverse Events of Special Interest (AESI)
- Definition of Treatment Emergent Adverse Event (TEAE)
- Expert adjudication process (Expert Clinical Committee Charter)
- Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- Analytical methods (e.g., rationale for data pooling or methods for evidence synthesis); statistical principles and sensitivity analyses to be considered.
- When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) should be carefully followed.
 - a. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
 - a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - i. (DV) Protocol deviations
 - ii. (DA) Drug Accountability
 - iii. (PC, PP) Pharmacokinetics
 - iv. (MB, MS) Microbiology
 - v. (CF) Clinical Findings

- b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - i. Tumor information
 - ii. Imaging Data
 - iii. Complex Inclusion/Exclusion Criteria
3. Variables
- a. All required variables are to be included.
 - b. All expected variables should be included in all SDTM datasets.
 - c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
 - d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
 - e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
 - f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
4. Specific issues of note:
- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
 - b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
 - c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues

1. Please specify which ADaM datasets you intend to submit.
2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
5. Please indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets should use the unique subject ID (USUBJID), which should be unique across the submission. The unique subject identifier should be retained across the entire submission.

General Items

1. Controlled terminology issues
 - a. Please use a single version of MedDRA for a submission. It does not have to be the most recent version for the ISS.
 - b. We recommend that the WHO drug dictionary be used for concomitant medications.

- c. Please refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements should be addressed. The sponsor should explain calculations that result in any changes in ranges for laboratory measurements.

The meeting ended.

Minutes Preparer: Patricia Madara

Chair Concurrence: Eric Colman, M.D.;
Deputy Director
Division of Metabolism and Endocrinology Products

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 69888	GI 1	ARENA PHARMCEUTICAL S	LORCASERIN HYDROCHLORIDE
IND 69888	GI 1	ARENA PHARMCEUTICAL S	LORCASERIN HYDROCHLORIDE

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/s/

PATRICIA J MADARA
09/01/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,888

Arena Pharmaceuticals, Inc.
Attn: Donald G. Grilley, RPh., M.A.
Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Grilley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for APD356.

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2006. The purpose of the meeting was to provide Agency guidance related to the Phase 3 development of ADP356.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

MEETING MINUTES

MEETING DATE: May 1, 2006
TIME: 11:30 AM – 1:00 PM
LOCATION: White Oak Campus, Building 22
APPLICATIONS: IND 69,888 (APD356)
TYPE OF MEETING: Type B; End of Phase 2
MEETING CHAIR: Eric Colman, M.D.; Acting Deputy Director
MEETING RECORDER: Patricia Madara

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

CDER Participants:

Office of Drug Evaluation II

Robert Meyer, M.D. Office Director

Division of Metabolism and Endocrinology Products

Mary H. Parks, M.D.	Acting Director
Eric Colman, M.D.	Acting Deputy Director
Eileen Craig, M.D.	Medical Officer
Julie Golden, M.D.	Medical Officer
Amy Egan, M.D.	Medical Officer
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Pat Madara, M.S.	Regulatory Project Manager

Division of Biometrics II

Todd Sahlroot, Ph.D.	Biometrics Team Leader @ DMEP
Lee Ping Pian, Ph.D.	Biometrics Reviewer @ DMEP

General Pharmacology/Toxicology Comment:

- Draft study reports of the 6-month rat toxicity study, and the 12-month monkey toxicity study must be submitted prior to the initiation of Phase 3 trials.

Questions and Answers (Bullet Format, Agency answers are in bold):

Note, only additional Agency comments (made at the meeting) are in bold font; only additional sponsor comments are in italics.

Clinical:

1. Exposure: Will the following proposed exposures be adequate to support an NDA submission?

Approximately 1500 patients exposed to efficacious dose for 1 year in blinded, placebo-controlled studies

At least 300 patients exposed to efficacious dose for 2 years, some in open-label studies

Agency response

- Echocardiograms notwithstanding, your proposed exposures meet the exposure requirements in the Draft Guidance for the Clinical Evaluation of Weight Control Drugs, and therefore may be adequate to support an NDA submission. Please see the response to question 4 for further discussion. You may wish to be more conservative in your drop-out estimate of 40% and increase this to 50%, in order to ensure adequate exposures after one year. Please see additional clinical comments below regarding your study design (run-in period).

