

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203858Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203858

SUPPL #

HFD #

Trade Name Juxtapid

Generic Name lomitapide

Applicant Name Aegerion Pharmaceuticals

Approval Date, If Known 12/21/2012

### **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 X

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 X

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.

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:

d) Did the applicant request exclusivity?

YES X      NO

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

5 years

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

YES       NO X

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?

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 X

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 X

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

NDA#

NDA#

NDA#

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



Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

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: Kati Johnson  
Title: Regulatory Health Project Manager  
Date: 12/21/2012

Name of Office/Division Director signing form: Eric Colman, MD  
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATI JOHNSON

12/27/2012

please sign for Eric Colman

MARY H PARKS

12/27/2012

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203858 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Juxtapid Established/Proper Name: Iomitapide mesylate Dosage Form: Capsules		Applicant: Aegerion Pharmaceuticals, Inc Agent for Applicant (if applicable): N/A
RPM: Kati Johnson		Division: Metabolism and Endocrinology Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is 12/29/2012</li> </ul>		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		X None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?                  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)                  Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)                  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input checked="" type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	X
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	X Included
Documentation of consent/non-consent by officers/employees	X Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	AP 12/21/2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Attached to AP letter
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	2/29/2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Attached to AP letter
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	2/28/2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	(b) (4) <input type="checkbox"/> not acceptable on 5/29/12 <input type="checkbox"/> not acceptable on 7/27/12 <input type="checkbox"/> not acceptable on 10/25/12
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 5/8/2012 <input checked="" type="checkbox"/> DMEPA 10/15/2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 11/14/12 <input type="checkbox"/> ODPD (DDMAC) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	5/9/2012
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan drug designation</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications ( <i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	X No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	X N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 4/12/2011 (CMC) 7/5/2011 (clinical)
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 8/9/2004; 2/23/2007; 9/28/2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	N/A
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	10/17/2012
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	X
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/21/2012
Division Director Summary Review ( <i>indicate date for each review</i> )	X None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	X None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 3
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	11/27/2012, 12/7/2012
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 34 of 11/27/2012 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	12/21/2012
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	12/21/2012
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input type="checkbox"/> None 11/8/2012, 12/19/2012, 12/21/2012
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested 10/31/2012

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
<b>Biostatistics</b>		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/30/2012
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None 5/7/12; 11/5/12; 11/9/12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None
<b>Nonclinical</b>		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input type="checkbox"/> None 12/7/2012
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/13/12
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 11/5/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> No carc 8/1/12
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 8/1/12 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None requested
<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None 4/25/12; 9/21/12; 10/18/12
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input type="checkbox"/> None 10/26/12 (Biopharm)

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	Page 132 of 10/18/12 CMC review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	N/A
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 12/2/2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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KATI JOHNSON  
12/27/2012



NDA 203858

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Aegerion Pharmaceuticals, Inc.  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) submitted and received February 29, 2012, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Mesylate Capsules, 5 mg, 10 mg, and 20 mg.

We also refer to your November 27, 2012, correspondence, received November 27, 2012, requesting review of your proposed proprietary name, Juxtapid. We have completed our review of the proposed proprietary name, Juxtapid, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 29, 2012, 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 Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

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/  
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CAROL A HOLQUIST  
12/13/2012

From: Johnson, Paul  
To: Martha Carter; Mark Marzly  
Cc: Sara Jera  
Subject: NDA 203888 Lom lipide Rev and REMS request  
Date: Friday, November 09, 2012 12:06:49 PM

Hi Martha and Mark,

Here are the requests from the final review of your proposed REMS. The track changes on the DHCP/Professional Association letters didn't come thru when I cut and pasted it into this e-mail, but it looks like it has been almost entirely revised.

We conveyed our understanding that the prescriber authorization was for new prescriptions, not refills.

See below:

Safe use conditions – The proposed safe use condition consists of a "Prescription Authorization" form integrated with each new prescription (not refills) that will include the following statements attesting to the safe and appropriate use of

Lomitapide.

Hope that helps.

Let me know if you have any questions.

Please submit a revised REMS proposal including the following goals and elements:

1. Goals

- To educate prescribers about the approved indication for use of lomitapide, the potential risk of hepatotoxicity associated with the use of lomitapide, and the need to monitor patients during treatment with lomitapide as per product labeling
- To limit access to therapy with lomitapide to patients with a clinical or laboratory diagnosis consistent with HoFH

2. REMS Elements

1. Elements to assure safe use to include:

- a. Health care professionals (HCP) who prescribe lomitapide are specially certified (ETASU A) – including mandatory prescriber certification consisting of prescriber training and enrollment. FDA agrees in principle with the sponsor's proposal for prescriber certification, however, prescriber training should not be limited to reviewing the product label, Medication Guide, and Prescriber's Guide but will require a more formal approach such as a computer-based training module including knowledge verification questions at the end of each training module.

The prescriber enrollment form must include prescriber demographics, contact information, identifiers (e.g., National Provider Identification (NPI) number), and a section to attest understanding of the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS program requirements.

Communications to certified prescribers, including letters addressed to healthcare providers and professional societies, will be distributed as stipulated under ETASU A. The sponsor should develop and maintain a REMS website. A document with suggested revisions to the healthcare provider and professional society letters is appended. Please note that the objective of this document is to provide guidance, the text included in the final version of this document must be consistent with the approved label.

- b. Pharmacies that dispense lomitapide are specially certified (ETASU B) – pharmacy certification will assure that lomitapide is dispensed only when prescribed by certified prescribers and after documentation of safe use conditions. Certification will be linked to ability to purchase and dispense lomitapide. The pharmacy certification process must include training of pharmacy representative regarding the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS program requirements. The pharmacy enrollment form must include pharmacy/pharmacy representative contact information and a section to attest understanding of the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS program requirements.

Communications to certified pharmacies, including letters addressed to pharmacies or pharmacy representatives, will be distributed as stipulated under ETASU B.

- c. Lomitapide will be dispensed to patients with evidence or other documentation of safe-use conditions (ETASU D) – The proposed safe use condition consists of a "Prescription Authorization" form integrated with each new prescription that will include the following statements attesting to the safe and appropriate use of lomitapide:

- I understand that TRADENAME is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).
- I certify that this patient has a clinical or laboratory diagnosis consistent with HoFH.
- I understand that lomitapide has not been studied in pediatric patients less than 18 years.
- I attest that I have obtained the liver-related laboratory tests for this patient as directed in TRADENAME's prescribing information.

(b) (4)

An example of the Prescription Authorization form is appended.

2. An implementation system – at a minimum, the Implementation System must include the following elements:

- a mechanism to train and certify prescribers and pharmacists
- a database of all enrolled prescribers and pharmacies
- a mechanism to ensure that lomitapide is distributed only to certified pharmacies
- audits of dispensing data to ensure that lomitapide is only being dispensed to patients who are prescribed lomitapide by certified prescribers
- a lomitapide REMS Program Coordinating Center to support, prescribers, pharmacies, and patients participating in the REMS Program
- a system to monitor and audit certified pharmacies to ensure that all processes and procedures are in place and functioning to support the requirements of the REMS

3. A timetable for submission of assessments – 6 months and 12 months after approval and annually thereafter.

3. REMS Supporting Document

a. The REMS Supporting Document must be consistent with all changes made to the REMS document.

b. REMS Assessment Plan - include, at a minimum, the following elements:

- prescriber and pharmacy certification statistics
- 1 documentation of prescriber and pharmacist awareness of the REMS materials and knowledge of REMS program requirements

2 analyses of drug utilization data, and analyses of adverse event reports received during the assessment period and cumulatively, in particular, reports of liver toxicity

4. General Comments

- **Resubmission Requirements and Instructions:** Submit the revised proposed REMS for lomitapide with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.
- **Format Request:** Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single MS Word document.

ATTACHMENTS

- Proposed Lomitapide REMS Prescription Authorization Form
- Examples of Revised Dear Healthcare Provider /Professional Association LettersProposed Lomitapide REMS Prescription Authorization Form

(b) (4)



Kati Johnson  
Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-123 (Phone)

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/s/  
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KATI JOHNSON  
11/13/2012

**From:** [Johnson, Kati](#)  
**To:** [Martha Carter](#); [Mark Murray](#)  
**Cc:** [Egan, Amy](#)  
**Subject:** NDA 203858, Lomitapide, Proposed PMRs  
**Date:** Friday, November 09, 2012 9:49:24 AM

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Martha/Mark,

Here are the PMRs that we spoke to you on the phone about yesterday. We have provided the clarifying information you requested.

My apologies for not getting them to you yesterday.

1. **Non-clinical:** A juvenile toxicology study to evaluate the effects of lomitapide on learning, memory, behavior, growth, and long bone development with and without vitamin and essential fatty acid supplementation to determine whether any observed effects are due directly to lomitapide or secondarily to the inhibition of absorption of fat soluble vitamins and/or essential fatty acids. This study should be completed before any formal pediatric studies are initiated.

In response to your question, the juvenile toxicology study [REDACTED] (b) (4)

Submit dates for Final Protocol Submission, Study Completion, and Final Report Submission. A protocol is not considered final until FDA and sponsor have reached agreement on it. Allow sufficient time for protocol review, comment, and agreement by FDA (3-6 months).

(b) (4)

3. **Epidemiology:** A long-term prospective observational cohort study (registry) of patients with HoFH treated with lomitapide. The registry will continue for 10 years from the date of last patient enrollment.

Submit dates for Final Protocol Submission, Study Completion, and Final Report Submission. A protocol is not considered final until FDA and sponsor have reached agreement on it. Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months).

4. **Pharmacovigilance:** Enhanced pharmacovigilance program for reports of malignancy, teratogenicity, and hepatic abnormalities in patients treated with lomitapide for a period of 10 years from the date of approval to collect data that will be analyzed to better define these risks. The enhanced pharmacovigilance program includes the following [REDACTED] (b) (4)

Submit dates for Final Protocol Submission, Annual Assessment and Summary Report Submission, Study

Completion, and Final Report Submission. A protocol is not considered final until FDA and sponsor have reached agreement on it. Allow sufficient time for protocol review, comment, and agreement by FDA (6-9 months).

Contact me if you have any questions,  
Kati

Kati Johnson  
Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-1234 (Phone)

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KATI JOHNSON  
11/09/2012

## Johnson, Kati

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**From:** Johnson, Kati  
**Sent:** Friday, November 02, 2012 2:24 PM  
**To:** 'Martha Carter'; 'Mark Murray'  
**Subject:** NDA 203858, Lomitapide, labeling comments

Martha, here are the labeling comments we spoke about yesterday. The formatting is a bit funky. Please let me know you received it.

### A. Container Label and Carton Labeling

a. Delete or minimize the graphic embedded next to the proprietary name. The graphic competes with the prominence of the proprietary and established names and product strength, which should have the most prominence on the labels and labeling.

b. Increase the prominence of the established name (which includes dosage form). Ensure that the prominence of the established name is commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing feature in accordance with 21 CFR 201.10(g)(2).

c. The dosage form is part of the established name. Thus we request you to relocate “capsules: to appear following the active ingredient. For example: “(lomitapide mesylate) capsules”.

d. The use of the same color font for the proprietary name, established name, and product’s strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

~ Thus, revise the color font of the 10 mg or the established name, so that the strength and the established name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths or used in the name.

~ Revise the color font of the 20 mg strength or the proprietary name, so that the strength and the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

e. The gray writing on white background does not provide enough contrast and the information is difficult to read. We recommend that the color font of the writing be revised to provide greater contrast against the white background to increase readability.

f. We recommend the “Dispense the accompanying Medication Guide to each patient” statement be moved to the principle display panel. This can be achieved by minimizing the company’s logo or relocating it to the side panel.

g. We recommend that the statement “28 capsules” not to be highlighted so that it does not compete with the prominence of the proprietary and established names and product strength, which should have the most prominence on the labels and labeling.

### B. Insert Labeling

a. Dosage and Administration in Highlights of Prescribing Information and Full Prescribing Information:

i. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe

## Medication Practice's List of

Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. 2 As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:

~ Revise all instances of the symbols 'IU' to read 'international units'. The symbol 'IU' is a dangerous abbreviation because this symbol is often mistaken as IV (intravenous) or the number 10 (ten).

~ Revise all instances of the symbol '>' to read "greater than." The symbol '>' is a dangerous abbreviation that could be mistaken and used as opposite of intended.

- ii. Prior to the use of abbreviations EPA, ALA, DHA, spell out to what EPA, ALA, and DHA refer.

Kati

Kati Johnson  
Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-1234 (Phone)

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/s/  
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KATI JOHNSON  
11/05/2012

## MEMORANDUM OF TELECON

DATE: November 1, 2012

APPLICATION NUMBER: NDA 203858 lomitapide mesylate

BETWEEN:

Name: Aegerion Pharmaceuticals  
Martha Carter, Chief Regulatory Officer & SVP  
Mark Murray, Senior Director, Regulatory Affairs  
Paul Merrigan, Vice President, Global Marketing

Phone: (b) (4)

AND

Name: Division of Medication Error Prevention and Analysis  
Yelena Maslov, PharmD - TL  
Sarah Vee, PharmD - SE  
Margarita Tossa, M.S. - SRPM

SUBJECT: Discussion of denial of the proposed proprietary name (b) (4) and providing an advice and additional options to the Applicant.

The Applicant was informed that DMEPA wanted to provide recommendations and additional options to the Applicant regarding the proprietary name review in consideration of the upcoming NDA PDUFA Goal date (12/29/2012).

The Applicant was notified that DMEPA finds the proposed proprietary name, (b) (4) (b) (4). Thus, DMEPA finds the proposed proprietary name, (b) (4), unacceptable (b) (4).

The Applicant tried to impose on the proposed REMS for this product and stated that the risk of Medication Errors could/should be eliminated. DMEPA has noted that the proposed REMS were considered during the proprietary name review and in the decision making process, however, DMEPA still finds the name (b) (4) unacceptable.

DEMPEA proposed two options to the Applicant:

Option 1:

- DMEPA is willing to work with the Applicant and can conduct preliminary safety assessment of the 3-4 proposed proprietary names submitted by Aegerion via email prior to the official submission of one name for the full review. The

Applicant was advised to submit the names by 10:00 am on the following day (Friday, November 2, 2012). DMEPA will make every effort and work with the Applicant in order to have an approved proprietary name by the NDA PDUFA Goal date, but can not guarantee that Aegerion will have an approved proprietary name for their product.

Option 2:

- Aegerion may rebut DMEPA's assessment of (b)(4). However, if the Applicant rebuts DMEPA's assessment and the name is still found unacceptable the product may be approved without a proprietary name.

The Applicant agreed to submit via email 4 names for the preliminary safety assessment. Aegerion expressed their appreciation of having the TCON with DMEPA and getting comments and advises on the proposed proprietary name (b)(4) and on the options provided by DMEPA.

Margarita Tossa, M.S.  
Safety Regulatory Project Manager  
FDA/CDER/OSE/RMS

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/s/  
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MARGARITA V TOSSA  
11/05/2012

YELENA L MASLOV  
11/05/2012



NDA 203858

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Aegerion Pharmaceuticals, Inc.  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) submitted and received February 29, 2012, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Mesylate Capsules, 5 mg, 10 mg, and 20 mg.

We also refer to your August 8, 2012, correspondence, received August 9, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reason:



We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

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/  
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KELLIE A TAYLOR on behalf of CAROL A HOLQUIST  
10/26/2012



NDA 203858

**GENERAL ADVICE**

Aegerion Pharmaceuticals, Inc.  
Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Capsules.

Your application contained a protocol entitled *A Long-Term Prospective Observational Cohort Study (Registry) of Patients with Homozygous Familial Hypercholesterolemia Treated With Lomitapide*.

We have the following comments and recommendations:



(b) (4)





If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

*{See appended electronic signature page}*

Amy G. Egan, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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<sup>i</sup> Hunt JR & White E. Retaining and tracking cohort study members. *Epid Rev* 1998;20(1):57-70.

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/s/  
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AMY G EGAN  
10/17/2012



NDA 203858

## GENERAL ADVICE

Aegerion Pharmaceuticals, Inc.  
Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Capsules.

A risk evaluation and mitigation strategy (REMS) is being required for lomitapide because of increased hepatic transaminases and hepatic steatosis which has the potential to progress to steatohepatitis, cirrhosis, and liver failure. Because of the limited safety information available, the REMS is required to limit broader use of lomitapide in patients with less severe forms of hypercholesterolemia where the benefit-risk profile has not been established.

### REMS Goals:

- To educate prescribers about the approved indication for use of lomitapide, the potential risk of hepatotoxicity associated with the use of lomitapide, and the need to monitor patients during treatment with lomitapide as per product labeling
- To limit access to therapy with lomitapide to patients in whom therapy with lomitapide is medically appropriate

### REMS Elements:

- Elements to Assure Safe Use (ETASU)
  - (A) Healthcare professionals (HCPs) who prescribe lomitapide are specially certified
  - (B) Pharmacies that dispense lomitapide are specially certified
  - (D) Lomitapide will be dispensed to patients with evidence or other documentation of safe-use conditions
- Implementation System
- Timetable for Submission of Assessments of the REMS (6 months, 12 months, and then annually following approval)

In order for HCPs to be certified, they must undergo an educational program and enroll in the lomitapide REMS program by acknowledging understanding of the risks of lomitapide therapy; the need to monitor hepatic transaminases during treatment; and the indication for use. They must also agree to counsel patients about the risk of hepatotoxicity, the need to have regular blood tests performed to monitor for evidence of liver injury or dysfunction, and to attest that the patient is an appropriate candidate for lomitapide therapy prior to prescribing lomitapide.

Patient enrollment or patient acknowledgement of risks associated with the use of lomitapide is not being required. FDA proposes the following safe use condition: the prescriber will need to attest on an authorized prescription form, for each prescription, that he/she is aware that lomitapide is indicated for patients with homozygous familial hypercholesterolemia and the drug is medically appropriate for the patient. The form does not require a patient signature.

A sample form is attached. The prescriber would fill out the form and send it directly to a certified pharmacy. (We acknowledge that you have proposed using specialty pharmacies to fill prescriptions.) You (Aegerion) would not directly receive patient specific information but would receive aggregate data from specialty pharmacies based on their contracts and information needed for assessments.

Certified pharmacies would need to have systems in place to ensure that only certified prescribers prescribe lomitapide to patients in whom therapy with lomitapide is medically appropriate. The certified pharmacies do not need to ensure that the appropriate laboratory testing has been performed prior to dispensing lomitapide.

We ask that you consider how to incorporate into the REMS:

- e-prescribing
- closed medical care systems (for example, VA, large HMOs, DOD)
- inpatient use

A Medication Guide is not being required as part of the REMS. FDA is requiring a Medication Guide as part of labeling to mitigate other safety concerns associated with the use of lomitapide:

- Teratogenicity – patients should be informed to discontinue lomitapide in the event of a pregnancy, and to remain off lomitapide throughout the duration of the pregnancy.
- Reduction in fat-soluble vitamins and essential fatty acids – patients should be informed of the need to supplement their diet with fat-soluble vitamins and essential fatty acids
- Drug-drug interactions – patients should be informed of certain medications they should avoid while taking lomitapide because the co-administration would increase their risk of serious adverse events

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

*{See appended electronic signature page}*

Amy G. Egan, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:

Sample REMS Prescription Authorization Form

2 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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AMY G EGAN  
08/29/2012



NDA 203858

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Aegerion Pharmaceuticals, Inc.  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) submitted and received February 29, 2012, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Capsules, 5 mg, 10 mg and 20 mg.

We also refer to your May 30, 2012, correspondence, received May 30, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is unacceptable for the following reasons:



We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

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/  
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CAROL A HOLQUIST  
08/03/2012



NDA 203858

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Aegerion Pharmaceuticals, Inc.  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) dated and received February 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Capsules, 5 mg, 10 mg and 20 mg.

We also refer to your March 1, 2012, correspondence, received March 1, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of the proposed proprietary name, (b) (4), and have concluded that it is unacceptable for the following reasons:

(b) (4)



We note that you have proposed an alternate proprietary name in your submission dated March 1, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

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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<sup>1</sup> IMS Health, National Sales Perspectives, December 2010.

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/s/  
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CAROL A HOLQUIST  
05/29/2012



NDA 203858

**FILING COMMUNICATION**

Aegerion Pharmaceuticals, Inc.  
Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Dear Ms. Carter:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lomitapide Capsules, 5, 10, and 20 mg.

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 **December 29, 2012**.

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 **November 5, 2012**.

During our filing review of your application, we identified the following potential review issues:  
**Clinical Pharmacology**

1. Please advise when you will submit the lomitapide population pharmacokinetic data. The following are the general expectations for submitting future population pharmacokinetic datasets and models:
  - a. All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been *excluded from the analysis* should be flagged and maintained in the datasets.

- b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_cfl.txt, myfile\_out.txt).
- c. A model development decision tree and/or table which gives an overview of modeling steps.
- d. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

### **Chemistry, Manufacturing, and Controls**

2. You have not provided adequate information to show (b) (4) the product safety or efficacy. Propose and justify acceptance criteria for (b) (4) in the drug substance specification. In addition, justify the lack of (b) (4) testing in the product stability specification given that the limited data in the NDA (b) (4)
3. It is not clear (b) (4) You claim that this issue only pertains to batch 1713-1713-07-001 because (b) (4) Therefore, your requested retest date of (b) (4) at room temperature is unrealistic.
4. Provide drug substance solubility (over pH range) for (b) (4)
5. Submit permeability data for (b) (4)
6. Submit ratio information for the drug substance (b) (4) in the clinical drug product batch(es).
7. Provide dissolution data for drug product (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded

upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for 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.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

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/  
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ERIC C COLMAN  
05/08/2012



NDA 203858

**NDA ACKNOWLEDGMENT**

Aegerion Pharmaceuticals, Inc.  
Attention: Martha J. Carter  
Chief Regulatory Officer and Senior Vice President  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Dear Ms. Carter:

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: Lomitapide mesylate Capsules, 5 mg, 10 mg, 20 mg

Review Priority Classification: Standard

Date of Application: February 29, 2012

Date of Receipt: February 29, 2012

Our Reference Number: NDA 203858

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 April 29, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also 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).

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/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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KATI JOHNSON  
03/05/2012



IND 50820

**MEETING MINUTES**

Aegerion Pharmaceuticals, Inc.  
Attention: Martha Carter  
Chief Regulatory Officer and Senior Vice President  
101 Main Street, Suite 1850  
Cambridge, MA 02142

Dear Ms. Carter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lomitapide Capsules.

We also refer to the meeting between representatives of your firm and the FDA on June 15, 2011. The purpose of the meeting was to discuss your proposed NDA submission for the treatment of Homozygous Familial Hypercholesterolemia (HoFH).