2. Efficacy: Is the proposed primary endpoint acceptable to support a claim of weight loss?

Agency response

- The proportion of subjects achieving a $\geq 5\%$ weight loss from baseline at one year is an acceptable primary endpoint to support a weight loss indication. However, an analysis of the difference between groups in mean change (absolute and %) in body weight from baseline to Year 1 will be an important part of the statistical review in order to estimate the actual size of the treatment effect. Consideration should be given to complete follow-up of all patients regardless of compliance (adherence) to study medication.

3. Is the proposed definition of "weight maintenance" acceptable to support a claim of maintaining previously attained weight loss?

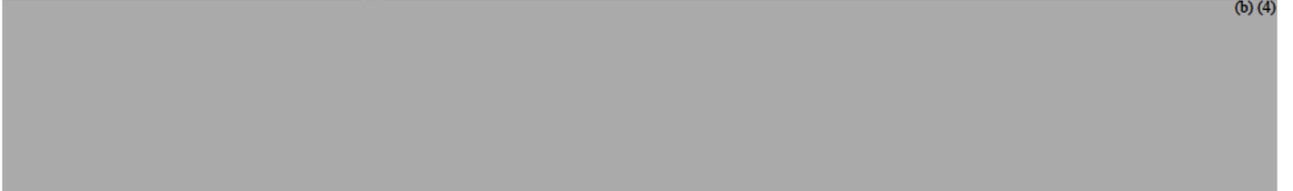
Agency response

- You have suggested that maintenance of weight loss will be defined as a statistically significantly ($p < 0.05$) lesser weight change from Week 52 to Week 104 in patients who remain on 10 mg QD or 10 mg BID APD356, as compared to patients re-randomized from the corresponding dose of drug to placebo. Since the regulatory status of, and criteria for, weight maintenance are actively being discussed by Agency reviewers, we cannot provide a definitive answer to your question. However, because weight maintenance is tied to weight loss, at a minimum we think that a labeled indication of weight maintenance should demonstrate clinical significance (e.g., at the end of two years, the proportion of subjects who have a $\geq 5\%$ reduction from baseline body weight is statistically significantly greater in the drug-treated group than in the group re-randomized to placebo, with mean weight change at Week 104 from baseline and from Week 52 demonstrating statistical significance).

Agency response



5. Is the overall clinical development proposal adequate to support an NDA submission for the use of APD356 for the following indications?



Agency response

- The clinical development program should be designed to assess safety and efficacy in adults \geq 18 years old who are obese (that is, a BMI \geq 30 kg/m²), or in those who have a BMI \geq 27 kg/m² with at least one co-morbid condition. See responses above and comments below for specific issues related to the clinical development proposal.

Additional Clinical Comments:

- You will need to perform echocardiograms at screening and exclude individuals with echocardiographic evidence of clinically significant valvular abnormalities. This would obviously include patients with FDA-defined, drug-induced valvulopathy.
- You should have a plan for detailed evaluation and long-term follow-up of any valvulopathy cases that are found in the trial.
- You will need to perform echocardiograms in subjects in all trials lasting greater than 3 months in duration.
- Echocardiograms should be performed every 6 months in the clinical trials.
- You should have a plan for detailed evaluation and long-term follow-up of any cases of clinically significantly increased PA pressure + RV enlargement that are found in the trial.
- It was noted that you have defined the maximum tolerated dose (MTD) differently in males (40 mg) and females (20 mg) based on CNS findings. Pharmacokinetic analysis by gender, in addition to other subject characteristics of interest; such as BMI, should be performed.

- Detailed assessments of mood, suicidality, cognitive function, and the potential for psychosis using validated instruments will need to be performed. It is noted that you will be assessing the abuse potential of APD356 and performing neurological examinations. You should plan to have a predefined algorithm for psychiatric and/or neurological referral.
- The issue of the safety of studying APD356 and SSRIs concomitantly will need to be discussed further.
- You should plan to assess body composition (e.g., by DEXA) in at least one phase 3 trial.
- We recommend a two-week 'run-in' period of diet and exercise, during which time all subjects receive instruction in lifestyle modification (i.e., diet, exercise, and behavior modification), prior to randomization. The goal of the 2-week lead-in phase is to enrich the study population and thus minimize non-compliance and reduce the number of subjects that dropout during the course of the trial.