A copy of the official minutes of the meeting 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 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
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:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** Wednesday, June 15, 2011, 3:00 to 4:00 pm  
**Meeting Location:** FDA White Oak Campus  
Building 22, Conference Room 1311

**Application Number:** IND 50820  
**Product Name:** Lomitapide Capsules, 5 mg, 10 mg, 20 mg.  
**Indication:** Adjunct to diet and other lipid-lowering treatments (e.g., oral lipid-lowering drug therapy and LDL apheresis) to reduce total cholesterol, LDL-C, apo B, and triglycerides in patients with homozygous familial hypercholesterolemia (HoFH)

**Sponsor/Applicant Name:** Aegerion Pharmaceuticals, Inc.

**Meeting Chair:** Eric Colman, MD  
**Meeting Recorder:** Kati Johnson, Project Manager

**FDA ATTENDEES**

Division of Metabolism & Endocrinology Products

Mary Parks, MD-Director  
Eric Colman, MD-Deputy Director, Lipid Team Leader  
Amy Egan, MD-Deputy Director, Safety  
Mary Roberts, MD-Clinical Reviewer  
Karen Davis Bruno, PhD-Pharmacology/Toxicology Supervisor  
Hummer, Tim, PhD-Pharmacology/Toxicology Reviewer  
John Bishai, PhD-Safety Project Manager  
Kati Johnson-Project Manager

Office of Orphan Products Development

Henry Startzman, MD-Regulatory Review Officer  
Soumya Patel-Regulatory Review Officer

Office of Safety and Epidemiology

Suzanne Robottom, Division of Risk Management  
Margarita Tossa, Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology

Jaya Vaidyanathan, PhD-Team Leader  
Zhihong Li, PhD-Clinical Pharmacology Reviewer

Office of Translational Sciences, Office of Biostatistics

Todd Sahlroot, PhD-Deputy Director, Division of Biometrics II  
Cynthia Liu-Statistical Reviewer

Office of Compliance, Division of Scientific Investigations

Sharon Gershon, Good Clinical Practice Branch 2

**Aegerion Pharmaceuticals (Aegerion)**

John Balsler, PhD-President Veristat, Inc.; Consultant  
LeAnne Bloedon-Director of Clinical Operations  
Martha Carter-Chief Regulatory Officer and Senior Vice President  
Joseph F. Costa, PhD-Toxicologist, Consultant  
Barry Dvorchik, PhD-President, Barry Dvorchik & Assoc., Inc.; Consultant  
Mark C. Murray-Senior Director, Regulatory Affairs  
Daniel J. Rader, MD-Professor of Medicine and Pharmacology, University of  
    Pennsylvania, Consultant  
Diane L. Tribble, PhD-Chief Scientific Officer  
Ronald S. Vladyka-Executive Director, Manufacturing  
Cathy L. Walker-Manager, Regulatory Affairs

**BACKGROUND**

IND 50820 was submitted by Bristol-Myers Squibb (BMS) on June 18, 1996. The application was subsequently transferred to Daniel Rader, MD (University of Pennsylvania) on August 21, 2001 and to Aegerion on April 13, 2007. At this point, the application contained protocols for both Heterozygous Familial Hypercholesterolemia (HeFH) as well as HoFH. Dr. Rader submitted IND 77775 on May 16, 2007 to reference the HoFH portion of IND 50820 as he was going to remain the sponsor for the HoFH indication. However, on February 28, 2008, IND 77775 was also transferred to Aegerion.

In June 2007, all MTP inhibitors (except those investigating HoFH) were placed on Partial Clinical hold for studies longer than 6 months due to concerns for the risk of pulmonary phospholipidosis based on animal studies. Sponsors were asked to conduct a 3-month rat study to establish a NOAEL for pulmonary phospholipidosis. The firm responded on July 16, 2007 and December 29, 2008, but they were found deficient and the clinical hold was maintained. The partial clinical hold was removed on February 18, 2010 (see below).

On October 23, 2007, orphan drug designation was granted for HoFH.

The firm requested an End-of-Phase 2 (EOP2) meeting on May 20, 2009, and it was scheduled for August 12, 2009. At the August 5, 2009 internal meeting it was determined that given the lingering concerns regarding phospholipidosis and the fact that the firm has never studied Lomitapide on top of an optimal statin dose in the HeFH population, the EOP2 meeting was premature. In lieu of a meeting, a August 10, 2009 teleconference was held between the sponsor (Drs. Bill Sasiela [Chief Medical Officer] and Maurice Briggs[VP, Regulatory Affairs]) and the division (Dr. Eric Colman [Deputy Division Director and Lipid Team Leader] and Ms. Kati

Johnson [Project Manager]). See October 13, 2009 teleconference minutes. In this teleconference, the firm was told that the agency wanted to see the mouse carcinogenicity study results which included data on pulmonary phospholipidosis. The firm said these data could be submitted October 1, 2009. Based upon this estimate, the agency agreed to reschedule the meeting for November 9, 2009. In fact, the mouse carcinogenicity information was submitted October 26, 2009. The ongoing rat carcinogenicity study will complete the in-life phase in May/June 2010 with the final results due in October/November of that year.

At this November 9, 2009 meeting, the sponsor reiterated that the clinical development was focused on HoFH and “refractory HeFH” patients as these are populations with unmet medical needs. The agency cited the issues that require continued/attention/discussion: mouse carcinogenicity data (malignant tumors in the small intestine and liver at high doses), pulmonary phospholipidosis (now less of a concern given the number of approved products with this preclinical finding) and hepatic steatosis. See January 5, 2010 meeting minutes.

The partial clinical hold was removed February 18, 2010, in part due to the number of approved products with this preclinical finding (phospholipidosis) but which have not apparently translated into a clinical risk.

At a subsequent May 17, 2010 meeting, the sponsor informed us that they would be pursuing only the HoFH indication due to financial constraints. The agency voiced concern that, upon approval, there would be unauthorized prescribing. The sponsor was amenable to whatever postapproval supply constraints were necessary to ensure that the drug was available only to the HoFH population. See September 28, 2010 meeting minutes.

On March 3, 2011, the compound was granted orphan designation for the treatment of familial chylomicronemia.

A meeting to discuss chemistry, manufacturing and controls issues in anticipation of an NDA submission was held on April 5, 2011. See the April 12, 2011 meeting minutes.

In response to an April 14, 2011 request, on June 14, 2011 Lomitapide was denied Fast-Track designation for use in patients with HoFH. The drug development program was not designed to determine whether the product will reduce cardiovascular morbidity or mortality in the HoFH population or even in lower-risk populations from which study results could be extrapolated to the HoFH population.

Aegerion requested a Pre-NDA meeting on March 14, 2011, and it was granted March 21, 2011. The background package was submitted May 12, 2011. Preliminary responses were conveyed to the firm on June 10, 2011.

At this point in time, the sponsor is proposing to submit the NDA by the end of 2011.

Your questions are followed by our **bolded** responses. Any meeting discussion is in underlined text.

## QUALITY QUESTIONS

### **Question 1:**

*Aegerion proposes to place 3 drug product registration batches of each strength of lomitapide capsules on stability. At the time of NDA submission 3 months of real-time and 3 months of accelerated data on one registration batch of each strength of drug product (5 mg, 10 mg, and 20 mg) will be available. Aegerion has supportive stability data for up to 2 years on batches that are identical to the registration batches except for capsule size, capsule color, and batch size [REDACTED] <sup>(b) (4)</sup> Does the FDA agree that the drug product stability data are adequate for filing of the NDA?*

### **Sponsor Position:**

The NDA will contain supportive stability data from 5 clinical stability batches (3 batches for the 5 mg strength and 2 batches for the 20 mg strength) in addition to data from the first registration batch of each strength (5 mg, 10 mg, and 20 mg) (see Table 1 for additional details on storage conditions and time-points).

For lomitapide 5 mg capsules, 24 months of stability data will be available on 2 clinical batches, 1 of which has been prepared using API Registration Batch 1. In addition, 12 months of stability data will be available on a third clinical batch of lomitapide 5 mg capsules, which has been prepared using API Registration Batch 1.

For lomitapide 20 mg capsules, 24 months of stability data will be available on 1 clinical batch, which has been prepared using API Registration Batch 1. In addition, 12 months of stability data will be available on a second clinical batch of lomitapide 20 mg capsules, which has been prepared using API Registration Batch 1.

Considering that the 10 mg strength of lomitapide capsules is prepared from [REDACTED] <sup>(b) (4)</sup> [REDACTED] the stability of the 10 mg strength will be addressed by bracketing with the higher and lower dosage strengths.

**Table 1: Available Stability Data on Lomitapide Capsule Batches at the Time of NDA Submission**

STRENGTH/ USE OF BATCH	LOT No.	API LOT No. USED IN MANUFACTURE	BATCH SIZE (NO. CAPSULES)	STORAGE CONDITION	AVAILABLE DATA IN NDA (MONTHS)
5 mg / Clinical	L0108401	L0107803	(b) (4)	25 ± 2°C / 60 ± 5% RH	24
				40 ± 2°C / 75 ± 5% RH	6
	L0109391	L0109571 (API Reg. Batch 1)		25 ± 2°C / 60 ± 5% RH	24
				40 ± 2°C / 75 ± 5% RH	6
	L0206440	L0109571 (API Reg. Batch 1)		25 ± 2°C / 60 ± 5% RH	24
				40 ± 2°C / 75 ± 5% RH	6
	L0302138	L0109571 (API Reg. Batch 1)		25 ± 2°C / 60 ± 5% RH	12
				40 ± 2°C / 75 ± 5% RH	6
5 mg / Reg. Batch 1	TBD	API Reg. Batch 2		25 ± 2°C / 60 ± 5% RH	3
				40 ± 2°C / 75 ± 5% RH	3
10 mg / Reg. Batch 1	TBD	API Reg. Batch 2	25 ± 2°C / 60 ± 5% RH	3	
			40 ± 2°C / 75 ± 5% RH	3	
20 mg / Clinical	L0109390	L0109571 (API Reg. Batch 1)	25 ± 2°C / 60 ± 5% RH	24	
			40 ± 2°C / 75 ± 5% RH	6	
	L0203329	L0109571 (API Reg. Batch 1)	25 ± 2°C / 60 ± 5% RH	24	
			40 ± 2°C / 75 ± 5% RH	6	
	L0206441	L0109571 (API Reg. Batch 1)	25 ± 2°C / 60 ± 5% RH	24	
			40 ± 2°C / 75 ± 5% RH	6	

	L0302139	L0109571 (API Reg. Batch 1)	(b) (4)	25 ± 2°C / 60 ± 5% RH	12
				40 ± 2°C / 75 ± 5% RH	6
20 mg / Reg. Batch 1	TBD	API Reg. Batch 2	(b) (4)	25 ± 2°C / 60 ± 5% RH	3
				40 ± 2°C / 75 ± 5% RH	3

Consistent with the International Conference on Harmonisation (ICH) recommendations, 3 registration batches of lomitapide capsules will be manufactured and placed on longterm and accelerated stability evaluation. The batches will be manufactured at approximately (b) (4) of the proposed commercial scale. At the time of NDA submission, it is anticipated that 3 months of stability data, collected under both real-time and accelerated conditions, will be available on the first registration batch of each of the lomitapide capsule strengths.

Details on the planned stability storage conditions and long-term and accelerated stability time points for all registration batches as well as the planned dates when the stability reports will be available for the first drug product registration batches are presented in Table 2.

**Table 2: Proposed Overall Stability Program for Lomitapide 5 mg, 10 mg, and 20 mg Capsule Registration Batches to Support Expiry Dating**

STUDY	STORAGE CONDITION	STUDY DURATION	TEST INTERVALS	REGISTRATION BATCH 1 (TEST INTERVALS)	REGISTRATION BATCH 1* (AVAILABILITY OF DATA)
Long term	25 ± 2°C and 60 ± 5% RH	36 months	1, 3, 6, 9, 12, 18, 24, & 36 months	1 month	09-06-2011
				3 months	11-04-2011
				6 months	02-03-2012
Accelerated	40 ± 2°C and 75 ± 5% RH	6 months	1, 3, & 6 months	1 month	09-06-2011
				3 months	11-04-2011
				6 months	02-03-2012

\*Same date for 5 mg, 10 mg, and 20 mg strengths

Stability studies on Registration Batch 2 will be initiated in advance of the NDA filing; however, no data will be available at the time of NDA submission. Stability studies on Registration Batch 3 will be initiated soon after the NDA filing. Aegerion believes this submission approach is justified given the small batch size and stability history of previous batches of lomitapide drug product.

**On Friday, June 3, 2011, the firm provided the following information via e-mail followed by an official submission:**

“I want to bring to your attention an update to the briefing package for the pre-NDA meeting on June 15<sup>th</sup> (the package was submitted in Serial No. 0186 on May 12, 2011). While we would

still like a response to Question #1 (amount of stability required on commercial dosage forms to file the NDA) we have another approach we would like to discuss with you at the meeting, if possible.

In Table 2 on page 31 of the briefing package, we presented a timeline for the availability of stability data on lomitapide 5 mg, 10 mg, and 20 mg capsules. We learned this week that we will not be able to use the drug substance batch (registration batch 2) that was planned to make the drug product primary stability batches. Therefore, the amount of stability data expected to be available at the time of NDA submission as outlined in the background for Question 1 is no longer accurate.

In view of this, we would like to discuss the possibility of declaring the stability data on clinical drug product as primary stability data. This approach will allow us to provide at least 1 year long term stability data and 6 months accelerated data on at least 3 batches each of 5 mg and 20 mg capsules produced with drug substance from the first API registration batch; we would continue to rely on a bracketing approach to support the stability of the 10 mg capsule. The drug substance registration batch used to make the drug product lots was manufactured using the

(b) (4)

To support this proposed approach we would delay introducing changes to the drug product that were previously contemplated and described for commercial presentation and instead launch with a presentation that more closely resembles the clinical trial presentation. The differences between the primary stability batches and the proposed commercial presentation are summarized in the table that

follows.

**Table 1: Comparison of Clinical Drug Product to Proposed Commercial Drug Product**

	CLINICAL DRUG PRODUCT	PROPOSED LAUNCH DRUG PRODUCT
Capsule size		(b) (4)
5 mg	Size 1	
10 mg	Not applicable	
20 mg	Size 1	
Capsule color		
5 mg	Swedish orange <sup>1</sup> body & cap	
10 mg	Not applicable	
20 mg	Swedish orange body & cap	
Capsule Imprint	None	
Batch size		
5 mg	(b) (4)	
10 mg		
20 mg		
Container/closure System	(b) (4) HDPE bottle with induction seal and closure	
Capsule Count		
5 mg	25 and 35	
10 mg	Not applicable	
20 mg	35, 65 and 100	

(b) (4)

The delay in availability of drug substance registration batches also affects the amount of API stability that is proposed to be provided in the NDA. In the briefing package for the April 5, 2011 pre-NDA CMC meeting (see Table 24 on page 44 of Serial No. 0173 dated March 4, 2011), we proposed having 3 years of stability on one batch, 3 months of stability on a second batch and 1 month of stability on a third batch of drug substance. Our latest estimate is provided below.

**Table 2. Amount of Drug Substance Stability Data Available at Time of NDA Submission**

<i>Batch Type</i>	Registration 1	Registration 2	Registration 3
<i>Stability Data in NDA</i>	36 months	1 month	None

We would commit to continuing to collect stability data on these batches and it would be available as needed. Stability data on the drug substance and drug product lots proposed to be used for primary stability purposes are included in Serial No. 0162 dated November 10, 2010 should you wish to review them.

Although we recognize that you are likely hearing about this too late to address it in your preliminary responses, we would like to discuss this proposal during our June 15<sup>th</sup> meeting, if possible (and assuming Dr. Stephens and Dr. Tran are able to participate). If not, we can take the issue off the table for the June 15<sup>th</sup> meeting and have a separate conversation with our CMC reviewers. As noted above, we would still like an answer to the question we posed in the briefing package for the June 15<sup>th</sup> meeting as it would inform the timeline should we choose to launch with the original commercial drug product configurations.”

**FDA Preliminary Response:**

**We acknowledge receipt of your proposed stability package to support the three commercial drug product strengths. Overall, our stance has not changed since our comments sent on March 30, 2011. You should submit the NDA with at least 6 months long-term and 6 months accelerated stability data for at least one registration batch of each dose strength, or provide adequate bracketing data. In accordance with GRMPP timelines, a complete NDA should be submitted for filing and we cannot guarantee that we will review unsolicited amendments such as stability updates even if the content of the amendments may impact regulatory specifications and re-test dates. Stability updates may be submitted to the NDA during the review cycle that, if reviewed, will be considered in determining shelf life for your product.**

**Your amended proposal, sent June 3, 2011, would clearly meet our requirements for stability data if the clinical and commercial batches are adequately bridged. We acknowledge that the 10 mg dose strength relies on bracketing data by the 5 mg and 20 mg dose strengths. Comparability of these capsules and processes will be determined on review. Among the data necessary to bridge the clinical and the proposed commercial batches, you would need to demonstrate the following:**

- **No impact of capsule size on performance or stability**
- **No impact of capsule printing on performance or stability**
- **Adequate protection (desiccant) from moisture permeability in your container closure system**

**Also, confirm that you intend to submit a post-approval supplements to the NDA to implement the capsule presentation and manufacturing process changes originally submitted for your April 5, 2011 Type B meeting. A comparability protocol could be included in the NDA, as a precursor to these post-approval changes.**

**Finally, we would like to know why you will not be able to use the second drug substance batch to manufacture drug product as originally proposed.**

Meeting Discussion: The sponsor described their proposed bridge for the clinical and commercial batches. They will continue with the size 1 capsule. They are proposing 3 small GMP batches and will evaluate this against the clinical trial material. (b) (4)

The performance information will be included in the NDA, but the sponsor may only have 1 month of accelerated data. The agency stated their preference for at least 3 months of data. The sponsor said they would provide as much data as possible, and would add additional data points to accumulate more data in a shorter period of time.

The sponsor said that, based on the new plan, they will have 24 months of primary stability data.

The sponsor confirmed that the NDA would contain a comparability protocol.

With regard to the reason why the second drug substance batch could not be used, the sponsor responded that it was a combination of human error and issues with the catalyst. Because of these issues, the sponsor concluded that the batch would not be representative of the proposed market product.

## NONCLINICAL QUESTIONS

### **Question 2:**

*Aegerion is conducting a nonclinical central nervous system safety pharmacology study with lomitapide and hERG assays with lomitapide and the metabolites M1 (BMS-203215) and M3 (BMS-203304). There are no plans to conduct respiratory or cardiovascular (in vivo) safety pharmacology studies with lomitapide because the clinical program included pulmonary function tests (with normal results) and a separate Thorough QT study is being conducted. A 104-week carcinogenicity study in rats was completed and the report was submitted to IND 50,820 on March 11, 2011 (Serial No. 0174). Ongoing studies for which final reports will be submitted to the NDA include biotransformation studies in rats and dogs, 3-month and 2-year oral investigative studies in rats, and a Segment III oral reproductive toxicology study. With the addition of the studies cited here, we consider the nonclinical package for lomitapide to be complete with no further studies required for the NDA submission. Does the Agency agree?*

### **Sponsor Position:**

Lomitapide was evaluated in non-GLP general pharmacology and safety pharmacology studies; noteworthy findings are discussed below. A listing of all completed, ongoing, and planned nonclinical studies is provided in Appendix 1.

In the general pharmacology evaluation, no drug-related changes in activity or behavior; hypnotic, convulsive, or anticonvulsive activity; or GI motility were noted in rodents following single oral doses  $\geq 30$  mg/kg. However, spontaneous locomotor activity was significantly decreased at oral doses of 10 mg/kg, 30 mg/kg, and 100 mg/kg (transient and in a non-dose-related manner) in mice. In dogs, intravenous administration of lomitapide at a dose of 20 mg/kg produced significant but generally transient effects including increases in respiratory rate, decreases in blood pressure, heart rate, and femoral arterial blood flow, and an increase in T-wave amplitude on electrocardiograms. No effects were observed after intravenous doses of up to 4 mg/kg.

In the *in vitro* portion of the safety pharmacology evaluation, of the 31 receptors and channels tested in a radioligand binding assay, only 4 showed significant levels of binding inhibition by lomitapide: the serotonin 5HT receptor types 1 and 2, nonselective sigma channel, and type 2 sodium channel; IC<sub>50</sub> values were  $\geq 0.3$   $\mu$ M which equates to a

$\geq 600$ -fold selectivity for the inhibition of MTP activity relative to binding to these receptors.

Lomitapide had no drug-related effects on general behavior in rats at 150 mg/kg.

In normotensive rats given lomitapide at 150 mg/kg, no significant effects on mean arterial pressure and only a mild decrease (18%) in heart rate at 24 hours post dosing

were observed when compared to control values (parameters were directly measured).

In conclusion, there were no important changes in animals given high lomitapide doses relative to clinical doses in these studies. The effects in the *in vitro* assay occurred only at lomitapide concentrations much higher than were associated with MTP inhibition and those observed at clinical doses. Based on these results, it was anticipated that lomitapide had little potential for any undesirable pharmacologic activity. This has been borne out in clinical trials, as no drug-related adverse central nervous system, pulmonary, or cardiovascular effects have been observed to date. The ongoing central nervous system safety pharmacology study in rats, the hERG evaluation of lomitapide and metabolites M1 and M3, and the Thorough QT study in humans will provide further information on secondary pharmacologic effects of lomitapide. Lastly, in the preliminary comments for the 17 May 2010 End-of-Phase-2 Meeting (correspondence dated 13 May 2010), the Agency did not identify additional safety pharmacology studies as being required when asked if the nonclinical package was adequate.

**FDA Preliminary Response:**

**Yes, the nonclinical program that is described in the pre-NDA meeting package appears to be consistent with the number and type of nonclinical studies that are typically expected to support the submission of a marketing application for a medical indication requiring chronic treatment. The adequacy of the data to support marketing approval will be determined after the NDA has been submitted.**

**The Division has the following additional comments:**

- 1. The exposure at the highest dose used in the rat carcinogenicity study is approximately only 3- to 4-fold higher than the highest anticipated clinical exposure. Please explain the dose selection rationale used for the carcinogenicity study (#733PC002).**
- 2. Can the sponsor comment on the purpose of the ongoing exploratory 2-year rat study (#733PC0004) and the dose levels that are being used?**
- 3. Metabolite M20 is detected in human plasma but not rat or dog plasma. Although the sponsor states that M20 was detected in rat urine, it is uncertain whether systemic exposure occurred in rats. Please comment on why this metabolite was not observed in rat or dog plasma and whether the formation of M20 would be more likely to occur through hepatic metabolism versus renal metabolism in rats and dogs.**
- 4. In the appropriate nonclinical sections of the marketing application, the sponsor is encouraged to include/discuss the following (note: these suggestions are not intended for discussion at the pre-NDA meeting, but rather to guide the sponsor during NDA preparation):**
  - a. Compare and contrast the lung electron microscopy findings between the most recent studies conducted by Aegerion (neutral lipid accumulation) and the initial studies conducted by Bristol-Myers Squibb (phospholipidosis).**

**The sponsor should discuss why different conclusions have been made regarding the liability of lomitapide to induce phospholipidosis in rodents.**

- b. Discuss the implication of neutral lipid accumulation versus phospholipidosis with respect to long-term human safety. The sponsor should include any data or literature that addresses long-term human safety and whether lipid accumulation could be linked to the small intestine and liver tumors observed in the mouse carcinogenicity study and the extent of this risk for humans.**
- c. Exposure margin calculations should be made using the clinical exposure achieved at the highest clinical dose proposed for approval. On page 7 of the pre-NDA meeting package, it states that the maximum clinical dose will be 60 mg, however exposure margin calculations in the nonclinical section of the meeting package use a clinical dose of 50 mg.**

Meeting Discussion: With regard to the above agency comments, the sponsor provided the following information:

1. The high-dose level used in the rat carcinogenicity study was based on a broader dyslipidemic population, not HoFH, for which the maximum anticipated dose would be 10 mg. Based on human exposure data for the 10 mg dose, exposure at the high dose used in the rat carcinogenicity study represents an approximate 25-fold exposure margin. The sponsor also pointed out that the Division had previously agreed that only a single carcinogenicity study would be required to support the marketing application for the HoFH population and that a second carcinogenicity study would be required to support the marketing application for a broader dyslipidemic population. Because the sponsor is currently not developing the drug for the broader dyslipidemic population, the sponsor is relying on the mouse carcinogenicity data to support the marketing application for the HoFH population and the rat carcinogenicity study is considered to be supplemental information.
2. The exploratory 2-year rat study (#733PC0004) is no longer ongoing; the report has been finalized but has not yet been submitted to the agency. It was initiated in response to a hemorrhagic issue observed in the rat due to vitamin K deficiency. The study was initiated 3 months prior to the start of the carcinogenicity study so that adjustments could be made to the carcinogenicity study before animals became moribund because of vitamin deficiency. The exploratory study data showed that deficiencies in Vitamin A and E occurred after approximately 1 year of dosing. This issue was addressed in the carcinogenicity study by providing the animals supplemental vitamins. The mid-dose and high-dose levels were the same as those used in the carcinogenicity study (a low-dose group was not used). The exploratory study included only limited endpoints and an assessment of tumorigenicity was not included.
3. This was an error by the sponsor. Table #3 (on page 16 of the meeting minutes) should indicate that M20 was found in rat plasma in the amount of 2.5% of administered radioactivity. Based on this information, the sponsor calculated that exposure (AUC) to the M20 metabolite in rat toxicology studies was approximately two-fold higher than

human exposure at the maximum recommended clinical dose. The sponsor confirmed that the M20 metabolite was not detected in dog plasma.

4c. The sponsor noted that human exposure at 50 mg was used to calculate exposure margins because most of the exposure data is from the 50 mg dose rather than 60 mg. The sponsor suggested to model the exposure at 60 mg based on exposure at lower dose levels because exposure appears to increase linearly with dose. The sponsor also stated that even with the slightly higher exposure at 60 mg compared with 50 mg, the calculated exposure margins do not significantly change. The Division agreed that the use of modeled PK data for the 60 mg dose is acceptable and is preferred to the use of exposure data from the 50 mg dose for the purpose of calculating nonclinical exposure margins.

## CLINICAL QUESTIONS

### Question 3:

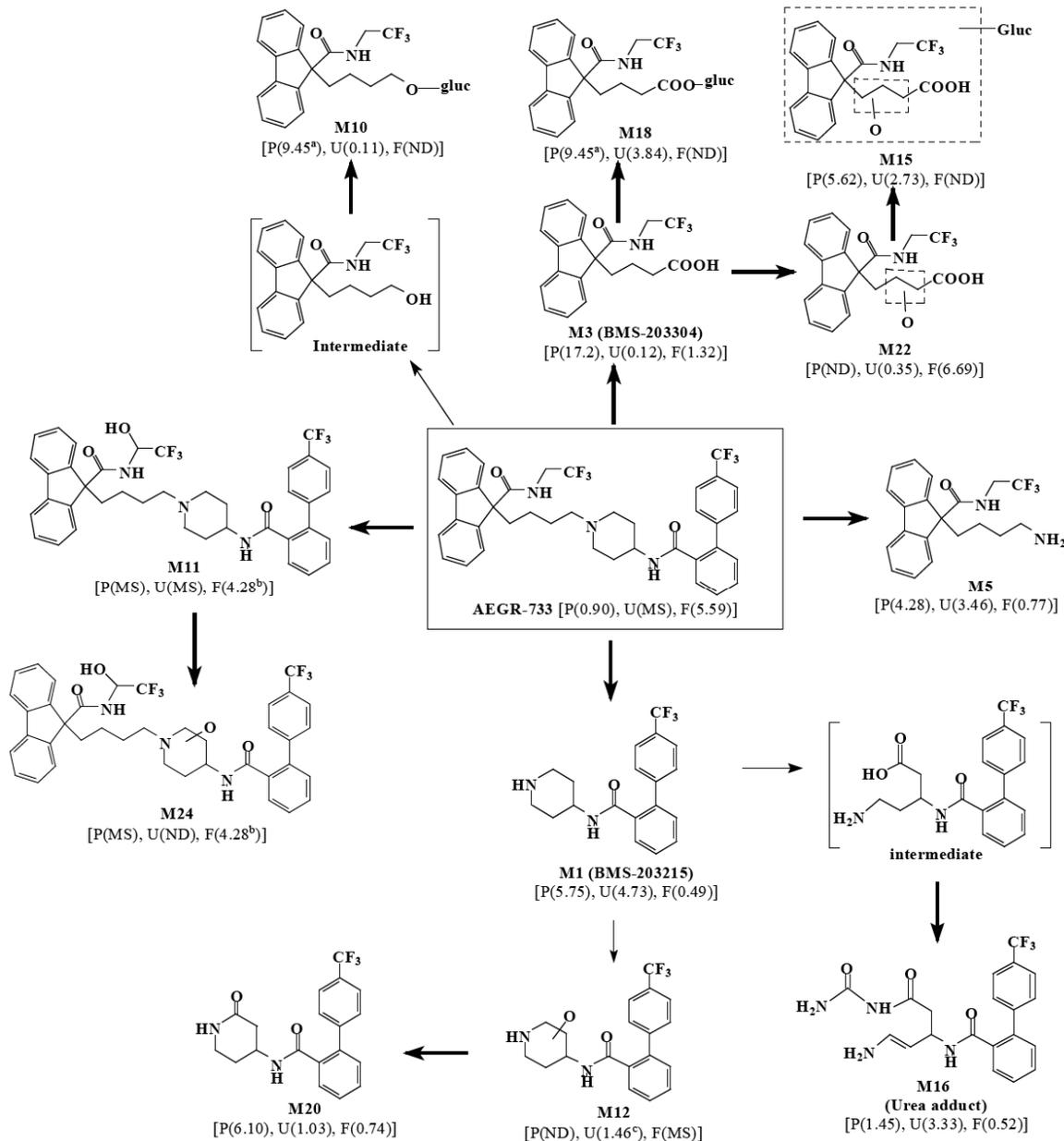
*In completed in vivo radiolabeled metabolite identification studies (rat, dog, and human), approximately 20 metabolites of lomitapide were identified in plasma, urine, and fecal samples from all 3 species. Aegerion confirmed that there are no unique human metabolites and qualified the primary metabolites M1 and M3 in the repeat-dose toxicology studies. We have concluded that only the primary M3 metabolite of lomitapide is a major metabolite (defined as having an AUC greater than 10% of the total radioactivity in plasma); therefore, no additional qualification of metabolites is necessary. Does the Agency agree with our assessment that there is only one major metabolite of lomitapide?*

### Sponsor Position:

Lomitapide follows first order, linear kinetics following intravenous administration. While there is some nonlinearity in lomitapide kinetics following oral administration at the lower doses, most likely due to saturation of the first pass effect, linearity is approached at steady-state between 25 mg and 100 mg. Following intravenous administration, the half-life for lomitapide in plasma is approximately 29 hours and the half-lives for both of the primary metabolites of lomitapide are about 21 hours. Despite a high degree of binding to plasma proteins (99.8%), lomitapide exhibits a large volume of distribution (mean = 1200 L).

Figure 1 depicts the proposed major metabolic pathways for lomitapide in humans. Additional data in parentheses shows the percent of the total radioactivity in the plasma (P) and the percent of the dose recovered in urine (U) and feces (F).

**Figure 1: Proposed Major Metabolic Pathways of Lomitapide in Humans**



Note: "a," "b," and "c" in the figure are meant to show metabolites that co-elute in the specific matrix; therefore, the value is the sum of the 2 compounds.

Lomitapide is first metabolized, by CYP3A4, to M1 and M3 (A major metabolite). The alcohol intermediate prior to the formation of M10, as well as the formation of M3, are most likely formed through a common short-lived aldehyde intermediate which is the normal mechanistic route for oxidative N-dealkylation. The 2 primary metabolites of lomitapide (M1 and M3), which were qualified in repeat-dose toxicology studies in mice, rats, and dogs, are then further oxidized and/or conjugated with glucuronic acid. Of these only M3 (BMS-203304), constitutes a major metabolite. A major metabolite, as defined in the Tripartite Guideline, *Guidance on*

*Nonclinical Safety Studies for the Conduct of Human clinical Trials and Marketing Authorization for Pharmaceuticals M3 (R2)*, 11 June 2009, is one having an AUC greater than 10% of the total plasma radioactivity AUC.

Table 3 presents a comparison between lomitapide and metabolites identified in plasma from rats, dogs and humans.

**Table 3: Lomitapide and Circulating Plasma Metabolites (>5% Total Radioactivity AUC) Identified in the Plasma of Rats, Dogs, and Humans Following Oral Administration of <sup>14</sup>C-Lomitapide**

CIRCULATING PLASMA METABOLITES (>5% TOTAL RADIOACTIVITY AUC)			
Compound	Dose of Lomitapide		
	10 mg/kg	2 mg/kg	50 mg
	Species		
	Rat	Dog	Human
Lomitapide	5.6	30.3	0.89
M1 (BMS-203215)		15.7	5.75
M2 (BMS-224433)	33.2	6.7	
M3 (BMS-203304)	3.2	4.6	17.2
M5 (Cleavage product like M3)		16	4.28
M11 (intact parent hydroxylated)	14		
M13		6.4	
M14 (Glucuronide of oxidized M3)	20.3		
M15 ( Glucuronide of oxidized M3)			5.6 <sup>a</sup>
M18 + M10 (Glucuronide of M3; acyl +ether)	4.32% (Bile)	3.8	9.45
M20 (Oxidized M1)			6.1 <sup>a</sup>
M24 (Oxidized M11)	14		

<sup>a</sup> Metabolite recovered in rat urine. Therefore, it was not considered a unique human metabolite.

No unique human metabolites have been observed. Metabolites M15 and M20 were recovered in the urine of rats, indicating that these metabolites are formed *in vivo* and are therefore not unique human metabolites. In human plasma, M18 co-elutes with M10 and could not be separated. Their combined value in plasma was 9.45% of the total plasma radioactivity. Given that glucuronides are highly water soluble and do not readily penetrate tissues, the value of 9.45% in plasma may reflect a limited volume of distribution of these glucuronides. In human urine, M18 comprises 3.84% of the dose; in the feces, the aglycone (M3) comprises 1.32% of the dose. Thus, exposure to M18 may only be about 5% of the dose.

**FDA Preliminary Response:**

**Based on Table 3, it appears that there are multiple metabolites of lomitapide present at higher levels in plasma as compared to the parent drug. Clarify whether any of these metabolites are pharmacologically active. Characterization of all major metabolites in pharmacokinetic studies is important to understand the overall exposure-response of lomitapide in terms of both efficacy and safety. Further, dose-adjustment, if any, based solely on changes in parent exposure may not be adequate.**

**Also refer to Guidance for Industry (Safety Testing of Drug Metabolites:**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079266.pdf>) for definition of major metabolites.**

Meeting Discussion: The sponsor reiterated that a major metabolite, as defined in the ICH M3 (R2) Guideline, *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, 11 June 2009, is one having an AUC greater than 10% of the total plasma radioactivity AUC. The agency stated that this guidance provides recommendations as to when non-clinical testing of metabolites may be needed. However besides drug-drug interaction evaluation, the characterization of all metabolites in human studies is important for understanding the exposure-response of lomitapide in terms of both efficacy and safety. The Agency asked if the pharmacological activity of metabolites is known, the sponsor did not have this information. The sponsor was encouraged to characterize all metabolites. The sponsor was also advised to pay attention to the latest version of drug-drug interaction guidance that will be rolled out soon. It was indicated that the adequacy of this data will be a review issue.

**Question 4:**

*Based on feedback from the Agency at the 07 February 2007 and 17 May 2010 meetings (see minutes dated 23 February 2007 and 28 September 2010, respectively) Aegerion has completed, or will complete prior to NDA filing, a series of additional drug-drug interaction and safety studies to support the lomitapide NDA. The status of these studies is described below. Does the Agency agree that we have adequate drug-drug interaction and safety studies to support the NDA filing?*

**Sponsor Position:**

A series of drug-drug interaction studies and safety studies has been conducted, or is being conducted, with lomitapide. A listing of these studies is provided in Table 4. Further details on these studies are provided in the sections that follow.

**Table 4: Listing of Additional Drug-Drug Interaction and Other Safety Studies with Lomitapide**

PROTOCOL	NO. OF SUBJECTS	LOMITAPIDE DOSE	TYPE OF STUDY
AEGR-733-002	80	10 mg	Drug-drug interaction study with simvastatin 20 mg, atorvastatin 20 mg, rosuvastatin 20 mg, fenofibrate 160 mg, ezetimibe 10 mg, extended release niacin 1000 mg
	45	60 mg	Drug-drug interaction study with atorvastatin 20 mg, rosuvastatin 20 mg, dextromethorphan 30 mg
AEGR-733-019	16	60 mg	Drug-drug interaction study with simvastatin 40 mg
AEGR-733-015	28	50 mg	Drug-drug interaction study with Ortho-Cyclen (norgestimate (0.180 mg/0.035 mg estradiol)
AEGR-733-018	30	60 mg	Drug-drug interaction study with ketoconazole 200 mg, twice daily
AEGR-733-013	16	60 mg	Drug-drug interaction study with warfarin 10 mg
AEGR-733-011	56	75 mg, 200 mg	Thorough QT study
AEGR-733-021	12	60 mg	Renal impairment study
AEGR-733-017	32	60 mg	Hepatic impairment study

#### **Drug-Drug Interaction Studies**

Under *in vitro* experimental conditions, lomitapide was metabolized by human hepatocytes moderately at 10  $\mu$ M and extensively at 1  $\mu$ M. The major metabolic routes of lomitapide metabolism by human and animal (mouse, dog, and rat) cryopreserved hepatocytes is mono-oxidation at various positions and N-dealkylation followed by further oxidation and/or glucuronidation. The P450-mediated metabolism of lomitapide was investigated in human liver microsomes and in recombinant CYP enzymes by monitoring the formation of 5 prominent metabolites with and without selective P450 chemical inhibitors. The results indicate that CYP3A4 is the dominant enzyme in the phase I metabolism of lomitapide.

As a result of these investigations, Aegerion initiated a number of drug-drug interaction studies with drugs that might be co-administered with lomitapide or are substrates or inhibitors of CYP3A4. Study AEGR-733-002 investigated the effects of lomitapide 10 mg and/or 60 mg on various lipid-lowering therapies (simvastatin, atorvastatin, rosuvastatin, fenofibrate, ezetimibe, niacin) and with dextromethorphan, as previously reported in Serial No. 0120, dated 12 Aug 2008. Recent studies investigating additional substrates or inhibitors of CYP3A4 included simvastatin, oral contraceptives, and ketoconazole. *In vitro* studies also indicated that lomitapide was a weak to moderate inhibitor of warfarin metabolism as determined by the formation of 2 hydroxylated metabolites of warfarin. Thus, a warfarin drug-drug interaction study also was conducted.

#### ***Simvastatin Interaction (AEGR 733-019):***

Plasma concentrations of simvastatin (lactone) were higher following co-administration of simvastatin 40 mg with lomitapide 60 mg compared to simvastatin administered alone.

Simvastatin (Lactone) undergoes first pass metabolism by CYP3A4. The statistical analysis results showed that in comparison with simvastatin alone, co-administration of simvastatin with lomitapide resulted in an increase in AUC<sub>inf</sub> and C<sub>max</sub> of simvastatin, with point estimates of the geometric mean ratios of the treatments (90% confidence interval [CI]) (simvastatin + lomitapide versus simvastatin alone) of 199% (158.01%, 251.56%) for the AUC<sub>inf</sub>, and 202% (154.91% , 262.87%) for C<sub>max</sub>. These results indicate that the combination dose of 40 mg simvastatin plus 60 mg lomitapide resulted in a statistically significant increased exposure to simvastatin. Based on these data lomitapide could be classified as a mild inhibitor of CYP3A4.

Plasma concentrations of simvastatin acid also were higher following co-administration of simvastatin with lomitapide compared to simvastatin administered alone. Simvastatin acid concentrations are driven by the concentrations of simvastatin lactone present in the plasma. The conversion of the lactone to the acid is generally nonenzymatic and therefore not directly influenced by lomitapide inhibition of CYP3A.

***Ketoconazole Interaction (AEGR-733-018):***

When administered for 7 days, ketoconazole, a known strong inhibitor of CYP3A4, was observed to inhibit the metabolism of lomitapide as demonstrated by a 15-fold increase in lomitapide C<sub>max</sub> and a 26-fold increase in AUC<sub>inf</sub>. This demonstrates the impact of inhibition of CYP3A4 on lomitapide metabolism and clearance. It suggests that lomitapide should not be co-administered with strong inhibitors of CYP3A4.

***Warfarin Interaction (AEGR 733-013):***

Results of the statistical analyses showed that in comparison with warfarin alone, coadministration of warfarin with lomitapide resulted in an increase in AUC<sub>inf</sub> of warfarin R(+) and warfarin S(-). For warfarin R (+), the point estimate of the geometric mean ratio of the treatments (90% CI) (warfarin plus lomitapide versus warfarin) was 128% (122.18%, 133.68%). For warfarin S (-), the point estimate of the geometric mean ratio of the treatments (90% CI) (warfarin plus lomitapide versus warfarin) was 130%. C<sub>max</sub> of warfarin R(+) was similar following co-administration of warfarin with lomitapide compared to administration of warfarin alone whereas the C<sub>max</sub> for warfarin S(-) increased with a point estimate of 115%. These results indicate that the combination of 10 mg warfarin and 60 mg lomitapide significantly increased the AUC<sub>inf</sub> of warfarin. The effect of warfarin on the individual enantiomers of warfarin was also reflected in changes in INR.

The effect on INR suggests that patients on warfarin and lomitapide should have their clotting times monitored, and dosage adjustments in warfarin made as appropriate.

**Hepatic and Renal Impairment Studies**

Aegerion also has studies completed or planned to assess the intrinsic factors of hepatic impairment and renal impairment on lomitapide pharmacokinetics in line with FDA guidance on these issues (see minutes dated 28 September 2010). Both are designed as single-dose studies.

The hepatic impairment protocol (AEGR-733-017) enrolled 8 subjects who are classified (by Child-Pugh) as mildly hepatic impaired and 8 subjects who are classified as moderately impaired. As part of the planned analysis, each group will be paired against healthy subjects (N=8 per group; total control group: N=16) who are within  $\pm 15\%$  body mass index (BMI),  $\pm 5$  years in age and of the same gender.

The renal impairment protocol (AEGR-733-021) is that of a reduced design. Six subjects on dialysis will be administered a 60 mg oral capsule dose of lomitapide within 2 hours of completion of dialysis and blood will be drawn for analysis of lomitapide over the next 72 hours (i.e., prior to the next scheduled dialysis session). The control group will include 6 healthy volunteers and will be matched with the dialysis group only with regard to gender. If the analysis demonstrates a clinically significant difference in lomitapide pharmacokinetics between healthy volunteers and patients on dialysis, Aegerion will move forward with a complete renal impairment study enrolling subjects with mild and moderate renal impairment.

### **Gender**

In the meeting minutes dated 28 September 2010, FDA noted a concern that, “lomitapide appears to have a higher exposure in women than men.” The data that raised this concern must be viewed with caution as males were treated in a different study, at different sites and at different times from females; thus, the comparison may not be valid and the conclusions drawn may be erroneous. As the drug is administered in a dose-escalation scheme to a MTD on the basis of individualized safety/tolerability criteria, Aegerion believes the need for a separate gender study is obviated.

### **FDA Preliminary Response:**

**The following comments needs to be addressed:**

- a. It is noted that there was significant interaction with strong CYP3A4 inhibitor (ketoconazole) with 15-fold increase in  $C_{max}$  and 26-fold increase in AUC. You propose that lomitapide be not administered with strong inhibitors of CYP3A. In addition to this you also need to address the potential of DDI of lomitapide with other CYP3A inhibitors (moderate & mild).**
- b. The *in-vitro* induction potential of lomitapide on drug metabolizing enzymes and transporters should be investigated. You should also investigate the inhibition/induction potential of the major metabolites such as M1 and M3, on major CYP enzymes in *in-vitro* systems. Based on the *in-vitro* results, you may need to investigate the effect *in-vivo*.**

Meeting Discussion: The sponsor proposed to address the CYP3A4 interaction in labeling; the package insert will indicate to avoid taking lomitapide with moderate or mild CYP3A4 inhibitors in addition to strong CYP3A4 inhibitors. The agency agreed with this approach. The firm was encouraged to use simulations to evaluate the effect of mild and moderate CYP3A4 inhibitors on lomitapide. The labeling language will be review issue.

It was also strongly recommended that the sponsor address the in-vitro induction potential of lomitapide and its major metabolites on major CYP enzymes.

**Question 5:**

*The Sponsor believes that the pharmacokinetic properties of lomitapide are adequately described across the intended clinical dose range, and in light of the individualized approach to dosing, does not plan to include any additional pharmacokinetic evaluations (including a formal population pharmacokinetic analysis) in the NDA. Does the Agency agree?*

**Sponsor Position:**

As described above, Aegerion has conducted a series of drug-drug interaction and safety studies that have included multiple evaluations of the pharmacokinetic properties of lomitapide. The pharmacokinetic properties of 60 mg lomitapide are currently being evaluated in patients with hepatic impairment and patients with renal impairment, to address the impact of these potential co-morbidities relative to unaffected controls. Collectively, these studies should provide an adequate assessment of factors that may impact the pharmacokinetic properties of lomitapide at the highest clinical doses.