Additional sponsor comment:

- *The sponsor commented that they had debated using the FDA criteria for assessing valvulopathy but felt their criteria were more robust. They proposed looking for the percentage of patients that show any increase in regurgitation at any valve. They noted that their study was powered to detect a 1.3 fold increase in incidence. The sponsor noted that they had decided against screening echocardiograms because many people have some degree of insufficiency and there was no evidence to suggest that preexisting valvulopathy would result in a drug-induced worsening.*
- *The sponsor noted that their rates for any valvular regurgitation worsening in placebo vs. treated groups were based a previous study. The sponsor was not aware of rates of unexposed individuals in the published literature.*

Post-meeting comment: The sponsor was referred to the following references for prevalence and incidence estimates, respectively: Singh JP, Evans JC, Levy D et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). Am J Cardiol. 1999;83: 897-902; and Hopkins PH, Polukoff GI. Risk of valvular heart disease associated with use of fenfluramine. BMC Cardiovascular Disorders. 2003;3:1-13.

- *The sponsor noted that "run-ins" were extremely confusing to practitioners and were not needed if strong retention strategies were in place.*

Additional Agency response:

- **The Agency noted that it is important to detect the incidence of FDA-defined valvulopathy; there is no value in looking at the rate for all valves individually when the concern is drug-induced valvulopathy. The FDA criteria are considered more medically meaningful than those proposed by the sponsor.**
- **It is important to determine the excess risk acceptable for a weight loss drug. The protocol should allow for blinded evaluation of all groups for FDA-defined valvulopathy.**

- **As the sponsor's protocol is currently proposed, small difference in valvular regurgitation incidence between drug and placebo might be difficult to detect.**
- **The Agency asked if the firm intended to get weights on all drop-outs. When questioned as to how this would enhance the analysis, the Agency replied that drop-outs would be included in the true intent-to-treat analysis. A positive finding including follow-up data for patients off drug would allow for a robust conclusion regarding the efficacy of the drug.**
- **It was reiterated that if the risk of valvulopathy had not been fully characterized, echocardiograms would be required in all trials.**
- **The Agency asked what degree of valvulopathy at baseline would result in exclusion.**

Additional Sponsor Comments:

- *The sponsor pointed out that they were not proposing screening echocardiograms. This is because the 12-week data don't suggest any progression of valvulopathy. Therefore, there was no reason to think that patients with underlying disease at baseline were more sensitive to progression.*
- *The sponsor said that they would come up with criteria for exclusion and asked if evaluation of the data at 6 months by the DSMB would be sufficient.*

Additional Agency response:

- **The Agency responded that evaluation at 6-months by the DSMB would probably suffice.**
- **It was noted that there are special issues with obesity drugs. It was noted that in some ways, weight is a surrogate marker, which means that we must be assured of safety when a drug is approved. It was also pointed out that the standards for safety were treated much differently than those for efficacy.**
- **The sponsor was informed that there should be interaction with Controlled Substance Staff (CSS) to obtain guidance related to design of studies to evaluate abuse potential.**

Additional exchanges:

- *The sponsor asked if the guidances would change before the trial results are submitted in three years. The Agency responded that it is unlikely that the fundamental components of the guidance will change significantly in the near future.*
- *The sponsor asked if the best method of communication was via special protocol assessments (SPA). The Agency noted that it was just one method, especially useful for pivotal studies, but communication by other channels was also available.*

CMC:

Drug Substance:

1. Does the agency concur that the proposed designation of Starting Material is acceptable?

Agency response

- Yes, the proposed starting material, (b) (4) is acceptable provided the specification is revised as follows:
 - Identity testing by a more specific method, such as IR, and
 - Impurities (identified and any unknown) to have individual acceptance criteria.

Additional comment:

- In the specification for the starting material in the NDA, acceptance criteria should be established and justified for all attributes listed.

2. Does the Agency concur that the API specification is acceptable?

Agency response:

- Yes, the proposed tests in the specification are acceptable provided that the lack of controls on polymorphism and particle size be adequately justified in the NDA (to include screening/developmental results and information on the effects of these attributes on the performance of the drug product).