The Phase 3 study utilizes individualized dosing involving escalation at specified intervals up to a MTD (<60 mg) based on safety and tolerability criteria. This dosing protocol takes into account the possibility of individual variations in response to lomitapide and thereby largely obviates the need for unique dosing instructions for population subsets. Thus, Aegerion does not envision that a population pharmacokinetics analysis based on sparse sampling using currently available data would add significantly to the pharmacokinetics database nor lead to changes in the dose range or dosing protocol. Therefore, Aegerion does not plan to include a population pharmacokinetics analysis in the NDA.

**FDA Preliminary Response:**

**We believe that population PK approach will help address the effects of covariates (e.g., age, gender, race etc.) on lomitapide PK, as well as be used to characterize exposure-response relationships for efficacy and safety parameters.**

**Additional comment: If the formulation used in your pivotal Phase 3 trial is different from the to-be-marketed formulation, a bridging study will be needed to establish bioequivalence between these formulations.**

Meeting Discussion: The sponsor stated that, given the small size of the Phase 3 trial as well as the titration scheme used, a population PK analysis will not provide useful information. The sponsor proposed the conduct of a population PK analysis later in development by combining data from pediatric studies. The agency agreed with the sponsor's proposal.

**Question 6:**

*As previously discussed with the Agency (see minutes dated 23 February 2007), there is no placebo control arm in the single, pivotal Phase 3 study. Does the Agency agree that the lack of*

*a placebo control and a single pivotal trial do not preclude filing or approval of the lomitapide NDA given the patient population we are treating?*

**Sponsor Position:**

The Sponsor had originally proposed including a placebo group in the Phase 3 clinical trial (Study UP1002/733-005); however, the placebo group was removed, with the Agency's concurrence, in this rare orphan population (see minutes dated 23 Feb 2007). Aegerion believes that an open-label design without a placebo arm for the single Phase 3 trial in the orphan disease, HoFH, is appropriate for several reasons:

- Patients with HoFH are at extremely high risk for cardiovascular events and thus it is appropriate to provide all patients with an investigational drug that may lower LDL-C by as much as 50% [Cuchel 2007 *New Engl J Med*] in combination with standard of care in this long-term interventional study;
- The study's primary and key secondary endpoints are objective lipid measurements obtained at a central laboratory and thus treatment effects can be appropriately evaluated with a single arm (baseline-controlled) design;
- Strong measures of control for efficacy were included that allowed for appropriate evaluation of the endpoints: a minimum 6-week run-in period was incorporated to stabilize concomitant lipid-lowering therapies and the low-fat diet; 2 separate baseline measures of efficacy were used to calculate a mean baseline for future comparison; and background therapies, including apheresis, were to remain unchanged through Week 26 (the primary endpoint); and
- LDL-C reductions in the 50% range, which were observed in the Phase 2 study, were considered to be easily discernable from baseline measurements in this conservatively powered study, making the requirement for a placebo control for efficacy determinations noncritical.

The sample size for the primary endpoint in the single Phase 3 study is based on data from the Phase 2 protocol in patients with HoFH (Study UP1001). Based on the assumption that there would be greater heterogeneity in the Phase 3 study as compared to the Phase 2 study from the use of various combinations of concomitant lipid-lowering therapies, a 25% change in LDL-C with a 30% standard deviation and a 15% drop out rate was assumed. Based on these assumptions, using a 2-sided  $\alpha$  of 0.05 and 90% power, 20 patients were needed for enrollment; however, the sample size was increased to 25 patients to allow a more adequate assessment of safety as discussed with the Agency (23 Feb 2007 minutes). A total of 29 patients were enrolled with 6 patients discontinuing early from the trial (prior to Week 26).

In terms of the precedent for approving an NDA with a single, open-label Phase 3 trial, we cite the example of Carbaglu (carglumic acid) which was approved in 2010 on the basis of a retrospective case series plus a prospective study in 3 patients with N-acetylglutamate synthase (NAGS) deficiency. Quoting the definition of substantial evidence contained in Section 505(b) of the FD&C Act, the summary basis of approval notes that although the data were not derived from traditionally defined adequate and well controlled investigations, the "...data submitted for review do stand as evidence 'on the basis of which it could fairly and responsibly be concluded by experts that the drug

will have the effect it purports or is represented to have.””

**FDA Preliminary Response:**  
**We agree.**

Meeting Discussion: None

**Question 7:**

*In Phase 3 Study UP1002/733-005, 29 patients with HoFH were treated at doses up to 60 mg. As part of the NDA submission, a total of 23 of the 29 will have been followed for at least 56 weeks, and 10 patients will be presented from long-term extension Study AEGR-733-012. Therefore, we expect the total population of HoFH treated patients to be 31 (29 from Study UP1002/733-005 and 2 unique patients from Study UP1001) treated at doses up to approximately 60 mg (mean highest dose of 67 mg in Study UP1001, as dosing was weight based) with the longest treatment period with lomitapide being approximately 3 years. Additional exposure data will be available from previous or ongoing clinical trials and include approximately 950 subjects treated at doses of up to 60 mg. In view of the rarity of the HoFH population and the high unmet medical need, we believe these data are adequate to support an NDA for the treatment of patients with HoFH. Does the Agency agree that we have adequate safety exposure in the indicated population to support administration at maximum doses of up to 60 mg?*

**Sponsor Position:**

Studies UP1001 (n=6) and UP1002/733-005 (n=29) included a total of 35 patients with HoFH. Four patients in Study UP1001 also received treatment in Study UP1002/733-005. Thus, 31 unique patients with HoFH have been exposed to lomitapide across 2 clinical trials.

In Study UP1001, 6 patients with HoFH were washed out of all concomitant lipid lowering therapies, including apheresis, 4 weeks before treatment. Mean doses at each of the escalation steps (every 4 weeks) were 2.0 mg, 6.7 mg, 20.1 mg, and 67.0 mg per day. In Study UP1002/733-005, lomitapide was administered in combination with stable concomitant lipid-lowering therapies to reach an individually determined MTD up to 60 mg for 78 weeks (approximately 1.5 years). Patients who successfully completed this protocol were eligible to enroll into long-term extension Study AEGR-733-012 and continue treatment on their MTD. In Protocol UP1002/733-005, the mean dose at Week 26 was 45 mg and at Week 56 was 40 mg with the distribution of doses at MTD as presented in Table 5.

**Table 5: Dose Distribution at 26 and 56 Weeks in Study UP1002/733-005**

WEEK 26		WEEK 56	
MTD	Number of subjects	Dose	Number of subjects
5 mg	1	5 mg	1
10 mg	0	10 mg	0
20 mg	5	20 mg	7
40 mg	6	40 mg	6
60 mg	10	60 mg	9
80 mg	1	80 mg	0

All 31 unique patients received treatment for a minimum of 16 weeks. Twenty-three of the 31 patients with HoFH were exposed to lomitapide at doses ranging from 5 mg to 60 mg for a minimum of 1 year (see Table 5). For the NDA, data will be available for 18 patients who have been exposed for at least 1.5 years, and 10 who have been exposed for at least 2 years; MTD for patients receiving treatment for at least 2 years ranges from 20 mg to 60 mg.

Aegerion believes the available exposure data from single pivotal Phase 3 Study UP1002/733-005 in patients with HoFH as well as that from other populations is sufficient to support an NDA for HoFH.

**FDA Preliminary Response:**

**We agree, but please note that the functional HoFH definition of patients with average fasting LDL >300 mg/dL on maximally tolerated lowering therapy closely resembles the severe refractory heterozygous FH population and expands the target population almost 10-fold. In previous meetings, the Division expressed our position that the use of lomitapide outside the homozygous FH population would require additional clinical studies due to the shift in risk/benefit ratio.**

Meeting Discussion: Dr. Rader explained the additional definition of “functional HoFH” as patients on maximal tolerated lipid lowering therapy with LDL >300 mg/dL was to address the practical limitations of documenting the following to identify the HoFH population in clinical practice:

- functional mutations in both LDL receptor alleles or alleles known to affect LDL receptor functionality,
- skin fibroblast LDL receptor activity < 20% of normal, or
- untreated total cholesterol > 500 mg/dL and triglycerides < 300 mg/dL with both parents having documented total cholesterol >250 mg/dL

Dr. Rader recognized that the treatment indication for lomitapide will need to align with the inclusion criteria of the Phase 3 trial. Additionally, Dr. Rader understood that inclusion of patients on maximal tolerated therapy with LDL >300 mg/dL for treatment with lomitapide

(which was not an inclusion criterion in the Phase 3 trial) is a REMS issue that will be addressed as part of the NDA review process.

**Question 8:**

*Aegerion believes that a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use will be important to ensure that drug use is confined to the specific population identified in the proposed label and, further, that risks are minimized in the marketed use of lomitapide. In this briefing package we outline the key elements of the proposed plan. Does the Agency agree that the proposed elements of the REMS are appropriate to ensure the safe use of lomitapide?*

**Sponsor Position:**

Aegerion will institute a REMS program to ensure safe use and appropriate access to lomitapide once it is in the marketplace. It is Aegerion's intention that the REMS program will facilitate the following:

- Ensure that only the appropriate patient populations are treated with lomitapide;
- Enable informed risk-benefit decisions for patients treated with lomitapide and lomitapide-prescribing physicians;
- Educate prescribers, patients, and pharmacies on the safe-use conditions for lomitapide; and
- Introduce measures to monitor and minimize risks of adverse events in patients treated with lomitapide.

A primary component of the REMS program will be to ensure that lomitapide is available only to the addressable population, patients with functional HoFH, defined as follows:

- a) Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality (e.g., apo B defective mutations); or
- b) Skin fibroblast LDL receptor activity <20% normal; or
- c) Untreated total cholesterol >500 mg/dL and triglycerides <300 mg/dL with both parents having documented total cholesterol >250 mg/dL; or
- d) Patients with average fasting LDL-C >300 mg/dL on maximally tolerated lipid lowering therapy as decided by the treating physician.

The Phase 3 study specifically included patients meeting criteria (a), (b), or (c). Eighteen of the patients in the Phase 3 study also met criterion (d). This criterion is additionally proposed, since in many cases, patients may (1) not have adequate medical records to document their pretreatment LDL-C levels or those of their parents, (2) not know their parentage, or (3) have genetic defects that are not readily detectable. With regard to the latter, the lack of evidence of a specific genetic mutation does not exclude FH, since in approximately 20% of patients with definite FH, a genetic mutation cannot be identified using current state-of-the-art-methodologies [Hopkins 2011 *J Clin Lipidol*]. LDL apheresis is indicated for functional FH patients if their LDL-C levels are >300 mg/dL after at least 6 months of maximally tolerated drug therapy, and, in their recent guidelines, the National Lipid Association (NLA) defined functional HoFH based on an

LDL-C >300 mg/dL [Ito 2011 *J Clin Lipidol*].

Patients with LDL-C >300 mg/dL on maximum therapy are a small, well-defined cohort who can be clinically identified and readily differentiated from patients with forms of hypercholesterolemia in which lomitapide would not be indicated. In the study by Gagne et al. of 50 patients with HoFH on aggressive statin therapy, baseline mean LDL-C levels were 325 mg/dL [Gagne 2002 *Circulation*]. In Aegerion's Phase 3 study, in which all patients had genetically proven HoFH, the mean baseline LDL-C was 336 mg/dL  $\pm$  114 mg/dL; only 11 of 29 patients had baseline LDL-C values <300mg/dL (on maximal tolerated lipid lowering therapy as directed by their treating physician). These results illustrate the stringency of the LDL-C >300 mg/dL threshold and are consistent with previously defined criteria for functional HoFH. Based on primary market research, Aegerion estimates that there are approximately 3,000 patients in the US over the age of 18 who will meet the definition of HoFH that includes the >300 mg/dL criterion.

The REMS program will be designed to ensure the appropriate identification of patients meeting the aforementioned criteria for treatment with lomitapide. It will also educate physicians regarding the appropriate approaches for evaluating the sufficiency of background therapies as well as efforts to maximize such therapies prior to the introduction of lomitapide.

In addition to ensuring that the proper patients are treated, the REMS program will aim to ensure that physicians and patients are well educated regarding possible side effects and management of those side effects, and that the best practices are maintained in terms of monitoring for potential safety risks. Aegerion recognizes that the use of lomitapide is commonly associated with GI-related adverse events, mild to moderate elevations in liver transaminases and, in some patients, elevations in hepatic triglyceride content. Although we believe the risks to the health of the intended patient populations are minimal and will be more than balanced by substantial clinical benefits arising from reductions in atherogenic lipids, a comprehensive REMS program will be developed to address the following:

- Physician and patient knowledge of product and risks;
- Dietary guidance to minimize GI adverse events;
- Dose escalation and dose adjustments to minimize both GI and liver-related adverse events; and
- Appropriate monitoring of liver safety signals.

In light of the aforementioned considerations, Aegerion is proposing the following general approaches, but anticipates that these preliminary concepts will be modified as appropriate based on the clinical data available at the time of NDA submission:

- A distribution program to ensure that patients who are prescribed lomitapide meet the approved indication.
- A Medication Guide to be dispensed with each 30-day supply of lomitapide and

in accordance with 21 CFR § 208.24.

- Certification of healthcare professionals before they can prescribe lomitapide. We believe the main prescribing physicians will be lipidology specialists and will likely focus on certification of this specialized group of prescribers.
- Certification of dispensing pharmacies.
- Monitoring of LFTs (frequency to be determined).
- Dietary education.
- Enrollment of each patient who is treated with lomitapide into a registry.

Aegerion believes this approach to a REMS program will address the safety and access requirements for this patient population to ensure lomitapide is properly utilized and monitored.

**FDA Preliminary Response:**

**We acknowledge your submission of a proposed risk evaluation and mitigation strategy (REMS). At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be.**

**A complete review of the proposed REMS in conjunction with the full clinical review of the NDA will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.**

**If you plan to submit a REMS with the original NDA submission, please submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal. Provide in detail how Aegerion plans to restrict distribution to the defined HoFH population studied in the Phase 3 trial. Please include how documentation of HoFH status will be collected and confirmed, how distribution of lomitapide will be accomplished, and how the system will be monitored for compliance.**

Meeting Discussion: The sponsor committed to submitting the complete REMS in the NDA submission.

ADMINISTRATIVE QUESTIONS

**Question 9:**

*The data to be analyzed and submitted in support of the application for lomitapide are derived from 2 primary sources: early-phase studies conducted by BMS and later-phase studies conducted by Aegerion. In addition, Phase 2 Study UP1001 was conducted by University of Pennsylvania. Aegerion proposes to submit standardized data in support of the submission as SAS datasets in CDISC SDTM format for all data from all studies, including both efficacy and safety data, including a define.xml document. Annotated case report forms (CRFs) will also be submitted. Analysis datasets will be submitted in CDISC ADaM format, including a define.pdf document. The analysis datasets for the Integrated Summary of Safety (ISS) will consist of all*

*integrated safety data and any other data for demographics, drug exposure etc., as needed for safety data analysis. A similar approach to providing analysis datasets for the tables and analyses produced for the Summary of Clinical Efficacy (SCE) will be used. The integration of safety data from all clinical studies into a single database format will facilitate production of summary tabulations, for both pooled safety analyses and side-by-side presentations of results for comparison across stand-alone studies. Individual subject CRFs will be submitted for subjects who died, experienced any serious adverse events, or who discontinued a study due to an adverse event. Is this approach for data submission acceptable to the Agency?*

**Sponsor Position:**

The following is the planned outline of the content and format of the clinical data to be submitted in support of the application.

Early-phase studies conducted by BMS, including 6 Phase 1 studies and 1 Phase 2 study, were written in a format that predated the current ICH guideline format; therefore, these clinical study reports will be submitted as legacy documents. Later-phase studies conducted by Aegerion, including 4 Phase 2 studies, 2 Phase 3 studies in the HoFH indication (a pivotal trial plus its extension study), and 10 Phase 1 drug interaction and other special purpose studies, have been or will be written in the ICH E3 guideline format. The datasets from all studies will be provided in standardized format using the SDTM model. An accompanying define.xml will allow navigation between the annotated CRFs and the SAS datasets. The define document will include dataset name and location; variable names; formats; labels and locations; and description of the derivations for any derived variables.

A reviewer's guide will be provided that shows how data were standardized, what data handling conventions were used, and what quality control (QC) steps were taken to ensure data integrity and quality.

The CDISC ADaM format will be used to create all analysis datasets for the summary data analyses provided in the ISS and SCE. The programs used to create these analysis datasets will be submitted to the Agency, to make it easier to evaluate the connections between raw (SDTM) and analysis (ADaM) datasets.

Individual subject CRFs will be provided for the following:

- Deaths
- Serious adverse events
- Discontinuations due to adverse events

**FDA Preliminary Response:**

**The approach appears reasonable, however, narratives should also be provided for subjects who died, experienced any serious adverse events, discontinued from a study due to an adverse event, and experienced a special event of interest.**

**Your proposal for providing the statistical data is acceptable.**

Meeting Discussion: None

**Question 10:**

*The ISS will utilize all available safety data, with a primary focus on the HoFH indication, and with additional supportive information obtained from studies in patients with elevated LDL-C. The key safety and efficacy study (UP1002/733-005) and its extension study (AEGR-733-012) to support the indication for the NDA submission will be combined into 1 clinical study report. In addition, there are 6 supportive clinical studies in patient groups with elevated LDL-C treated with lomitapide. Primary safety conclusions will be drawn from analyses in these 2 groups of studies. Analyses of adverse events, serious adverse events, events resulting in study discontinuation, abnormal laboratory results, and events of special interest will be presented separately for studies comprised of single-dose regimens and multiple-dose regimens. Pooled results for appropriate classifications will be produced, including dose level of lomitapide, single-agent lomitapide versus combination treatment, and fixed-dose versus titrated dose of lomitapide. Individual study result tabulations will be provided for studies that may not be pooled due to substantial differences in study design or population. As appropriate, duration of exposure will be controlled in analyses of frequency of adverse events. Laboratory parameters will be analyzed using summary statistics on change from baseline and using shift tables with reference to normal ranges. Is this approach to production of the ISS acceptable to the Agency?*

**Sponsor Position:**

A complete ISS will be provided in Module 5.3.5.3; safety information will also be summarized within Module 2.7.4 (Summary of Clinical Safety). The key elements planned for inclusion in the ISS are as follows:

- The primary results for the ISS will be presented for patients with HoFH by summaries from Studies UP1001 and UP1002/733-005.
- Supportive summaries will be provided for long-term, controlled trials in subjects with high cholesterol, with pooled results from relevant study groups presented.
- Subjects with high-cholesterol and other risk-factors for cardiovascular disease, (including patients with HoFH and those who otherwise have high LDL-C levels), will be distinguished from subjects with moderately elevated cholesterol who are otherwise healthy.
- Secondary results will be provided for studies evaluating single doses of lomitapide.
- Individual study result tabulations will be provided for studies that may not be pooled due to substantial differences in study design or population (drug-drug interaction studies, early-phase dose-escalation studies, etc.).
- The ISS will focus on summary presentations and analysis of data to assess the safety profile of lomitapide related to the following:
  - Dose of lomitapide;
  - Differences between lomitapide and comparative active control treatments and between lomitapide and placebo;
  - Differences between fixed-dose and escalated-dose regimens;
  - Effects of duration of dosing, with rates of adverse events and laboratory abnormalities normalized by duration of exposure to study drug;
  - Differences between lomitapide given as monotherapy and in combination with other lipid-lowering treatments; and

- Differences in the fat composition of diet on safety profile.

All datasets used for the integrated analysis and presentation of summary results for the ISS will be provided in ADaM format, and all programs used to create the ADaM datasets will be provided, with a define.pdf document. Subgroup analyses are planned for the ISS, using pooled data, including demographic characteristics such as gender and age, as well as baseline disease characteristics such as LDL-C, type of concomitant lipid lowering therapy, and dietary fat. Adverse events of special interest will be defined and analyzed, including, for example: cardiac adverse events, liver function test abnormalities, and GI events. Key tables for the package insert, such as a table of common adverse events, will be generated. General rules for handling different durations of treatment, doses, and comparator will be presented.

**FDA Preliminary Response:**

**In general, this approach appears reasonable; however, you should provide further definitions of the adverse events of special interest. These events can be based on existing MedDRA SMQs or you can create your own, but inclusion or exclusion of selected preferred terms should be justified.**

Meeting Discussion: The sponsor requested some assistance from the agency in defining the adverse events to be included. They anticipated including GI, Liver, and muscle adverse events, but will send in an amendment to the IND to request some further clarification on the specifics.

**Question 11:**

*Aegerion proposes to provide an integrated analysis of the efficacy of lomitapide; the summary will include a detailed analysis of the efficacy results presented in the clinical study report for combined Studies UP1002/733-005 and AEGR-733-012 with supportive data for the HoFH indication provided by Phase 2 Study UP1001. In addition, Aegerion will provide integrated data across the supportive studies in patients with elevated LDL-C. The text for the integrated efficacy summary will be located in Section 2.7.3 of the application with supportive tables, figures, and listings located within the clinical study reports for Studies UP1002/733-005/AEGR-733-012 and UP1001 and in Section 5.3.5.3. Is this approach acceptable to the Agency?*

**Sponsor Position:**

The sponsor will be providing a Summary of Clinical Efficacy (SCE) in Module 2.7.3. The primary data to support the effectiveness and safety of lomitapide in patients with HoFH will be provided by the results of the Phase 3 Study UP1002/733-005, a 78-week single-arm, open-label study conducted with lomitapide in a total of 29 patients with this rare disease (see Section 10.1.2). The primary efficacy endpoint of the pivotal study is the percent change from Baseline to Week 26 in LDL-C. Secondary endpoints are the percent change in LDL-C from Baseline to Week 56, baseline to Week 78, and from Week 26 to Week 78, as well as changes from Baseline in other lipid parameters, including total cholesterol, non-HDL-C, triglycerides, VLDL-C, HDL-C, apo B, apo AI, and Lp(a). Additional long-term efficacy will be available for patients who entered long-term follow-on Study AEGR-733-012. These data will be combined with the data from

the pivotal study and included in a single clinical study report. The primary outputs to support the effectiveness of lomitapide in patients with the proposed indication will be provided in the clinical study report for the pivotal study. Additional supportive efficacy data in the indication will be derived from the Phase 2 Study UP1001 that treated 6 patients with HoFH. The efficacy endpoints in Study UP1001 include percent change from baseline to Weeks 4, 8, 12, 16 of treatment and 4 weeks post treatment for LDL-C, total cholesterol, triglycerides, VLDL-C, HDL-C, apo AI, AII, B, C-III and E and Lp(a). Note that 4 of the patients treated in this Phase 2 study were also treated in the Phase 3 study; however, the time between studies for each of these 4 patients was at least 4 years. Any insights on retreatment with lomitapide will be assessed for these 4 patients. The data from Studies UP1002/733-005 and UP1001 will be detailed separately in the SCE; no pooling of the data across these 2 studies will be conducted.

Additional data on the lipid-lowering effect of lomitapide will be provided from 5 clinical studies conducted by BMS and Aegerion in patients with elevated LDL-C (Appendix 2). These studies, which treated over 700 patients, evaluated lomitapide doses ranging from 2.5 mg to 25 mg QD. Two of the studies (AEGR-733-001 and AEGR-733-006) evaluated a dose-escalation regimen similar to the regimen used in the pivotal and supportive efficacy studies with the dose of lomitapide increasing from a low dose initially to increased dose levels every 4 weeks as tolerated by the patient. Four studies (AEGR-733-001, AEGR-733-003B, AEGR-733-004, and AEGR-733-006) investigated the efficacy and safety of lomitapide in combination with other lipid-lowering therapies, including ezetimibe and atorvastatin. In all 5 studies, lipid parameters were obtained at baseline and over time on treatment. The efficacy data from these studies will be presented across these studies based on lomitapide dose level, monotherapy versus combination therapy, and by control regimen (placebo and active control). In addition to providing information on the overall lipid-lowering effect of lomitapide, these 5 supportive studies will provide a larger sample size to assess dose response, time course of response, and any potential efficacy differences across patient subgroups (e.g., by gender, age, race, baseline LDL-C, etc.). Any tabulations of these supportive data across studies will be included in Module 5.3.5.3.

**FDA Preliminary Response:**

**The NDA submission should have a separate integrated summary of effectiveness (ISE) that provides comprehensive analyses of the data beyond the SCE. Please refer to the Guidance for Industry: Integrated Summary of Effectiveness for further information. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>**

Meeting Discussion: None

**Question 12:**

*The treatment period (through Week 78) of pivotal Study UP1002/733-005 as well as extension Study AEGR-733-012, are ongoing. In the teleconference held on 28 July 2010 (minutes dated 28 September 2010), the Agency noted that submission based on 56-week data from pivotal*

*Phase 3 Study UP1002/733-005 was acceptable. Aegerion is proposing to submit complete data through the following cutoffs for each of these studies:*

- *UP1002/733-005: Week 56 data (data cutoff mid-April 2011; database lock late May 2011)*
- *AEGR-733-012: data cutoff late Feb 2011 (database lock late April 2011)*

*Are the proposed data cutoffs acceptable to the Agency given an end of 2011 filing date?*

**Sponsor Position:**

For the NDA filing, Aegerion is proposing to submit data through the data cutoffs noted above from ongoing pivotal Phase 3 Study UP1002/733-005 and extension Study AEGR-733-012.

Aegerion recognizes that the gap between these data cutoffs and the proposed filing date are >6 months; however, Aegerion believes the cutoffs are acceptable for the following reasons:

- The database lock for Study UP1002/733-005 is scheduled to occur in late May (approximately 7 months in advance of the planned filing). Taking a later data cut (i.e., end of June) would result in only 1 additional visit each for the 5 active patients.
- The data from extension Study AEGR-733-012 will be presented with Study UP1002/733-005 in 1 clinical study report (since these are the same subjects and the trials were uninterrupted); therefore, a data cutoff was selected for Study AEGR-733-012 that would capture the visit closest to the data cutoff for Study UP1002/733-005. For the extension study, visits are scheduled at 12-week intervals; therefore, a late February data cutoff allowed for inclusion of the latest AEGR-733-012 time point prior to the Study UP1002/733-005 data cutoff.
- Taking a later data cutoff for AEGR-733-012 (i.e., within 6 months of the planned filing date) would result in only an additional 2 visits each for 2 of the active patients and 1 additional visit each for the other 8 active patients.
- In addition, prior to submission of the NDA, Aegerion plans to update the filing with more recent data (i.e., 3 months out) on any serious adverse events or discontinuations due to adverse events that occur after the noted data cutoffs.

**FDA Preliminary Response:**

**This approach is acceptable; however, adverse events of special interest that occur after the noted data cutoffs should also be included in the safety update prior to filing the NDA submission.**

Meeting Discussion: None

**Question 13:**

*Aegerion believes that lomitapide should qualify for priority review. Does the Agency agree?*

**Sponsor Position:**

The FDA Manual of Policies and Procedures (MaPP) for Review Classification Policy: Priority (P) and Standard (S) (MaPP 6020.3) states that priority review applies when:

Preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies.

We believe we have shown, as described in our application for fast-track designation (see Serial 0182, dated 14 April 2011) and as summarized below, that lomitapide provides a significant improvement compared to marketed products in the treatment of HoFH.

In patients with hypercholesterolemia who do not have HoFH, LDL-C reductions of up to approximately 60% have been reported for the top doses of the most potent statins (atorvastatin, 80 mg; rosuvastatin, 40 mg) [Vaughan 2004 *Circulation*]. Patients with HoFH are, however, refractory to the effects of statins, with LDL-C reductions ranging from 0 to approximately 30% depending upon the nature of the LDLR defect [Lipitor 2009 package insert; Crestor 2010 package insert; Zocor 2010 package insert]. In a report by Gagne, et al., plasma LDL-C levels were reported to exceed 300 mg/dL in genotype-confirmed patients with HoFH being treated with a maximum dose of statins (atorvastatin or simvastatin, 80 mg/day) [Gagné 2002 *Circulation*]. Statins nonetheless remain standard pharmacologic therapy for these patients due to the lack of other effective agents. The outcome benefits of statins in large clinical trials are primarily attributed to the LDL-C-lowering effects [Baigent 2005 *Lancet*; Robinson 2005 *J Am Coll Cardiol*]; thus, these benefits are almost certainly reduced in patients with HoFH who maintain high LDL-C levels, generally >300 mg/dL despite maximum medical therapy. The addition of ezetimibe or bile-acid sequestrants (e.g., colestipol, cholestyramine) can result in incremental LDL-C lowering in patients with HoFH in the range of approximately 10% to 20% above those obtained with statins [Gagné 2002 *Circulation*; Marais 2008 *Atherosclerosis*; Zetia 2009 package insert]. Moreover, ezetimibe has been shown to be less effective in reducing LDL-C when coadministered with maximal (versus lower) doses of statins, which is common in patients with HoFH [Ballantyne 2003 *Circulation*].

Because of the severity of the LDL-C elevations and the fact that patients with HoFH are generally refractory to lipid-lowering drug therapy and have very high LDL-C levels despite maximal therapy, other treatments are highly desirable. For example, LDL-C apheresis, which is mechanical filtration of the blood to selectively remove LDL, is recommended for treatment of HoFH [Thompson 2008 *Atherosclerosis*]. This procedure transiently reduces LDL-C levels by approximately 50% [Thompson 2010 *Atherosclerosis*; Uauy 1992 *J Pediatr*; Jaeger 2002 *J Pediatr*]. LDL-C levels rebound after the procedure and, thus, treatments must be repeated every 1 to 2 weeks to effect an acceptable time-averaged LDL-C reduction [Tonstad 2004 *Curr Treat Options Cardiovasc Med*].

Access to this treatment option is limited, because this procedure is typically only available in specialized lipid centers. There are only approximately 42 centers in the US that use 1 of the 2 FDA-approved apheresis medical devices (Liposorber [Kaneka] and H.E.L.P. [B. Braun]). In addition to access, use of LDL-apheresis is associated with significant quality of life issues, including repetitive and long treatment sessions, which may lead patients to reject this option even when available.

Patients with HoFH also may be treated surgically. The portacaval shunt and ileal bypass surgeries have been cited to be among the treatment options for patients with HoFH, but do not have long-term effectiveness and are not commonly used.

The most extreme treatment option is liver transplantation; however, owing to the shortage of suitable donor organs and the risks associated with the surgical procedure, as well as the required lifelong immunosuppressive therapy, liver transplantation is not widely used for patients with HoFH.

In summary, a number of treatment options exist for reducing LDL-C in patients with HoFH including lipid-lowering drugs, LDL-C-apheresis, and several surgical procedures. However, even with the aggressive utilization of these therapies, patients with HoFH generally remain well above their LDL-C treatment targets due to the severity of the initial LDL-C elevations and a reduced response to drug therapy. Plasma LDL-C levels exceeding 300 mg/dL are still being reported in genotype-confirmed patients with HoFH being treated with a maximum dose of statins (atorvastatin or simvastatin, 80 mg/day) [Gagné 2002 *Circulation*]. Consistent with these observations, in the Aegerion Phase 3 study of lomitapide in 29 enrolled patients with HoFH on maximally tolerated lipid lowering therapy, which could include drugs and LDL apheresis, the mean baseline plasma LDL-C value was  $337 \pm 115$  mg/dL (data on file). These results illustrate the clear need for additional therapeutic options for patients with HoFH.

**FDA Preliminary Response:**

**A review designation (priority or standard) will be determined at the time of NDA filing.**

Meeting Discussion: None

**Additional clinical comments to the sponsor provided to the sponsor with the preliminary responses on June 10, 2011.**

- 1. The NDA will be reviewed utilizing the CDER Clinical Review Template. To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template (see Appendix A, below).**
- 2. Include the number of patients, if any, who satisfy the criteria for Hy's Law: AST or ALT > 3x ULN, with ALP < 2x ULN and total bilirubin > 2x ULN. Each case should include a detailed narrative.**

3. **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.**
4. **Key ISS tables (deaths, SAEs, AEs of special interest, and AEs leading to discontinuation) should hyperlink to the relevant CRFs and narratives.**
5. **For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated and a table of the discrepancies between listed and verbatim reasons for dropout should be submitted. Also, please provide the verbatim terms for discontinuations due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other.”**
6. **Besides descriptive statistics and shift tables, categorical changes in laboratory values and relevant safety endpoints should be presented. For example increases in >5% hepatic fat, >10% hepatic fat, >15% hepatic fat, >20% hepatic fat from baseline; categorical decreases in fat soluble vitamins, and categorical increases in INR values at any time, persistent (defined as occurring at 2 consecutive visits), and at final visit.**
7. **Provide tables describing the number and frequency of total subjects and by dose experiencing changes in concomitant medications such as anti-coagulant therapy and multivitamin supplementation.**
8. **Provide information regarding compliance versus noncompliance with the low-fat diet and the adverse events experienced by patients.**
9. **Provide information regarding the number and frequency of adverse events depending on the dose of statin used with lomitapide.**
10. **In the efficacy evaluation please compare the efficacy of lomitapide with and without use of LDL apheresis. When reporting the change in lipid values, provide the length of time between last apheresis session and lipid level.**
11. **This is a standard table not designed specifically for the lomitapide development program, and therefore includes columns that may not be appropriate to lomitapide analyses. Modify the table to conform to the lomitapide NDA.**

**Please 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

<u>System Organ Class</u>	<u>Preferred Term</u>	<u>Pooled Placebo</u>	<u>Pooled Active Comparator</u>	<u>All Pooled Comparator</u>	<u>All Pooled Study Drug Doses</u>	<u>Pooled Study Drug Dose A</u>	<u>Pooled Study Drug Dose B</u>	<u>Pooled Study Drug Dose C</u>	<u>Pooled Study Drug Dose D</u>	<u>etc (column for each Study Drug dose studied)</u>
			<u>N=</u>		<u>N=</u>	<u>N=</u>	<u>N=</u>	<u>N=</u>	<u>N=</u>	
		<u>N=</u>	<u>n (%)</u>	<u>N=</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	
		<u>n (%)</u>		<u>n (%)</u>						

Table X: Incidence of All Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

<u>System Organ Class</u>	<u>Preferred Term</u>	<u>Pooled Placebo</u>	<u>Pooled Active Comparator</u>	<u>All Pooled Comparator</u>	<u>All Pooled Study Drug Doses</u>	<u>Pooled Study Drug Dose A</u>	<u>Pooled Study Drug Dose B</u>	<u>Pooled Study Drug Dose C</u>	<u>Pooled Study Drug Dose D</u>	<u>etc (column for each Study Drug dose studied)</u>
		<u>N=</u>	<u>N=</u>		<u>N=</u>	<u>N=</u>	<u>N=</u>	<u>N=</u>	<u>N=</u>	
		<u>n (%)</u>	<u>n (%)</u>	<u>N=</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	
		<u>n (%)</u>		<u>n (%)</u>						

N = number of patients in dose group

n = number of patients who experienced a given event

Source: (link to dataset)

12. Consider meeting with the primary reviewers to demonstrate maneuvering through the electronic submission. 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.

13. To assist the clinical reviewer in selecting sites for inspection, please include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator

- 3. Location: City State, Country**
- 4. Number of subjects screened**
- 5. Number of subjects randomized**
- 6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites**
- 7. Number of protocol violations (Major, minor, definition)**
- 8. Financial disclosure information for each investigator**

## Appendix A

The NDA will be reviewed utilizing the CDER Clinical Review Template. To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

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. **Section 6.1.8 Analysis of clinical information relevant to dosing recommendations**
4. **Section 6.1.9 Discussion of persistence of efficacy and/or tolerance effects**
5. **Less common adverse events (between 0.1% and 1%).**
6. **Section 7.4.2 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.**
7. **Section 7.4.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.**
8. **Section 7.4.2 - Marked outliers and dropouts for laboratory abnormalities.**
9. **Section 7.4.3 - Analysis of vital signs focused on measures of central tendencies.**
10. **Section 7.4.3 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.**
11. **Section 7.4.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.**
12. **Section 7.4.4 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.**
13. **Section 7.4.4. – Standard analyses and explorations of ECG data.**
14. **Section 7.6.4 – Overdose experience.**
15. **Section 7.5.1 - Explorations for dose dependency for adverse findings.**
16. **Section 7.5.2 - Explorations for time dependency for adverse findings.**
17. **Section 7.5.3 - Explorations for drug-demographic interactions.**
18. **Section 7.5.4 - Explorations for drug-disease interactions.**
19. **Section 7.5.5 - Explorations for drug-drug interactions.**
20. **Section 7.5.5 - Dosing considerations for important drug-drug interactions.**
21. **Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.**

**ISSUES REQUIRING FURTHER DISCUSSION**

None

**ACTION ITEMS**

None

**ATTACHMENTS AND HANDOUTS**

Division of Scientific Investigations (DSI) documents pertaining to the future NDA submission

Division of Scientific Investigations has two types of requests for data to be submitted to the NDA in preparation for clinical site and sponsor inspections; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

**I. Request for general study related information and specific Clinical Investigator information**

A. Please include the following information in a tabular format in the original NDA for each of the pivotal Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for each of the pivotal Phase 3 clinical trials:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for each of the pivotal Phase 3 clinical trials:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

**II. Request for Site Level Data**

1. For each site in the pivotal clinical trials: Name of primary investigator, accurate address and phone number, e-mail contact
2. For each pivotal trial: Sample blank CRF with annotations
3. For each pivotal trial: Site-specific individual subject data ("line") listings from the datasets:
  - a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Line listings by site and subject, of treatment assignment (randomization)
  - c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
  - d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable

- e. Line listings by site and subject, of AEs, SAEs, deaths and dates
- f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
- h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
- i. Line listings by site and by subject, of laboratory tests performed for safety monitoring

**III. Request for Individual Patient Data Listings format:**

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application.

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# Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

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## **I. INTRODUCTION**

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

## **II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET**

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

- 
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
  - Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR”.

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

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### **III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)**

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

**Exhibit 1: Summary Level Clinical Site Data Elements**

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: General Structure of Data Submission Template

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATI JOHNSON  
07/05/2011



IND 50820

MEETING MINUTES

(b) (4)

Agent for Aegerion Pharmaceuticals

(b) (4)

Dear

(b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lomitapide.

We also refer to the meeting between representatives of your firm and the FDA on April 5, 2011. The purpose of the meeting was to discuss the CMC development history and currently available CMC information prior to an NDA submission.

A copy of the official minutes of the April 5, 2011, 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 Khushboo Sharma, Regulatory Project Manager/me at (301)796-1270.

Sincerely,

*{See appended electronic signature page}*

Eric Duffy, Ph.D.  
Division Director  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

<b>Sponsor Name:</b>	Aegerion Pharmaceuticals, Inc.
<b>Application Number:</b>	IND 50,820
<b>Product Name:</b>	Lomitapide (AEGR-733)
<b>Meeting Requestor:</b>	Aegerion Pharmaceuticals, Inc.
<b>Meeting Type:</b>	Type B
<b>Meeting Category:</b>	Pre-NDA CMC Meeting
<b>Meeting Date and Time:</b>	Tuesday, April 05, 2011 1:30-2:30pm EST
<b>Meeting Location:</b>	Food and Drug Administration, White Oak Campus, Silver Spring, MD
<b>Received Briefing Package</b>	March 05, 2011
<b>Meeting Chair:</b>	Eric Duffy, Division Director
<b>Meeting Recorder:</b>	Khushboo Sharma, Regulatory Project Manger (ONDQA)

**FDA ATTENDEES:**

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Eric Duffy, Division Director  
Ali Al Hakim, Branch Chief  
Suong Tran, CMC Lead  
Olen Stephen, Chemist  
John Duan, Biopharmaceutics Reviewer  
Steven Hertz, Consumer Safety Officer  
Khushboo Sharma, Regulatory Project Manager

**EXTERNAL ATTENDEES:**

Martha Carter, CRO & SVP  
Marc Anderson, Principal  
Barry Dvorchik, Consulting Pharmacologist  
Sean Evans, CMC

(b) (4)

Ron Vladyka, Ex. Director Manufacturing  
Cathy Walker, Manager RA

**1.0 Discussion**

**Lomitapide Active Pharmaceutical Ingredient (API)**

- 1 The extent of characterization works available for lomitapide API and planned for inclusion in the NDA are summarized in Sections 10.1.2 and 10.1.5. Does the FDA concur that lomitapide API will be sufficiently characterized to support commercial drug registration?

*FDA Preliminary Response: The methods and scope of your characterization studies appear to be sufficient. Note that the data will be reviewed at the time of NDA submission for adequacy.*

*Meeting Discussion: None*

- 2 The synthesis of lomitapide API is summarized in Section 10.1.4. Does the FDA concur that our proposed strategy will provide sufficient information in the NDA to support commercial drug registration?

*FDA Preliminary Response: Your proposed synthetic scheme that includes defined starting materials and isolated intermediates appears sufficient for filing the NDA. Additional questions may be raised in the review process, however.*

*Meeting Discussion: None*

- 3 Aegerion plans to validate lomitapide API synthesis steps (b) (4) in Figure 1, designating as regulatory starting material (b) (4) as shown in Figure 1 and Figure 2 and listed in Section 10.1.4.3. Does the FDA concur with this validation approach and the designation of these compounds as regulatory starting materials for the commercial batch production?

*FDA Preliminary Response: Your proposed validation plans and defined starting materials appear appropriate. Note that degradation pathways and impurity mapping will be helpful in assessing starting material and intermediate acceptance criteria as well as drug substance/drug product specifications. For example, drug substance process impurities may impact starting material acceptance criteria if the process impurity is traced back to its starting material source. While we do not agree to the starting materials at this time, your choice appears reasonable.*

*Meeting Discussion: The sponsor needed clarification on the last sentence of the preliminary response, as the agency stated that the starting material choice is reasonable, but we do not agree to it.*

*The agency made the clarification that full stability data needs to be reviewed prior to making a formal agreement on the starting material. Given the data in the briefing package, the starting material choice is reasonable; however, a formal agreement cannot be made at this time.*

- 4 In Section 10.1.4.3, Aegerion has presented provisional specifications for the proposed regulatory starting materials as well as a strategy for finalizing these specifications for commercial batch production. Is the FDA in agreement with the proposed specifications and strategy for the regulatory starting materials?

*FDA Preliminary Response: Refer to response 3.*

*Meeting Discussion: None*

- 5 Aegerion has proposed to isolate (b) (4) intermediates during the synthesis of lomitapide API. The provisional specifications for these isolated intermediates and the strategy for finalizing specifications for commercial batch production are presented in Section 10.1.4.4. Is the FDA in agreement with the proposed specifications and strategy for the isolated intermediates?

*FDA Preliminary Response: Refer to response 3.*

*Meeting Discussion: None*

- 6 An alternative validation option has been considered whereby Aegerion would designate intermediates (b) (4) as regulatory starting materials for the validation / commercial batches (see Figure 1). (b) (4)

Providing (b) (4) suitable specifications are established for (b) (4), what is the FDA's current philosophy on an approach whereby only synthesis (b) (4) would be validated and (b) (4) would be designated as the regulatory starting materials for commercial production of lomitapide API?

*FDA Preliminary Response: (b) (4) do not meet our current criteria for starting materials. Specifically, these proposed starting materials are (b) (4)*

*We note that you propose these compounds as controlled intermediates. Hold-time studies and forced degradation studies may enable you to develop an enhanced list of specifications and justified hold time that may fit your marketing and production needs.*

*Meeting Discussion: None*

- 7 Are the proposed lomitapide API release and stability specifications and strategy to establish additional specifications as set forth in Section 10.1.7 acceptable to the FDA?

*FDA Preliminary Response: In general the specifications look appropriate. Note that the (b) (4) degradant (b) (4) may also be appropriate for these specifications. Furthermore, for specified impurities, identification and qualification thresholds should follow ICH Q3B. Specification limits will be established with regard to toxicity results, stability data, and manufacturing capabilities as described in your meeting package. Forced degradation studies may also support your proposed specifications.*

*Meeting Discussion: None*

- 8 Aegerion proposes to use (b) (4) API to manufacture lomitapide drug product. (b) (4) is planned to be included in the next 2 API registration batch campaigns to ensure the (b) (4). This plan, existing particle size data, and the rationale for inclusion of this control are presented in Section 10.1.8.3. Further discussion on how Aegerion will determine if a specification for particle size is necessary for the API is also presented. Does the Agency agree with this approach?

*FDA Preliminary Response: In general, your proposal to use of (b) (4) drug substance may be appropriate. At the time of filing, you should present pharmaceutical development data that demonstrates no effect on drug product critical quality attributes as a function of the (b) (4) drug substance. For instance, (b) (4) content uniformity data for the lomitapide (b) (4) may demonstrate that the (b) (4) process is insensitive to the drug substance particle sizes used in those batches. As you planned, the dissolution behavior of the drug product will be obtained in different pH's to examine the influence of particle size on the performance of the drug product. We have the following recommendations: 1) The f2 factor or other appropriate methods should be used when dissolution profiles are compared; 2) The dissolution methodology should be justified (see Response for Question 19).*

*Meeting Discussion: None*

- 9 Aegerion proposes to place 3 registration batches of lomitapide API on stability (see Section 10.1.6, Section 10.1.9, Section 10.1.10 and Section 10.3.1). Two (2) of these lomitapide API registration batches have not yet been manufactured. Does the FDA accept batch 1 ((b) (4) Lot L0109571) as our 1st registration batch, along with the additional 2 batches to be manufactured and the supporting stability data from the clinical and developmental API batches as sufficient batch data to support a commercial registration and expiry dating of lomitapide API?