Additional comment:

- In the specification for the drug substance in the NDA, acceptance criteria should be established and justified for all attributes listed.

3. Does the Agency agree that the planned registration stability program will meet the requirement for NDA submission?

Agency response

- Yes, the proposed stability program for the drug substance is acceptable.

Additional comments:

- Individual numerical results for Impurities (identified and any unknown), including the (b) (4), should be provided in the NDA.
- Stress testing of the drug substance should be conducted per ICH guidelines.
- If particle size has any impact on the performance of the drug product, this attribute should be added to the stability specification.

Drug Product:

1. Does the Agency agree with the proposed specifications for APD356 Tablet (10mg)?

Agency response

- No, we do not agree because the justification for the lack of dissolution and (b) (4) impurity testing is not adequate for a complete assessment. The following additional information should be included in the NDA for an assessment of your proposal to exclude these 2 attributes from the product specification:
 - In order to justify the lack of (b) (4) Impurity testing of the commercial product: Data to show insignificant (b) (4) during manufacture of the product and on long-term storage. Alternatively, developmental information can be provided to show that the manufacturing process and storage avoid physical conditions that would result in (b) (4).
 - (b) (4)

Additional comment:

- If polymorphism has any impact on the performance of the drug product, this attribute should be added to the specification.
2. Does the Agency agree with Arena's approach to use dissolution profiling, batch analysis, and stability data to establish comparability of different APD356 tablet presentations used in development?

Agency response

- Yes, we agree with the approach to use dissolution profiling, batch analysis, and stability data to establish comparability of different APD356 tablet presentations used in development.

Additional comment:

- Comparative dissolution profiles should be provided for the final commercial tablets with and without the final identifiers (color and embossing/debossing/imprinting) to show that the identifiers have no effect on the drug dissolution.
3. Does the Agency agree that the planned registration stability program will meet the requirement for NDA submission?

Agency response

- Yes, the planned stability program is acceptable (b) (4) (see Response to Question # 1). We recommend that both attributes be monitored in the primary stability batches.

Additional comments:

- Photostability testing per ICH guidelines should be conducted on the drug product with

identifiers (color, imprinting, embossing/debossing).

- If polymorphism has any impact on the performance of the drug product, this attribute should be added to the stability specification.
- Stability data will be required for a physician sample packaged in blisters.
- A (b)(4) design will require a justification and will account for both container size and fill.
- The proposed (b)(4) stability data for the 3 primary batches, and (b)(4) of the commercial tablet with identifiers should be included in the NDA for filing; alternatively, an early subset of data can be submitted for the NDA filing with a commitment to provide the remaining data (i.e., up to 12 months) within 5 months of the NDA submission.

Biopharmaceutics:

1. Does the agency concur that the Capsule formulation can be used in a Phase 3 pivotal clinical trial?

Agency response

- Based on the information provided, it appears appropriate to use the capsule formulation in the initial Phase 3 trial. However, the need to conduct a bioequivalence trial between the capsule formulation and the to-be-marketed tablet formulation would depend on the classification of BCS. You are required to submit all the data which would be used to support the BCS claim for review. Please refer to the Guidance for Industry entitled "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System."

2. Does the Agency concur that the BCS and related Biowaiver guidance are applicable for ADP356 drug product manufacturing with regard to changes in formulation, manufacturing process and site?

Agency response

- See question #1.

3. Does the Agency agree that equivalence between the proposed APD356 Tablet (i.e., the commercial presentation with and without product identifiers), and the APD356 Prototype Tablet and the APD356 Capsule can be demonstrated using in vitro dissolution profiling and that an additional bioequivalence study will not be required?

Agency response

- See question #1.

Additional Comments:

- You are required to conduct a food effect study with the commercial tablet. The test meal should be high fat (approximately 50% of total caloric content of the meal) and high-calorie

(approximately 800 to 1000 calories).

- In order to select an appropriate dissolution method and specification for commercial tablets, you should submit dissolution profiles for the 10 mg tablets from 3 batches (12 units/batch) under three different conditions.

Minutes Preparer: _____ /s/

Pat Madara

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Chair Concurrence: _____ /s/

Eric Colman, M.D.

Acting Deputy Director

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

/s/

Patricia Madara

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