*FDA Preliminary Response: The current batch data is sufficient to support filing. However, the adequacy of the data to support NDA approval will be determined upon review. We note that the current registration batch has (b) (4). Are there any plans to address this in the future? As noted above, forced degradation studies (heat, moisture, oxidative, acidic, alkaline conditions) will be necessary to support this approach of limited manufacturing and stability data.*

*Meeting Discussion: The sponsor elaborated that force degradation studies were performed on the drug substance as part of the validation for the analytical methods.*

However, they needed our opinion on whether the [REDACTED] (b) (4) specification was appropriate.

The agency clarified that even though [REDACTED] (b) (4) guidelines, they were high compared to other products seen. Therefore, the clinical team would need to weigh in on the decision for [REDACTED] (b) (4) specifications.

- 10** Is the proposed registration batch stability protocol and stability plan for lomitapide API in Section 10.1.9.3 acceptable to the Agency?

*FDA Preliminary Response:* Your general plan for the drug substance stability protocol is acceptable. We acknowledge your hypothesis that the [REDACTED] (b) (4) degradant seen in historical stability data is [REDACTED] (b) (4). As noted above, forced degradation studies on the drug substance will augment the stability data you intend on submitting.

*Meeting Discussion:* None

- 11** Does the Agency agree with the paced validation approach proposed in Section 10.1.10 to minimize waste of this low volume orphan drug by avoiding manufacture of too much product at one time, which may expire prior to being consumed by the patient population?

*FDA Preliminary Response:* Refer to question 22 for feedback on the proposed validation approach.

*Meeting Discussion:* The sponsor wanted to know what approach they could use so that the agency would agree to the validation strategy.

The agency explained that the master validation protocol should be submitted in the NDA. Additionally, the validation protocol should also be mentioned in the cover letter which directs the reviewer to the appropriate section

- 12** Given the anticipated low volume needs for this orphan drug, does the FDA agree with the market application plans for lomitapide API as described in Section 10.3.1?

*FDA Preliminary Response:* Refer to question 20 for feedback on the proposed market application plans.

*Meeting Discussion:* None

- 13** Are there any additional issues concerning lomitapide API which need to be resolve prior to submission of the NDA?

*FDA Preliminary Response:* We have no further comments at this time.

*Meeting Discussion:* None

- 14** Does the Agency have any additional feedback with respect to the lomitapide API?

*FDA Preliminary Response: We remind you that, in accordance with Good Review Management Principles and Practices (GRMPPs) timelines, a complete NDA should be submitted for filing, and we cannot guarantee that we will review unsolicited amendments such as stability updates even if the content of those amendments may impact regulatory specifications and re-tests dates.*

*Meeting Discussion: None*

### **Lomitapide Drug Product (Capsules)**

- 15** Does the FDA agree that, based on the consistency with the 5 and 20 mg strengths of lomitapide drug product and the proposed registration batch stability program (see Section 10.2.12), the information regarding the 10 mg strength of lomitapide drug product planned for inclusion in the NDA submission is adequate to support a decision of approvability?

*FDA Preliminary Response: We agree that your current plans would provide sufficient information for filing the NDA. Adequacy of the information to support marketing of the 10 mg strength will be determined on review. We suggest that you provide the following data (if available) to support the 10 mg dose strength.* <sup>(b) (4)</sup>

*Additionally, provide a biowaiver request for the 10 mg dosage strength or clarify that this strength will be included in the clinical studies.*

*Meeting Discussion: The sponsor is planning on adding 10 mg strength; however it is not being studied in the clinic. Additionally, the product meets the solubility criteria for BCS class I product; but the permeability studies have not been performed yet. Therefore, the sponsor needed clarification from the agency regarding their option for a biowaiver. The Agency stated that if the sponsor feels that the product meets the criteria for BCS Class I, then they should submit the data according to the BCS guidance as an amendment to the IND as soon as possible because a designation of BCS Class I needs approval by the BCS committee. The committee will review the data and provide the appropriate class designation.*

*On the other hand, if there is not enough information to support a BCS Class I designation, then the sponsor can submit a biowaiver request by bracketing the 10 mg strength with the 5 mg and 20 mg and providing data to show the composition similarity and dissolution profile similarity.*

- 16** Does the FDA agree that the available 5 mg and 20 mg capsule data will be supportive of the 10 mg strength at the time of NDA submission and that the commitment to assess three registration batches of the 10 mg product on stability will be sufficient to support registration (see Section 10.2.12.5)?

*FDA Preliminary Response: At least one registration batch for the 10 mg dose strength will be required for filing. Again, in accordance with GRMPPs timelines, a complete NDA should be submitted for filing, and we cannot guarantee that we will review unsolicited amendments such as stability updates.*

*Meeting Discussion: None*

- 17** Does the FDA concur with the proposed lomitapide drug product registration batch sizes and the plan to manufacture 3 registration batches of each drug product strength using lomitapide API Registration Batches 2 and 3 (see Section 10.2.12.5)?

*FDA Preliminary Response: This proposal is acceptable.*

*Meeting Discussion: None*

- 18** Does the FDA agree that the manufacturing strategy for the first 2 registration batches of lomitapide capsules, 5 and 10 mg, and the 3rd registration batches manufactured as validation batches as described in Section 10.2.12.5 provides the necessary information on the process to support manufacture of commercial lots?

*FDA Preliminary Response: since the 5 mg and 10 mg dose strengths are manufactured from (b)(4) of the proposed commercial scale, your proposal to manufacture the first 2 registration batches of each dose strength from (b)(4) is acceptable. Content uniformity and assay testing (with stratified sampling throughout the filling run) for the first two registration batches should be submitted that demonstrates there are no complications with filling the different capsule sizes.*

*Meeting Discussion: None*

- 19** Are the proposed lomitapide drug product release and stability specifications and strategy to establish additional specifications as set forth in Section 10.2.7.1 acceptable to the FDA?

*FDA Preliminary Response: In general the specifications appear appropriate. Adequacy of these specifications will be determined during review.*

*The dissolution specification is not justified because no data has been provided. You need to provide a dissolution development report, in which the selection of the proposed apparatus, rotation speed, medium, volume of the medium, temperature and surfactant use are justified and all the data are provided including individual, mean, standard deviation and plots. In general, the proposed Q value (b)(4) and the time point of 60 minute may not be appropriate for an immediate release product. The use of surfactant should be justified regarding the necessity, the type, and the concentrations. You may submit the detailed justification with all supporting data as listed above in order to reach an agreement for the dissolution specification before you finalize the stability program.*

*Meeting Discussion: The sponsor asked for a clarification for the Agency's concern with the specification of Q (b)(4) at 60 mins, as it is stated to be the worst case scenario. The Agency stated that there was not enough data provided in the briefing package to support the proposed specification. The Agency suggested that the sponsor analyze their data and either revise the specification or provide a justification for the proposed specification. The sponsor is encouraged to submit their justification of specification for*

*dissolution as an amendment to the IND and provide a desk copy to Khushboo Sharma (Regulatory Project Manager).*

- 20** Aegerion proposes to place 3 drug product registration batches of each strength of lomitapide capsules on stability (see Section 10.2.12.5). Does the FDA agree that the combination of the planned registration batch stability data to be included in the NDA along with the extensive supporting stability data from the clinical and developmental drug product batches will be acceptable to support expiry dating of the drug product?

*FDA Preliminary Response: We acknowledge your plan to submit several years of supportive stability data for drug product encapsulated in larger sized capsules (Size 1). Comparability of these capsules with the proposed marketed presentation will be determined on review. Your intention to file the NDA with only 1 or 3 months of long term stability data on a single batch is not acceptable. You should file with at least 6 months long-term and 6 months accelerated stability data for at least one registration batch of the 5 mg and 20 mg dose strengths. Shelf life determination is generally determined according to ICH Q1E. Extension of expiry can be done post approval in accordance with an approved protocol; we recommend you provide a stability extension protocol. Refer to comments regarding the release specifications as these apply to stability specifications as well.*

*Meeting Discussion: The sponsor clarified that the reason for the proposing to file the NDA with only 1 or 3 month stability data is due to the EOP2 meeting that occurred last summer. During the meeting, the reviewer requested a 56 week follow up which put the stability program on a lag.*

*The agency suggested that the sponsor should provide the schedule of the stability program via email to Khushboo Sharma (Regulatory Project Manager). Additionally, the sponsor should mention this question again in the briefing document for the Pre-NDA clinical meeting on June 15, 2011, so that ONDQA can address this issue at that meeting after reviewing the schedule of the stability program internally.*

- 21** Are the proposed lomitapide drug product registration batch stability protocols in Section 10.2.12 acceptable to the FDA?

*FDA Preliminary Response: The proposed stability storage conditions and time intervals appears adequate. Refer to question 20 regarding the amount of stability data that will be required at filing.*

*Meeting Discussion: None*

- 22** Does the Agency agree with the paced validation approach being proposed in Section 10.2.12.5 to minimize waste of this low volume orphan drug by avoiding manufacture of too much product at one time, which may expire prior to being consumed by the patient population?

*FDA Preliminary Response: Based on the information submitted in the meeting package, the FDA can not make an evaluation of the acceptability of the validation approach at this time. While the agency does not approve, disapprove or grant "the ability to release" batches concurrently, products granted orphan drug status are recognized in situations where potentially the distribution of any given lot before completion of the*

*initial process qualification study may be justified. Your criteria for batch release for this situation and a final determination of acceptability will be made on the totality of data and justification submitted in the NDA and on a pre-approval inspection.*

*Meeting Discussion: None*

- 23** Given the anticipated low volume needs for this orphan drug, does the FDA agree with the market application plans for drug product as described in Section 10.3.2?

Revised Question:

Given the anticipated low volume needs for this orphan drug, does the FDA agree with the proposed submission approach, as discussed in Section 10.3.2, to include 1 month (possibly 3 months) of real-time and accelerated stability data on one registration batch of each strength of lomitapide drug product in the NDA at the time of submission? Stability data on this registration batch as well as on two additional registration batches of each strength to be manufactured will continue to be collected and will be submitted in Annual Reports to support expiration dating or made available if requested by the FDA.

*FDA Preliminary Response: Refer to question 20 for feedback on stability data necessary for filing the NDA.*

*Meeting Discussion: None*

- 24** Are there any additional issues concerning lomitapide capsules which need to be resolved prior to submission of the NDA?

*FDA Preliminary Response: We have no other immediate concerns at this time.*

*Meeting Discussion: None*

- 25** Does the Agency have any additional feedback with respect to the lomitapide drug product?

*FDA Preliminary Response: Clarify whether you will submit a biowaiver request for the 10 mg dosage strength or that this strength will be included in the clinical studies. Again, in accordance with GRMPPs timelines, a complete NDA should be submitted for filing, and we cannot guarantee that we will review unsolicited amendments such as stability updates even if the content of those amendments may impact regulatory specifications and re-tests dates.*

*Meeting Discussion: None*

## 2 ACTION ITEMS

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
1. The sponsor is recommended to submit 10 mg strength dosing data to the BCS designation committee prior to NDA submission as an amendment to the IND	Aegerion	Prior to NDA submission
2. The sponsor is encouraged to submit their justification of specification for dissolution as an amendment to the IND and provide a desk copy to Khushboo Sharma (Regulatory Project Manager).	Aegerion	Prior to NDA submission
3. The sponsor is requested to submit the schedule of the stability program via email to Khushboo Sharma (Regulatory Project Manager)	Aegerion	Prior to the clinical Pre-NDA meeting (June 15, 2011).

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ERIC P DUFFY  
04/12/2011



IND 50820

**MEETING MINUTES**

Aegerion  
Attention: William Sasiela, PhD  
Chief Medical Officer  
Center Pointe IV  
1140 Route 22 East, Suite 304  
Bridgewater, NJ 08807

Dear Dr. Sasiela:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lomitapide (AEGR-733).

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on May 17, 2010. The purpose of the meeting was to your proposed plans for Phase 3 development.

We also refer to the July 28, 2010 teleconference to discuss the feasibility of your proposal to submit an NDA limited to the HoFH patient population.

A copy of the official minutes of these interactions 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 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** End-of-Phase 2 (EOP2)  
**Meeting Date and Time:** Monday, May 17, 2010, 11 am – 12 noon  
**Meeting Location:** FDA White Oak Campus, Bldg. 22, Conference Rm. 1313

**Application Number:** IND 50820  
**Product Name:** Lomitapide (AEGR-733)  
**Indication:** Hypercholesterolemia  
**Sponsor/Applicant Name:** Aegerion

**Meeting Chair:** Eric Colman, MD  
**Meeting Recorder:** Kati Johnson

**FDA ATTENDEES**

Division of Metabolism & Endocrinology Products

Eric Colman, MD-Deputy Director, Lipid Team Leader  
Mary Roberts, MD-Clinical Reviewer  
Tim Hummer, PhD-Pharmacology/Toxicology  
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology

Sally Choe, PhD-Team Leader  
Ritesh Jain, PhD-Biopharm Reviewer

Office of Translational Sciences, Office of Biostatistics

Todd Sahlroot, PhD-Deputy Director, Division of Biometrics II  
Cynthia Liu-Statistician

**SPONSOR ATTENDEES**

Aegerion Pharmaceuticals, Inc.

William Sasiela, PhD-Chief Medical Officer  
Will Lewis-President  
Christine Pellizzari-General Counsel

(b) (4)

Barry Dvorchick, PhD-Clinical Pharmacology Consultant  
Joseph Costa, PhD-Toxicology Consultant

## **1.0 BACKGROUND**

Lomitapide is an MTP inhibitor currently under development for the treatment of HeFH (IND 50820) and HoFH (IND 77775). Lomitapide was granted orphan designation for the HoFH indication on October 23, 2007. The firm requested this meeting on March 23, 2010 to discuss non-CMC development issues.

This application was initially sponsored by Bristol Myers Squibb, then Daniel Rader, MD (University of Pennsylvania), and now Aegerion (as of April 13, 2007). Previous meetings with the various sponsors include the following:

**-February 7, 2007**-EOP2 meeting with Dr. Rader (minutes issued February 23, 2007)

-An EOP2 meeting was scheduled for August 12, 2009, however during the internal pre-meeting it was determined that this was premature. In lieu of a meeting, there was an **August 10, 2009** telephone conversation to discuss some lingering issues. When the firm committed to providing the carcinogenicity study results in early October, the EOP2 meeting was rescheduled for November 9, 2010.

**-November 9, 2010**-EOP2 (minutes issued January 5, 2010)-the firm indicated that the development program would focus on HeFH and HoFH. The agency cited the issues that require continued attention/discussion: mouse carcinogenicity data (malignant tumors in the small intestine and liver at high doses), pulmonary phospholipidosis (now less of a concern given the number of approved products with this finding) and hepatic steatosis. In response to our request, the sponsor compiled a concise document of their updated development plans (submitted May 27, 2010)

The firm was issued preliminary responses to their questions on May 13, 2010.

### **May 17, 2010 meeting**

The background package stated that the sponsor would be pursuing both the HoFH and the severe, refractory HeFH indications. However, at the meeting, the firm said that, due to financial constraints, they are currently pursuing submission of an NDA solely for the HoFH population. The ongoing Phase 3 study for this indication has completed enrollment with 29 patients.

In response to a question, the firm surmised that approval of the drug in this small population would show potential investors that the drug is efficacious and could facilitate the availability of additional funds to conduct trials for a broader population, in addition to the cardiovascular outcomes study that would likely be required.

They recognized that any entry into the market would open the door for unauthorized prescribing, and were amenable to whatever postapproval supply constraints were necessary to ensure that the drug was available only to the HoFH population. The agency voiced the concern that this development proposal would be viewed as acceptable by any sponsor of an LDL-lowering compound.

The firm was requested to compile a document with their proposed contents for the future NDA submission. The agency would meet with management to determine the feasibility of this approach and discuss it with the firm in a teleconference. This information was submitted

May 27, 2010.

**July 28, 2010 Teleconference**

Attendees:

Division of Metabolism & Endocrinology Products  
Eric Colman, MD-Deputy Director, Lipid Team Leader  
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology  
Sally Choe, PhD-Team Leader  
Ritesh Jain, PhD-Biopharm Reviewer

**SPONSOR ATTENDEES**

Aegerion Pharmaceuticals, Inc.  
William Sasiela, PhD-Chief Medical Officer  
Will Lewis-President

(b) (4)

The sponsor was notified that the agency was not opposed to an NDA being submitted for this indication. At the time of submission, all patients will have been treated for a minimum of 56 weeks. This was found acceptable by the agency. The firm estimated that the NDA would be submitted in 3Q 2011. Discussion of the application at an Advisory Committee meeting is highly likely.

The preliminary comments conveyed to the firm included nonclinical, clinical and clinical pharmacology comments. The clinical pharmacology comments are repeated below (the questions numbers have been kept the same), followed by some additional comments made during the teleconference:

“3. Does the Division agree that the fed/fasted study and the design of the dosing regime in the Phase 3 studies support the proposed labeling for administration?”

**FDA Preliminary Response: Your proposed label says (b) (4)  
(b) (4) However, based on the submitted Phase 3 protocol, it is unclear how lomitapide will be administered with respect to meals in the Phase 3 trial. Please clarify the dosing of Lomitapide with respect to meals.**

4. Does the Division agree with the outline of the proposed human plasma metabolite isolation and identification study?

**FDA Preliminary Response: Your proposal appears acceptable.**

5. Does the Division agree that the relevant potential drug drug interactions for indications within the FH patient populations are addressed?

**FDA Preliminary Response: Your drug-drug interaction plan seems appropriate. However, we would like to remind you that the following concerns from the previous correspondences still stand:**

- a) *In vivo* DDI study to investigate the effect of lomitapide on the pharmacokinetics and pharmacodynamics of warfarin should be conducted.
- b) You should investigate the inhibition/induction potential of the major metabolites such as M1 and M3, on major CYP enzymes in *in vitro* systems. Based on the *in vitro* results, you may need to investigate the effect of the metabolites *in vivo*.
- c) Multiple metabolites of lomitapide have been identified in *in vitro* studies. Also based on the *in vitro* metabolism studies in human liver microsomes (HLM), M8 (28.4%) is the most abundant metabolite. Please clarify the rationale for monitoring only M1, M2, and M3 in your Phase I clinical trials.

6. Does the Division agree with the design of the QT study?

**FDA Preliminary Response: Attachment 1 contains the information that must be submitted to the IND. It will then be consulted to the QT Interdisciplinary Review Team.**

7. Does the Division agree with the design of the study in hepatic impaired patients?

**FDA Preliminary Response: Yes, your proposal appears acceptable.**

8. Aegerion believes that for the HoFH and severe HeFH patient populations, that special population studies in the elderly and renal impaired patients are not needed. Does the Division agree?

**FDA Preliminary Response: We believe that a renal impairment study is necessary. A dedicated study in the elderly population is not required.”**

The following additional comments/concerns were conveyed to the firm. It was stressed that the lack of the requested information would not necessarily be a filing issue, but a review issue.

1. Drug-drug interaction (DDI) study with warfarin evaluated only the PK of warfarin. The pharmacodynamic parameters of warfarin (e.g., INR) should also be assessed.
2. Lomitapide seems to be a CYP3A4 substrate and therefore, impact of CYP3A4 inhibitor (e.g., ketoconazole) on lomitapide PK should be addressed.
3. Lomitapide appears to have a higher exposure in women than men.
4. The firm has conducted a DDI with simvastatin, however the study was conducted using 10 mg of lomitapide. Since the proposed clinical dose for HoFH is 60 mg, a study should be done using that dose. When the firm inquired as to whether this information could be gleaned from the Phase 3 study, the Agency stated that a separate dedicated study would be preferable.
5. If the formulation of the product to be marketed is different from that studied in the pivotal studies, additional clinical studies may be required. The firm stated that the formulation has remained constant throughout the Phase 3 program.

6. Since metabolites are found in higher concentrations than that of the parent compound, the impact of these metabolites on inhibition/induction of CYP isoenzymes should be addressed.
7. M8 seems to be one of the major metabolites. The sponsor should consider analyzing this metabolite in future clinical studies.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

### **4.0 ACTION ITEMS**

1. The firm will be sending in the protocol for their proposed QTc study for review and comment.
2. As there have been virtually no discussion of chemistry, manufacturing and controls (CMC) issues throughout the development of the compound, the sponsor will be asking for either a meeting or written responses in the near future.
3. The sponsor will be requesting a pre-NDA meeting to be held in 1Q 2011.

### **5.0 ATTACHMENTS AND HANDOUTS**

None

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/s/

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KATI JOHNSON  
09/28/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 50,820

Daniel Rader, MD  
University of Pennsylvania School of Medicine  
654 BRB II/III  
421 Curie Boulevard  
Philadelphia, PA 19104

Dear Dr. Rader:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-201038.

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2007. The purpose of the meeting was to discuss your Phase 3 program.

The official minutes of that teleconference 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) 796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Regulatory Project Manager  
Division of Metabolism & Endocrinology Product  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF TELECON MINUTES

**MEETING DATE:** February 7, 2007  
**TIME:** 12 noon – 1:00 pm  
**APPLICATION:** IND 50,820  
**DRUG NAME:** BMS 201038  
**TYPE OF MEETING:** Guidance

**MEETING CHAIR:** Eric Colman, MD

**MEETING RECORDER:** Kati Johnson

### **FDA ATTENDEES:**

#### Division of Metabolism and Endocrinology Products

Eric, Colman, MD-Deputy Director  
Amy Egan, MD-Clinical reviewer  
Karen Davis Bruno, PhD-Supervisory PharmTox  
Dylan Yao, PhD-PharmTox Reviewer  
Kati Johnson,-Project Manager

#### Office of Translational Sciences, Office of Clinical Pharmacology

Jim Wei, PhD-Biopharm Team Leader  
Sang Chung, PhD-Biopharm Reviewer

### **EXTERNAL CONSTITUENT ATTENDEES:**

#### **University of Pennsylvania:**

Daniel Rader, MDIND sponsor  
LeAnne Bloedon, MS, RD-Project Manager  
Marina Cuchel, MD, PhD-Principal Investigator, Protocols UP 1002 and AEGR-733-002  
Jeffrey Barret, PhD-Director, Laboratory for Applied PK/PD  
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#### **Office of Orphan Drug Products, FDA (funding source for protocol UP 1002)**

Dr. Debra Lewis-Director, Grants Program  
Dr. Henry Startzman-Team leader, medical officer  
Ms. Lisa Lawrence-new trainee  
Diane Centeno-Deshields-Grant Project Officer

#### **Aegerion Pharmaceuticals**

Bill Sasiella, Chief Medical Officer  
Joseph Costa, PhD- Toxicologist

### **BACKGROUND:**

IND# 50,820 was submitted June 18, 1996, by Bristol-Myers Squibb for the development of BMS-201038, a microsomal triglyceride transfer protein (MTP) inhibitor, as a lipid-lowering agent. In August 2002, the IND was transferred to Dr. Daniel Rader at the University of Pennsylvania. Dr. Rader was originally developing BMS-201038 for the treatment of homozygous familial hypercholesterolemia (FH). At one point, the sponsor proposed to change the population being studied to “severe refractory hypercholesterolemia”. In the November 29,

2006 meeting request document, the sponsor stated their intent to return to the homozygous FH population.

An EOP-2 meeting was previously held with the Sponsor in July 2004 to discuss the phase three clinical program.

#### **MEETING OBJECTIVES:**

To come to an agreement on the sponsor's pivotal trial for the treatment of homozygous familial hypercholesterolemia, an orphan indication.

#### **DISCUSSION POINTS:**

1. Sponsor Original Question: The phase III clinical trial is being funded with a grant from the FDA Office of Orphan Products Development (OOPD). After the grant was awarded, the sponsor decided to expand the patient population that will be studied from "homozygous familial hypercholesterolemia" to "severe refractory hypercholesterolemia". The rationale for this expansion is detailed in the document included (Rationale for the request to expand target population for the phase III clinical protocol by OPD grant 1 R01 FD003098 (MTP Inhibitor IND 50,820 in Familial Hypercholesterolemia - PI: Cuchel, Marina, MD, PhD). OOPD has asked us to confirm with the Division that the study described in the Phase III clinical protocol, if successful, will be considered to be a pivotal clinical trial for a new drug application under the new indication (treatment of severe refractory hypercholesterolemia). Does the Division agree that this is a pivotal clinical study that could potentially support approval for this orphan indication?

**Division Response: You are proposing to greatly expand the size of the target population – from the original orphan population of 290 patients with the homozygous FH to potentially 580,000 patients with the heterozygous FH in the U.S. alone. You claim that of the 580,000 heterozygotes, only 10,000 meet the definition for the severe refractory hypercholesterolemia as defined in the protocol, yet you do not provide any reference for this estimate. Regardless, such an expanded population would certainly dictate a pivotal trial of more than 36 patients, some of whom may be exposed to the maximum tolerated dose for as little as 34 weeks. The potential toxicity of this drug as well documented (hepatic and pulmonary phospholipidosis) and this expanded study population does shift the risk-benefit ratio. It is notable that the previous statin trials in pediatric populations with heterozygous FH enrolled between 173 and 214 patients. The Division believes that a sample size of 36 patients will be inadequate to provide the necessary safety data to support approval of this particular drug in the expanded population. Furthermore, the forced titration scheme may not allow adequate exposure to the maximum tolerated dose. Support for the safety of this particular drug in the expanded population would require an exposure in a subset of patients to the maximum tolerated dose for at least 12 months. Finally, it is not clear that you have adequately determined a dose or doses to be carried forward into this Phase III protocol. Is an individual mg/kg dosage to be utilized in the clinical setting? This forced titration scheme and the small number of subjects currently proposed for study may be inadequate in defining the minimum effective dose with a favorable safety profile.**

Sponsor Counter Response: We greatly appreciate the Division's detailed response. With regards to your question about the target population, we proposed to expand the target population for the phase III study to include subjects that meet the FDA approved criteria for LDL apheresis (as we defined as having "severe refractory hypercholesterolemia") because these patients, similarly to patients with homozygous FH, have great unmet medical needs and may benefit from this novel therapeutic approach. Unfortunately, we were unable to locate a published reference to provide the actual US incidence of patients with "severe refractory hypercholesterolemia". In speaking with [REDACTED] (b) (4), lipidologists and cardiologists throughout the United

States, as well as our own experience, our best estimate is that 1% (n=5,800) of patients with heterozygous FH do not achieve, when treated, LDL-C levels <300 mg/dl (or <200 mg/dl if coronary heart disease is present) or do not tolerate maximum pharmacological therapy. If we add to this number the number of patients with homozygous FH (approximately 290 people in the US), we estimate that approximately 6,090 subjects in the US would meet the definition of “severe refractory hypercholesterolemia”. We recognize that this calculation is based on estimates only and does not answer the requests of the Division and its concern of a shift in the risk-benefit ratio. Thus, we propose to only enroll patients with homozygous FH, as proposed in the original study design (submitted as serial No. 072 on January 24, 2006).

With regards to the Division’s question regarding sample size, we now propose to include 25 subjects diagnosed with homozygous FH who would all receive BMS-201038 with no placebo control at the maximum tolerated dose for a minimum of 52 weeks. In the response to question #4, the Division recommended that in the expanded population, all homozygous FH patients should be treated with active drug without a placebo group. We have modified the study design to remove the placebo group and include a 6 week run-in period on current lipid lowering therapy and a subsequent 6 week follow-up period so that each subject serves as his/her own control (this is also addressed under our counter response to question #4). The revised sample size is based on each subject serving as his/her own control and evaluating change in LDL-C (primary end point) from baseline. In protocol UP 1001, 4 weeks at 1 mg/kg (mean dose in 6 subjects was 67 mg) produced a mean % reduction in LDL-C of  $50.9 \pm 9.3\%$ . We predict in the phase III trial there will be greater heterogeneity based on various combinations of concomitant lipid-lowering therapies used and thus have used the following conservative assumptions in calculating sample size for the primary endpoint (% change in LDL-C at 26 weeks compared to baseline): a 25% change in LDL-C with a 30% standard deviation and 15% drop out rate. Based on these assumptions, using an  $\alpha$  of 0.05 and 90% power, we will need 20 subjects. In order to adequately assess safety, we propose to include 25 subjects (~9% of the US population with homozygous FH), which based on 80% power allows for the detection of 20% change in LDL-C with a standard deviation of 30% and 15% drop out rate. **Does the Division concur that the sample size and duration of therapy is adequate to assess efficacy and safety for this pivotal trial in patients with homozygous FH?**

*2/7/07 Response: The proposed sample size and duration of therapy should be adequate for the assessment of efficacy in the proposed population.*

*The duration of therapy should be adequate to assess the safety of the drug in the proposed population; however, the sample size assumes a relatively small drop out rate given the dosages that the sponsor is proposing using and the known GI and hepatobiliary toxicity of the agent, and given the 24% drop-out rate in your Study CV145-009 where BMS-201038 25 mg was administered for 4 weeks. The sponsor will be unlikely to achieve such a low drop out rate given the proposed dosages of 60-80 mg daily, and the proposed duration of 52 weeks.*

*The rationale behind proposing that all patients be exposed to treatment, i.e., that there be no placebo arm, was not to decrease the sample size, but rather to enhance the safety database, so it is unclear why the originally proposed sample size (36) was reduced to the current number (25).*

*The sponsor is also encouraged to include sufficient numbers of women and Asians in the study population given that the behavior and potential toxicity of the drug is likely be enhanced in these populations.*

Meeting Discussion: With regard to the anticipated dropout rate, the sponsor stated that Study CV145-009 did not include dietary counseling. They are planning counseling in this study, so they are hoping that the dropout rate will be less. The sponsor also explained that the sample size was decreased because there would be no patients receiving placebo, in addition to the anticipated difficulty in finding the patients within the United States. In enrolling 25 patients, they anticipate 20 completers.

With regards to the Division's question regarding determining an adequate dose or doses to be carried into the phase III protocol, from the data derived from protocol UP 1001, we believe that a dose titration design is essential in maximizing gastrointestinal tolerability and may positively affect the effects on the liver, which are intrinsically linked to the mechanism of action of BMS-201038. Unique to the orphan population of homozygous FH, we believe this drug will be used in the clinical setting by starting at a low dose and titrating up to the highest tolerated dose based on tolerability and safety end points. In protocol UP 1001, we used an individual mg/kg dose approach and started at 0.03 mg/kg/day and increased to a maximum of 1 mg/kg/day (weight range of 6 subjects was 56.1-85.4 kg with an average of 67 kg). We originally decided to adopt a weight based design in the phase III study to be used in the clinical setting. The rationale for this approach was to maximize efficacy while minimizing toxicity in this very high risk orphan population. After receiving the Division's response to question #1, we have carefully reviewed all available pharmacokinetic data on BMS-201038 to assess whether body weight and/or gender affects the Area under the Curve (AUC) or Maximum Concentration ( $C_{max}$ ) of the parent compound. While there is little rationale for such a correlation given the high degree of protein binding (99.8%) and the extensive metabolism that BMS-201038 undergoes, we have conducted both non-compartmental and population pharmacokinetic analyses to explore such effects. Indices of body size and/or body weight do not explain a significant portion of the variation in drug exposure suggesting that weight-adjusted dosing is not an added benefit to improve patient response to therapy. Based on these results and carefully reviewing all data from clinical studies investigating BMS-201038, we have revised the design to include fixed dosing for all subjects. The doses used remain the same, but all subjects will initiate study drug at 5 mg and titrate up to a maximum dose of 60 mg as tolerated for a minimum of 52 weeks. Based on the morbidity and mortality associated with homozygous FH and the probability that even 60 mg is unlikely to normalize LDL-C levels, we would like an allowance for subjects who meet the following specific safety and efficacy criteria to titrate to an absolute maximum of 80 mg. We propose that all of the following 3 criteria must be met in order for subjects to titrate to 80 mg:

- 1) ALT, AST and Total Bilirubin within normal range at visit 8 (through 4 weeks at 60 mg/d). Exception is given if total bilirubin is elevated due to confirmed Gilbert's syndrome or hemolysis with subsequent normal value;
- 2) Subjects of ideal body weight must not have weight loss  $\geq 3\%$  based on body weight measured at any visit during visits 4-8 compared to visit 3 (baseline visit);
- 3) LDL-C must be  $> 200$  mg/dL at visit 8

Study drug will be reduced or discontinued based on safety end points as explained in Section 13.4 of the clinical protocol at any dose throughout the study.

#### **Does the Division agree with the revised design?**

2/7/07 Response: The Division concurs with a dose titration scheme to enhance tolerability. However, the proposed dosages do not provide adequate safety margins for the calculated NOAEL for pulmonary phospholipidosis. While the Division agrees that the patient population being proposed for study by the sponsor is a unique, high risk population whose risk for adverse cardiovascular events may justify treatment with BMS-201038 and assumption of risk for hepatic fat accumulation and pulmonary phospholipidosis, the Division will require that the Informed Consent document be updated to include information regarding the latter toxicity. Furthermore, the Informed Consent document should advise subjects that pulmonary phospholipidosis is a potential adverse event that is not readily "monitorable" in the clinical setting.

With respect to the pre-set safety end points, we recommend revision of the discontinuation of BMS-201038 criteria to include:

- Pregnancy
- Any one of the grade 3 or 4 hepatotoxicity adverse events
- Any adverse event which, in the opinion of the investigator, places the patient at increased risk.
- A liver biopsy meeting the histopathological definition of steatohepatitis.

Meeting Discussion: The sponsor agreed to both points: the requested revisions to the Informed Consent document and the revised study discontinuation criteria.

2. Sponsor Original Question: During the EOPII teleconference in July 2004, the Agency requested that at least one pharmacokinetic (PK) interaction study with a known potent p450 CYP3A4 substrate (simvastatin or atorvastatin) must be conducted prior to the Phase III study initiation and stated that other PK interaction studies can be conducted concurrently with the Phase III study (“...a PK interaction study with simvastatin [simvastatin or atorvastatin referenced in additional text] must be conducted prior to study initiation as this statin is exclusively metabolized by CYP3A4. Other PK interaction studies can be conducted concurrently with Phase 3 trial including studies using lipid-altering drugs that have approved indications for use in hoFH (e.g. atorvastatin, rosuvastatin and ezetimibe) as there is a potential for combination therapy in clinical practice.”).

A full clinical protocol describing a drug-drug interaction study to investigate the PK interactions of BMS-201038 when co-administered with 5 lipid lowering agents is currently filed under IND 50,820 and includes 5 distinct arms, one for each of 5 lipid lowering drugs (atorvastatin, simvastatin, pravastatin, ezetimibe and fenofibrate). PK analysis will be conducted at the end of each arm. The sponsor proposes to provide the Division with 2 preliminary clinical reports and a final report describing the data. A report will be submitted to the Division after each of the first 2 arms (atorvastatin and simvastatin) are completed and then a final report describing all data obtained as part of the study. Data in the 2 draft reports will be edited and checked under standard quality assurance operating procedures prior to submission to the Division. The sponsor proposes to contact the Division 30 days after each of the preliminary reports is received by the Division to confirm the approval to enroll subjects taking the lipid lowering medication studied in the provided report (atorvastatin or simvastatin). Because pravastatin, ezetimibe, and fenofibrate are not metabolized by CYP3A4 to a clinically significant extent, the sponsor proposes to enroll subjects taking these medications into the phase III study concurrently with the PK study investigating these medications. Does the Division concur with the plan as outlined above?

**Division Response: We agree with your plan to enroll subjects taking pravastatin, ezetimibe and fenofibrate in the phase III trial. However, the dose of 10 mg BMS-201038 is not acceptable for the drug/drug interaction study. To evaluate the maximum effects of BMS-201038 on the pharmacokinetics of these drugs, the highest proposed BMS-201038 dose of 80 mg/day for the Phase III trial should be used. To evaluate the pharmacokinetics of the ezetimibe, we recommend that you measure free ezetimibe, ezetimibe glucuronide, and total ezetimibe (free ezetimibe plus ezetimibe glucuronide).**

Sponsor Counter Response: We agree with the Division to measure free ezetimibe, ezetimibe glucuronide and total ezetimibe in ezetimibe-treated subjects and have added this to the revised protocol. We also agree with the Division that we need to conduct drug-drug interaction studies using higher dose of BMS-201038. Based on the revised phase III design, we propose to use 60 mg as the high dose instead of 80 mg as we anticipate < 10% of subjects in the phase III trial meeting criteria to titrate to 80 mg per day. The rationale is based on data from protocol UP 1001 and protocol CV145-002 which suggest doses at 85 mg (UP 1001) and 100 mg (CV145-002) are not well tolerated and associated with gastrointestinal intolerability. We propose to study the PK profile of 80 mg with a population PK study spare sampling approach imbedded in the Phase III study. For this purpose we modified the design of the phase III study to include a population PK study as secondary endpoint. This will be an integral part of the PK evaluation

of this drug in the target population, allowing the collection of information on the effect of dose, patients' weight and gender, concomitant medication etc.

We propose to study the effects of BMS-201038 at 60 mg on the pharmacokinetics of atorvastatin 20 mg and rosuvastatin 20 mg (15 subjects per arm) using the same design detailed in the current PK drug interaction study. The rationale for choosing atorvastatin and rosuvastatin is to use the 2 statins that are more frequently used in patients with homozygous FH. Further, we propose to not study ezetimibe or fenofibrate at higher doses of BMS-201038 if pharmacokinetic data from the drug-drug interaction study reveals no significant change in AUC or  $C_{max}$  and thus use these medications in the phase III trial. Both of these medications are not known to be metabolized by CYP3A4. Finally, we recognize the implications of this design on the labeling, i.e. specific information will need to be included about the pharmacokinetic effects of individual lipid lowering medications at specific doses.

2/7/07-We strongly recommend including simvastatin in addition to atorvastatin and rosuvastatin for the effect of BMS-201038 at 60mg on 3A4 metabolism.

Meeting Discussion: Dr. Rader stated that this study has already been conducted. Based on this information, the Agency said that we would extrapolate information from a previously conducted study of patients on BMS-201038 who were also taking atorvastatin.

3. Sponsor Original Question: The sponsor is not proposing to evaluate rosuvastatin in the formal PK study. In vitro and in vivo data reveal that clearance of rosuvastatin is not dependent on metabolism by 3A4 to a clinically significant extent confirmed by studies with ketoconazole, erythromycin, and itraconazole. If data from the PK study reveals that pharmacokinetics of atorvastatin and simvastatin are not significantly affected by coadministration of BMS-201038, the sponsor proposes to allow enrollment of subjects being treated with rosuvastatin into the phase III study beginning 30 days after both preliminary reports (atorvastatin and simvastatin) have been received. Does the Division agree?

**Division Response: No. We agree with your plan to allow enrollment of subjects being treated with rosuvastatin in to the phase III study. However, it should be noted that the pharmacokinetics of rosuvastatin may be affected through other mechanisms including the inhibition of organic anion transporting polypeptide C (OATP-C). Due to the potential for combination therapy in clinical practice, a PK interaction study with rosuvastatin needs to be conducted. This study can be included in the planned drug-drug interaction study and conducted concurrently with the phase III trial.**

Sponsor Counter Response: Rosuvastatin 20 mg has replaced pravastatin 20 mg in the drug-drug interaction study currently conducted. As explained in our counter-response to question #2, we are planning to study the interaction of BMS-201038 60 mg with atorvastatin and rosuvastatin, both at 20 mg. **Does the Division concur?**

2/7/07 Response: Yes

Meeting Discussion: none

**Additional comments by the Division:**

1. **During the EOP2 meeting, the agency asked you to provide information on the metabolic enzyme responsible for the test drug (the substrate of which enzyme for metabolism) or conduct a study to evaluate it. You are urged to submit the information and discuss with the agency whether the data indicates the need for additional drug-drug interaction studies.**

Sponsor Response: We agree with the Division for the need to conduct a study to evaluate the metabolic enzyme(s) responsible for BMS-201038. We propose to conduct a study to evaluate this question to be initiated concurrently with phase III. **Does the Division agree?**

2/7/07 Response: *We strongly recommend that this be done prior to initiation of Phase 3.*

Meeting Discussion: The sponsor agreed.

- 2. You pointed out that BMS-201038 may interact with the anti-coagulant, warfarin. It was found that two subjects in protocol UP1001 who were receiving warfarin had increases in International Normalized Ratio (INR) values which required adjustments to their warfarin dosage. Thus, a PK/PD drug-drug interaction study with warfarin is highly recommended.**

Sponsor Response: Based on the fact that the two subjects who received warfarin in the UP-1001 study experienced an increase in International Normalized Ratio (INR) while receiving BMS-201038, and that the compound is highly protein-bound, we recognize that there is likely an interaction between warfarin and BMS-201038. Because standard clinical care mandates regular monitoring of INR to assess warfarin therapy and adjust dosage accordingly, we propose to allow subjects on warfarin therapy to enroll in the phase III trial and to monitor their INR levels after each dose increase and then on a weekly basis or as needed and to adjust dosage accordingly. In addition, sparse sampling PK data will be collected during the duration of the study and population PK analysis will be used to evaluate the drug-drug interaction between these two drugs. As patients with homozygous FH are likely be receiving warfarin, we recognize that appropriate detailed information on concomitant warfarin treatment will need to be described clearly on the product label.

2/7/07 Response: *We would prefer an in vitro characterization study with warfarin prior to initiation of Phase 3 in order to see any potential for drug interaction during Phase 3.*

Meeting Discussion: The sponsor agreed.

- 3. Based on the in vitro study results where BMS-201038 is an inhibitor of 3A4 with a Ki value of 0.42  $\mu$ M and an inhibitor of CYP2D6, you proposed the drug/drug interaction study with five approved lipid-lowering agents. Although this study will assess the effects of BMS-201038 on the pharmacokinetics of drugs which are metabolized by CY3A4, the effects on the drugs which are metabolized by CYP2D6 will not be adequately assessed. A PK drug-drug interaction study with a CYP2D6 substrate is therefore recommended.**

Sponsor Response: We amended the current PK drug-drug interaction study to include the CYP2D6 substrate, dextromethorphan, in 15 subjects. Each subject will be given one initial oral dose of 30 mg of dextromethorphan followed by a 7 day period where subjects receive the study medication BMS-201038 at 60 mg per day. On study day 8, subjects will receive the second oral dose of dextromethorphan 30 mg and a last dose of BMS-201038 60 mg. Subjects will return in 1 week for a final safety visit. This design is the same used in this study for the lipid-lowering medications. **Does the Division agree with this proposed plan?**

2/7/07 response: Yes

Meeting Discussion: None

- 4. A thorough Phase I QT study with placebo and active control arms should be conducted either before the Phase III trial or concurrently with the Phase III trial.**

Sponsor Response: We will conduct a Phase I QT study concurrently with the phase III trial.

2/7/07 response: This is acceptable. We encourage you to submit the protocol for review prior to conducting the study. Anticipate an approximate review time of 60-75 days.

Meeting Discussion: None, however, additional information was provided on what the firm should submit to facilitate a prompt review (see Attachment I)

4. Sponsor Original Question: During the EOPII teleconference in July 2004, in response to question #6 regarding the stratification of patients by apheresis treatment for statistical analysis the Agency thought we could stratify also by weight in addition to apheresis (“*We think that you could also stratify by weight (2 strata) for a total of four strata. We recommend that you analyze the data using analysis of covariance including covariates for weight and aphaeresis and any other important prognostic variables...*”). Given the difficulty in stratifying for two variables in this limited number of subjects, the sponsor proposes to stratify by apheresis status and treat weight as one of the covariates entered in the analysis of covariance. Does the Division concur?

**Division Response: Given that the dose titration scheme adjusts for weight, it is not necessary to treat weight as one of the covariates in the analysis. You should, however, perform sub-group analyses (by dose) to see if the dosing is adequate in each sub-group. It is assumed that baseline LDL will be a covariate in the analysis. It is further recommended that the homozygous FH population be studied as a separate group and that all study patients be treated with drug, i.e., that there be no placebo group. An adequate run-in on current therapy should be conducted prior to treatment with the product with subsequent follow-up off drug so that each subject serves as his/her own control.**

Sponsor Counter Response: As described under counter response #1, our revised protocol is no longer using dosing that is weight based. We agree with the Division to perform subgroup analyses by dose as we anticipate subjects may reach various maximum tolerated doses. We also agree that baseline LDL-C will be a covariate in the analysis.

Regarding the Division’s request to study homozygous FH as a separate population within the larger “severe refractory hypercholesterolemia” population and exclude the placebo control, now we propose to only study patients with homozygous FH as explained under sponsor response #1. **Does the Division agree that no placebo is required for this trial as referenced in response #1?** We have added a minimum six week run-in period for all subjects where concomitant lipid lowering treatment must remain stable. Lipid levels will be performed prior to the run-in period and at 4 and 6 weeks during the run-in period. At the 6 week visit, BMS201038 therapy will be initiated. The concomitant treatment is to remain stable for the first 26 weeks of the study. In addition, a 6 week follow up period has been added following the last dose of BMS-201038 (AEGR-733) when concomitant lipid lowering therapy should remain stable. This design allows the subject to serve as his/her own control. In addition the absence of the placebo group allows that all subjects will be exposed to a minimum of 52 weeks at the maximum tolerated dose of study drug.

2/7/07 response: Yes

Meeting Discussion: None

5. Sponsor Original Question: The sponsor believes that the revised phase III study in 36 subjects that includes updated stopping rules for elevation of liver function tests as well as assessment of pulmonary function together with the PK interaction study currently filed under IND 50,820 adequately addresses issues concerning toxicity and safety assessment over the long term. Does the Division concur?

**Division Response: No. See answer to #1 above. Once all parties agree on the size of the target population, we can discuss an appropriate sample size for the phase 3 study.**

Sponsor Counter Response: See sponsor responses to #1 and #4 above. **Does the Division agree to the amended population and design as proposed?**

2/7/07 response: *Please see the response to Questions #1, #2 and #3. Please also see Additional Comments at the end of this document for recommended changes in your Inclusion/Exclusion Criteria.*

We would like to reiterate our position that while the study of BMS-201038 in high-risk patients such as those with homozygous FH is acceptable despite significant potential risk associated with drug-induced fat accumulation in the liver and lung (and perhaps the intestine), the use of BMS-201038 in a lower-risk population (e.g., heterozygous FH, type IIa and IIb patients) may not be justified in light of the documented preclinical toxicities observed at low multiples of the proposed clinical doses.

**Agency's Questions/Comments to the Sponsor:**

- 1. In your submission, you indicate that of the 580,000 heterozygotes in the U.S., "it has been estimated that approximately 1% of the functional heterozygous FH patients (approximately 5,800) treated with mono or combined pharmacological therapy do not achieve LDL-C levels <300mg/dL (or <200 mg/dL if with CHD) or do not tolerate maximum pharmacological therapy and consequently meet the definition of severe refractory hypercholesterolemia." You subsequently use 10,000 as the "n" for your target population. Can you please reference how you ascertained these numbers?**

Sponsor Response: see sponsor response #1 above. Our estimate is that approximately 6,090 subjects in the US have "severe refractory hypercholesterolemia" (5,800 functional severe heterozygous FH and 290 homozygous FH). We used the 10,000 number as an approximation by excess.

- 2. The exclusion criteria place very stringent restrictions on alcohol use. What is your rationale for these restrictions given the prevalence of alcohol use in the general population, as well as potentially in your target population?**

Sponsor Response: Our rationale for the alcohol exclusion criteria was based on minimizing the effects of alcohol on hepatic fat. We recognize the limitations and implications of this restriction and have revised the exclusion criteria to include current recommendations of no more than 2 drinks per day in men and 1 drink per day in women. **Does the Division agree with these criteria?**

2/7/07 response: *Yes*

Meeting Discussion: None

- 3. The dose titration scheme allows for patients to be treated at their maximum tolerated dose for 8.5 – 17 months, depending on the duration of their individualized titration. The sponsor is urged to follow patients for one year after their maximum tolerated dose has been achieved.**

Sponsor response: We have revised the design to include that all subjects receive maximum tolerated therapy for a minimum of 52 weeks.

- 4. The sponsor is reminded of the Division's previous request to include CK monitoring in the Phase 3 study.**

Sponsor response: Creatine phosphokinase was included in the previous protocol submitted to the Division under the definition of safety labs in footnote 3 of Appendix A and remains in the list of safety labs in the revised clinical protocol.

- 5. We recommend that you include measurement of plasma levels of beta-carotene, a fat-soluble compound, in the phase III safety assessment.**

Sponsor response: We have added beta-carotene to the other fat soluble compounds that will be measured and monitored prospectively.

- 6. We recommend that plasma levels of vitamin K be measured directly rather than indirectly with PT and PTT.**

Sponsor response: In the protocol submitted to the Division, we proposed to measure carboxylation of serum osteocalcin as a direct measure of vitamin K. **Does the Division agree?**

*2/7/07 Response: Yes*

Meeting Discussion: None

- 7. We recommend that patients be instructed to take their multivitamin at least one hour before or at least 4 hours after taking the MTP inhibitor.**

Sponsor response: We agree and a statement to include when to take the multivitamin has been added to the protocol under section, 6.7.1, Diet Instructions. The informed consent has been revised to include these instructions as well.

- 8. Please provide your rationale for excluding patients with type 1 or 2 diabetes.**

Sponsor response: We originally chose to exclude patients with diabetes because diabetes (in particular type 2 diabetes) is characterized by insulin resistance and increased risk of hepatic fat accumulation. We recognize the limitations of this restriction and have removed diabetes from exclusion criteria.

- 9. The sponsor is reminded that completion of at least one species carcinogenicity study at the time of NDA submission is required. (Given the expanded target population, the Division may require that two species be studied prior to NDA submission.)**

Sponsor response: Now that the sponsor proposes for the phase III trial to only include patients with homozygous FH, does the Division agree that one species studied prior to NDA submission is adequate?

*2/7/07 response: This is acceptable for homozygous FH, but not for a broader indication.*

Meeting Discussion: The sponsor stated that both rat and Mouse carcinogenicity studies are due to be initiated in April 2007.

- 10. The sponsor is reminded to submit final study reports of the completed genotoxicity test battery.**

Sponsor response: Bristol Myers Squibb performed four genotoxicity studies that were submitted to IND 50,820 as indicated below. A copy of these reports is included:

1. Exploratory Ames Reverse-Mutation Study in Salmonella (Study #95712, Serial 000, 6/18/96)
2. Ames Reverse-Mutation Study in Salmonella and Escherichia coli (Study #96630, Serial 000, 6/18/96)
3. Oral Micronucleus Study in Rats (Study #96629, Serial 000, 6/18/96)
4. Study No. 96686, Cytogenetics Study in Primary Human Lymphocytes (Study #96686, Serial 004, 11/18/96)

**Does the Division agree that these studies fulfill the requirements for the genotoxicity test battery?**

2/7/07 response: Yes

Meeting Discussion: None

- 11. The sponsor is reminded to submit the background data from the rabbit reproductive toxicology segment 2 study as requested by the Division in August, 2005.**

Sponsor response: We have enclosed a copy of the results of the rabbit toxicology segment 2 study, conducted by (b) (4) on BMS request

- 12. The sponsor is reminded to submit the reproductive toxicology segment 1 (fertility) study prior to initiation of Phase III.**

Sponsor response: We are current working with a vendor to conduct a fertility and early embryonic development reproductive toxicity study in rats. A final report will be submitted to the Division prior to the initiation of phase III.

Meeting Discussion: According to Dr. Rader, the reproductive toxicity study in rats will be initiated in March 2007.

- 13. Please forward a copy of your informed consent document for this study.**

Sponsor response: A copy of the informed consent is enclosed with this submission.

- 14. Adipose tissue levels of Vitamin E will need to be monitored in a sub-set of your patients in any study of over 6 months in duration.**

Sponsor response: We recognize the concern in vitamin E status, as deficient levels are responsible for many of the neurological conditions affecting patients with abetalipoproteinemia, who completely lack MTP and thus are unable to secrete apoB-containing lipoproteins. Vitamin E is almost exclusively transported by LDL particles. Vitamin E deficiency in patients with abetalipoproteinemia is due to the virtual absence in circulation of any apoB-containing lipoproteins. Adequate levels of LDL should be sufficient to transport vitamin E to the tissues. In the UP1001 study, baseline levels of vitamin E were abundantly above normal, in parallel with the dramatically elevated levels of LDL. After 4 weeks at the dose of 1 mg/kg/day (mean dose in 6 subjects was 67 mg), LDL cholesterol was reduced by 51%. Similarly alpha tocopherol levels

significantly decreased by 56%, yet levels remained within normal range in 5 subjects and above normal range in 1 subject.

Plasma levels of alpha tocopherol are a validated indicator of vitamin E status. If plasma levels of alpha tocopherol remain adequate there is no reason to believe there is concern for vitamin E insufficiency or deficiency at the tissue level. If levels are below normal limits, then we will need to assess storage levels as measured by adipose tissue and implement standard clinical care. To help maintain adequate levels of all fat-soluble nutrients, all subjects will be instructed to take a daily multi-vitamin either 1 hr before or at least 4 hr after the administration of BMS-201038. Thus, based on the above, we think that the risk of putting subjects at risk for vitamin E deficiency is minimal; however, we have procedures in place to identify susceptible subjects and follow up procedures if insufficiency is identified as described below. In the phase III study, vitamin E levels will be measured prospectively at every visit starting at baseline until the end of the study. If any subject has a confirmed (2 lab measures) alpha tocopherol level below normal range, we will measure adipose levels and treat according to standard clinical care procedures. **Is the proposed plan acceptable to the Division?**

2/7/07 response: The Division is willing to accept the sponsor's proposal to monitor plasma levels of alpha tocopherol as an indicator of vitamin E status, however, we would ask that the levels be reported as either Vitamin E/LDL or Vitamin E/HDL ratios and intervention (adipose tissue sampling) be proposed when those ratios become abnormal. Additionally, the sponsor is proposing to use a Centrum MVI as the only supplemental source of Vitamin E in the study (Centrum MVI contains 30 IU of Vitamin E). Given that these subjects will be on a host of concomitant lipid-lowering medications including fibrates and/or bile acid sequestrants, which in addition to BMS201038 have the potential to lower Vitamin E levels, it is recommended that a higher dose of Vitamin E supplementation be employed, e.g., 100-200 IU per day depending on the concomitant medications a given subject is taking.

Meeting Discussion: The sponsor stated their plans to monitor both Vitamin E levels as well as the Vitamin E/HDL ratio. When the sponsor suggested supplementation with Vitamin E 400 IU daily, the Agency said that was acceptable.

**Additional Question for the Division:**

- 1) In order to assess change in hepatic fat in the phase III trial, we propose to use Magnetic Resonance Imaging (MRI) without spectroscopy (MRS), which was originally proposed. Both MRI and MRS provide sufficient sensitivity for a reliable and quantitative assessment of liver steatosis in subjects without liver disease, but MRI is more readily available, less time consuming, & less expensive. **Does the Division object to the use of MRI to assess hepatic fat in the phase III protocol?**

2/7/07 response: Both the CT and MRI techniques are nonspecific and can be affected by various processes such as excess glycogen accumulation, edema, inflammation, etc. The best method for frequent, repetitive, and highly specific estimation of hepatic fat in vivo is localized <sup>1</sup>H MRS. "Methylene proton signals estimated by spectroscopy are specific for the mobile triglycerides and create a clear resonance peak. The <sup>1</sup>H MRS method has been validated against direct determination of triglyceride content of liver biopsies in the animals as well as in humans and has become the method of choice."

Meeting Discussion: After a brief discussion, Dr. Rader agreed to use MRS.

**Additional comments:**

- Subjects with the following pulmonary conditions should be excluded from your study:
  1. asthma
  2. COPD
  3. idiopathic pulmonary fibrosis
-

- 
- Subjects with the following liver diseases should be excluded from your study:
  1. NASH
  2. alcoholic liver disease
  3. autoimmune hepatitis
  4. primary biliary cirrhosis
  5. primary sclerosing cholangitis
  6. Wilson's disease
  7. hemochromatosis
  8.  $\alpha_1$  anti-trypsin deficiency
- Please also include the following medications to your list of prohibited concomitant medications:
  1. corticosteroids
  2. betaine

Meeting Discussion: The sponsor agreed to the revisions.

**Additional Questions:**

- ❖ Based on the results of this study, what dosage strengths are you planning on marketing?

Meeting Discussion: According to Dr. Rader, the starting dose will be 5 mg daily, with titration up to 60 mg daily based on safety (primarily liver) and efficacy (b) (4)

**Additional Discussion:**

In an October 31, 2006 submission to IND 50,820, the sponsor responded to the Agency's request to provide the final report for Study 97027 (Six Month Oral Investigative Study in Rats), which had previously been submitted on April 13, 1999, but was in storage. The following comments were conveyed to the firm, and some discussion took place:

The resubmitted 6-month rat toxicity study at 2 mg/kg/d with a reversibility observation does not establish a NOAEL for pulmonary phospholipidosis. Therefore a 3-month oral toxicity study in rats with both light and electronic microscopic examinations, toxicokinetics and recovery assessments is recommended as previously discussed.

In response to a question from the Agency, the sponsor agreed to submit an organized report showing that animals and humans make the same metabolites.

In response to a suggestion from the Agency, the firm agreed to monitor the major metabolites in the Phase 3 study.

**DECISIONS (AGREEMENTS) REACHED:**

None

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

The sponsor will submit an organized report showing that animals and humans make the same metabolites.

**ATTACHMENTS/HANDOUTS:**

See Attachment 1 for the information needed from the firm so that their soon-to-be submitted QTc protocol can be reviewed by the Agency.

Attachment 1

To assist in the review of a **Thorough QT Protocol**, the following items should be submitted:

- copy of the updated study protocol
- copy of the Investigator Brochure
- A completed Highlights of Clinical Pharmacology Table (Table 1 shown below)

**Table 1. Highlights of Clinical Pharmacology**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<input type="checkbox"/> Median (range) for parent <input type="checkbox"/> Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<input type="checkbox"/> Primary route; percent dose eliminated <input type="checkbox"/> Other routes
	Terminal t <sub>1/2</sub>	<input type="checkbox"/> Mean (%CV) for parent <input type="checkbox"/> Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 50,820

Daniel J. Rader, M.D.  
Associate Professor of Medicine and Pathology  
Director, Preventive Cardiology and Lipid Clinic  
University of Pennsylvania School of Medicine  
654 BRB II/III, 421 Curie Blvd.  
Philadelphia, PA 19104

Dear Dr. Rader:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BMS-201038 Tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 20, 2004. The purpose of the meeting was to discuss plans for a Phase 3 trial to support a New Drug Application (NDA) for the treatment of homozygous familial hypercholesterolemia (hoFH).

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) 827-9090.

Sincerely,

*{See appended electronic signature page}*

Valerie Jimenez  
Regulatory Project Manager,  
Division of Metabolic and Endocrine Drug  
Products, HFD-510  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF TELECONFERENCE MINUTES**

**MEETING DATE:** July 20, 2004

**TIME:** 11:00a.m. – 12:00 noon

**LOCATION:** 14B-39 Conference Room

**SPONSOR:** Dr. Daniel J. Rader

**TYPE OF MEETING:** End of Phase II (EOP2)

**DRUG:** BMS-201038

**APPLICATION:** IND 50,820

**MEETING CHAIR:** David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products (DMEDP)

**MEETING RECORDER:** Valerie Jimenez, Regulatory Project Manager

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name &amp; HFD#</u>
1. David Orloff, M.D.	Director	DMEDP, HFD-510
2. Mary Parks, M.D.	Deputy Director and Medical Team Leader	DMEDP, HFD-510
3. Karen Davis Bruno, Ph.D.	Pharmacology/Toxicology Team Leader	DMEDP, HFD-510
4. Hae Young Ahn, Ph. D.	Biopharmaceutics Team Leader	DMEDP, HFD-510
5. Dylan Yao, Ph.D.	Pharmacology/Toxicology Reviewer	DMEDP, HFD-510
6. Wei Qiu, Ph.D.	Biopharmaceutics Reviewer	DMEDP, HFD-510
7. Valerie Jimenez	Regulatory Project Manager	DMEDP, HFD-510

**EXTERNAL ATTENDEES AND TITLES:**

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Daniel J. Rader, M.D.	Sponsor	University of Pennsylvania
2. LeAnne Bloedon, MS, RD	Clinical Project Manager	University of Pennsylvania

3. Rajender Reddy, M.D.	Hepatologist	University of Pennsylvania
4. Lee Schacter, M.D.	DDS Partners/Financiers	University of Pennsylvania
5. Charles Swindell, M.D.	DDS Partners/Financiers	University of Pennsylvania
6. Daniel Kolansky, M.D.	Cardiologist & Safety Medical Officer	University of Pennsylvania
7. [REDACTED] (b) (4)	Phase 3 Investigator	Consultant
8. Marina Cuchel, M.D.	Lipid Specialist	University of Pennsylvania
9. Philippe Szapary, M.D.	Clinician and Phase 3 Investigator	University of Pennsylvania
10. Megan Wolfe, BS	Lipid Manager	University of Pennsylvania

## BACKGROUND:

On May 26, 2004, the Agency received a meeting request for an End of Phase 2 (EOP2) meeting from the sponsor to discuss Phase 3 trial plans for their product BMS-201038 Tablets, a microsomal triglyceride transfer protein (MTP) inhibitor. Additionally, the sponsor requests discussion of plans to submit a New Drug Application (NDA) for the treatment of hypercholesterolemia (hoFH).

## MEETING OBJECTIVES:

Obtain input from the Agency regarding the sponsor's proposed phase 3 trial design for support of an NDA submission as well as an application for orphan drug status [REDACTED] (b) (4).

## DISCUSSION:

**QUESTIONS:** (the sponsor's questions are in text and the Agency's response is in *italics*.)

1. The sponsor proposes to submit an NDA for the treatment of homozygous familial hypercholesterolemia based on the clinical data currently available and the proposed Phase 3 trial. Does the division agree that this would provide an adequate clinical package for registration of BMS-201038 for the treatment of homozygous familial hypercholesterolemia?

### ***FDA Response:***

*No; the sponsor is referred to the responses to questions below. There are concerns regarding the potential for significant drug-drug interactions as BMS-201038 appears to be a potent CYP3A4 inhibitor, and the clinical use of this product will likely be in patients taking high doses of simvastatin or atorvastatin which are CYP3A4 substrates. The sponsor will need to conduct drug-drug interaction studies with these two statins to determine to what extent the statin level will increase when co-administered with BMS-201038. While the sponsor may modify the current Phase 3 protocol to exclude use of a*

*3A4 substrate, the drug-drug interaction studies outlined in the biopharm response will still be necessary for appropriate labeling of this product and will need to be conducted prior to submission of a marketing application.*

2. The sponsor believes that based on the available data and in view of the dose titration proposed; there is sufficient safety and efficacy information to initiate the proposed phase 3 trial. Does the Division agree?

***FDA Response:***

*No; please see the responses to questions 1 and 5. Should the sponsor propose to conduct this study which allows background therapy with simvastatin (or atorvastatin), drug-drug interactions must be conducted prior to study initiation to ensure that dose selection (or use) of the statin is appropriate.*

3. While BMS-201038 has not, to date, been studied in combination with other lipid lowering agents, the sponsor believes that the protocol design (with careful dose titration and close monitoring) will adequately protect subjects. Does the Division agree?

***FDA Response:***

*No; please see response to questions 1, 2, and 5.*

4. The sponsor believes that the proposed phase 3 study design adequately addresses issues concerning toxicity in terms of protection of subjects and obtaining the data necessary to assess safety over the long term. Does the Division agree?

***FDA Response:***

*In addition to the responses to questions 1, 2, and 5, the sponsor was asked to modify the study drug discontinuation criteria for transaminase elevations. At present the stopping criteria allows for patients to have ALT/AST elevations > 10 x ULN on two consecutive measures before discontinuation of study drug. A more rigorous criterion should be established so that patients are not continued on therapy should ALT/AST levels exceed 20 x ULN at one single time point.*

*The sponsor was also asked to provide a summary of the PFT data from previously conducted studies and to include CK monitoring in the proposed Phase 3 study.*

5. The sponsor proposes to evaluate the pharmacokinetics of BMS-201038 and other co-administered lipid lowering agents as part of the proposed phase 3 trial and not in a separate protocol. Does the Division agree?

***FDA Response:***

*No. It is known that the test drug is an inhibitor of multiple CYPs, particularly a strong inhibitor of CYP3A4. Should the sponsor decide to proceed with the currently proposed study, a PK interaction study with simvastatin must be conducted prior to study initiation as this statin is exclusively metabolized by CYP3A4. Other PK interaction studies can be conducted concurrently with Phase 3 trial including studies using lipid-altering drugs that have approved indications for use in hoFH (e.g., atorvastatin, rosuvastatin and ezetimibe) as there is a potential for combination therapy in clinical practice.*

6. Because of the limited number of homozygous familial hypercholesterolemia patients available to participate in a clinical trial and the number of centers needed to carry out the trial, it is only possible statistically to stratify by one variable. The sponsor proposes to stratify patients based on whether or not their treatment includes apheresis rather than by center. Does the Division agree?

**FDA Response:**

*We think that you could also stratify on weight (2 strata) for a total of four strata. We recommend that you analyze the data using analysis of covariance including covariates for weight and apheresis and any other important prognostic variables. Covariates should be defined in the protocol.*

7. The sponsor believes that given the small number of patients with homozygous familial hypercholesterolemia in the US population (about 300) and the serious nature of their disease, completed carcinogenicity studies will not be required at the time of NDA submission. Does the Division agree?

**FDA Response:**

*Completion of at least one species carcinogenicity studies will be needed at the time of NDA submission. Given the limited patient population and indicated use the Division will consider proposals for a second species carcinogenicity assessment as a Phase 4 commitment. However the sponsor is encouraged to submit their proposal regarding study design, dose selection and timing of the carcinogenicity evaluation to the Division for further discussion.*

*We request that you submit the final study reports of the completed genotoxicity test battery, 12 month dog toxicity, in vitro metabolism and safety pharmacology studies to address the potential signal for QTc prolongation. Submission of the reproductive toxicology segment I (fertility) study prior to Phase 3 and segment III concurrently is acceptable provided any enrolled females of child bearing potential have negative pregnancy tests and are utilizing barrier contraception. The nonclinical toxicology data establishes GI inflammation, fatty liver infiltration and phospholipidosis (lung, liver) as the target organ toxicities at therapeutic exposures. The GI and liver findings are monitorable. Fatty liver infiltration was also seen in the clinic. However there is concern about the phospholipidosis observed in the chronic rodent toxicity studies without an established NOAEL. Dr. Rader noted that pulmonary function tests were performed in clinical studies and function was reported as normal, these reports will be sent in for review.*

8. The sponsor proposes to use MedDRA (Medical Dictionary for Medical Affairs) to collect and assess adverse events. Is this acceptable to the Division?

**FDA Response:**

*This is acceptable.*

9. The sponsor believes there are additional groups of patients who, based on the benefit-risk profile of BMS-201038, could benefit from treatment with this agent. Examples would include individuals with elevated triglycerides and LDL-cholesterol who remain at risk despite treatment with currently available agents at maximally tolerated doses. The

sponsor would appreciate guidance from the Division regarding trial design and sample size for evaluating BMS-201038 in such population.

**FDA Response:**

*A separate meeting request should be made to address an indication beyond homozygous familial hypercholesterolemia. The Division noted that the expanded use of the product in the additional groups of patients shifts the risk-benefit profile of the development program. The sponsor is proposing to target a larger patient population who may have other therapeutic options. In this setting, the safety concerns raised during this teleconference will likely need to be addressed at an earlier stage than for the more rare hoFH indication.*

**Additional Comments:**

- *Provide information of metabolic enzyme responsible for the test drug (substrate of which enzyme for metabolism) or conduct a study to evaluate it.*
- *Address the QT issue. A thorough Phase 1 QT study is recommended with placebo and active controls. The QT study can be conducted before the Phase 3 trial or concurrently with the Phase 3 trial.*

**Minutes Prepared by** /s/ 7/17/04

Valerie Jimenez  
Project Manager, HFD-510

**Chair Concurrence:** /s/ 8/18/04

David Orloff, M.D.  
Deputy Director, HFD-510

**MEETING MINUTES**

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/s/

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Valerie Jimenez  
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