

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202811Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202-811

SUPPL # N/A

HFD # 180

Trade Name LINZESS

Generic Name linaclotide

Applicant Name Forest Laboratories, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

N/A

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

N/A

d) Did the applicant request exclusivity?

YES  NO

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

5 years

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

YES  NO

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

N/A

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

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

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



Investigation #2

!

YES

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

=====

Name of person completing form: Brian Strongin

Title: CPMS

Date: 8-13-12

Name of Office/Division Director signing form: Victoria Kusiak

Title: Deputy Director, ODE III

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

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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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BRIAN K STRONGIN  
08/14/2012

VICTORIA KUSIAK  
08/14/2012

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 202-811 BLA #	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type:
Proprietary Name: LINZESS Established/Proper Name: linaclotide Dosage Form: Capsules		Applicant: Forest Laboratories, Inc. Agent for Applicant (if applicable):
RPM: Brian Strongin, R.Ph., MBA		Division: Division of Gastroenterology and Inborn Errors 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>		
<p>❖ Actions</p> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>September 9, 2012</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		
		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input checked="" type="checkbox"/> None

<sup>1</sup>The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists 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 type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 300px;"><input checked="" type="checkbox"/> MedGuide w/o REMS</span>  <span style="margin-left: 300px;"><input type="checkbox"/> REMS not required</span></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>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<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 checked="" type="checkbox"/> Other Information Advisory</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 BLA: 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: _____
<b>❖ Patent Information (NDAs only)</b>	
<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**

<p>❖ Copy of this Action Package Checklist<sup>4</sup></p>	<p>X</p>
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**Officer/Employee List**

<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>

**Action Letters**

<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) August 30, 2012</p>
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**Labeling**

<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<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>	<p>August 28, 2012</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>August 9, 2011</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>Amitiza and Lotronex</p>

<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>	<p>March 16, 2012; July 25, 2012</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>August 9, 2011 - Instructions for Use</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>Lotronex - Medication Guide</p>
<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>	<p>August 21, 2012</p>
<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>• <i>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.</i></li> </ul> </li> </ul>	<p>November 17, 2011 November 17, 2011; April 25, 2012; August 10, 2012</p>
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM September 14, 2011 <input checked="" type="checkbox"/> DMEPA February 16, 2012, April 25, 2012, August 21, 2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) June 28, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) June 28, 2012 <input checked="" type="checkbox"/> SEALD August 27, 2012 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PMHS June 14, 2012
<p><b>Administrative / Regulatory Documents</b></p>	
<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>	<p>October 5, 2011</p>
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2) <input checked="" 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 <u>May 9, 2012</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

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

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>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (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>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg April 21, 2011
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg May 17, 2007; July 14, 2008; August 25, 2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 24, 2012
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 29, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 15, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 6 templates
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	N/A
• Clinical review(s) <i>(indicate date for each review)</i>	October 4, 2011; July 17, 2012; August 2, 2012
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 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>	July 17, 2012 (IBS-C Review): page 25 August 1, 2012 (CIC Review): page 27
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None OSE - March 22, 2012; OBP/Immunology Consult - August 17, 2012
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

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

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	<input type="checkbox"/> None August 7, 2012
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested April 5, 2012; April 6, 2012; April 25, 2012, June 19, 2012
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    October 5, 2012; October 6, 2011; August 16, 2012
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    August 3, 2012
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None October 7, 2011; April 6, 2012, August 3, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    April 9, 2012
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    October 6, 2011, April 10, 2012; April 17, 2012 June 11, 2012
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None October 6, 2011; April 10, 2012; June 11, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc    February 7, 2012
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None    January 20, 2012 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
<b>✓ Product Quality Discipline Reviews</b>		
<ul style="list-style-type: none"> <li>• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None August 15, 2012	
<ul style="list-style-type: none"> <li>• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> <li>• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None September 28, 2011; April 3, 2012; August 15, 2012	
<b>❖ Microbiology Reviews</b>		
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input type="checkbox"/> None October 7, 2011; April 10, 2012	
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 169 of the April 3, 2012 Product Quality Review	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
<b>❖ Facilities Review/Inspection</b>		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: <input 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) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation	
<b>❖ NDAs: Methods Validation</b> <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input 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.

**From:** Wilkins Parker, Jamie  
**Sent:** Tuesday, August 21, 2012 1:23 PM  
**To:** Strongin, Brian K  
**Subject:** RE: LINZESS Carton/Container Labels with MedGuide statement - FDA Comments  
[Hi Brian](#)  
[These are adequate.](#)

[Thank you.](#)

[Jamie](#)

**Jamie Wilkins Parker, Pharm.D.**  
Acting Team Leader  
Division of Medication Error Prevention and Analysis  
FDA/CDER/OSE/OMEPRM  
WO22-4443  
301.796.6113 (p)

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**From:** Strongin, Brian K  
**Sent:** Monday, August 20, 2012 6:42 PM  
**To:** Wilkins Parker, Jamie  
**Subject:** Fw: LINZESS Carton/Container Labels with MedGuide statement - FDA Comments

[FYI. Please let me know if these responses are OK ASAP. Thanks.](#)

---

**From:** Kunka, Linda [<mailto:Linda.Kunka@frx.com>]  
**Sent:** Monday, August 20, 2012 05:22 PM  
**To:** Strongin, Brian K  
**Subject:** RE: LINZESS Carton/Container Labels with MedGuide statement - FDA Comments

[Hi Brian:](#)

[Attached please find the carton and container labels with the comments requested below incorporated. I will formally submit these to the NDA tomorrow.](#)

[Please let me know if you have any questions or if you would like us to make any additional edits. Sorry again for the delay. Thanks.](#)

[LK](#)

---

**From:** Strongin, Brian K [<mailto:Brian.Strongin@fda.hhs.gov>]  
**Sent:** Friday, August 17, 2012 9:14 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Carton/Container Labels with MedGuide statement - FDA Comments

[Here are our comments on the revised carton/container labeling that you sent yesterday. Please respond to these ASAP, no later than Monday morning if possible. Also, please submit the carton/container labels that you e-mailed to me yesterday. Let me know if you have any questions. Thanks.](#)

[Comments on the revised c&c labels:](#)

All Labels and Labeling:

1. The medication guide statement should be revised based on 21 CFR 208.24, to the following text: "ATTENTION PHARMACIST (or PRESCRIBER for the Professional Samples): Each patient is required to receive the enclosed Medication Guide" in bolded font. As it currently reads, it does not address an "authorized dispenser" as required in the regulation.

Professional Sample Kit Tray:

1. Enlarge and/or increase the prominence of the storage warning, as this is an important statement. This can be achieved via boxing of the statement, and/or enlarging the font size of the statement.

Professional Sample Kit Tray (4 count)

1. Add the storage warning to this labeling to be consistent with the carton labeling and container label for this professional sample count.

All Container Labels and Carton Labeling (Professional Sample and Retail)

1. Relocate the net quantity statement to a location away from the strength statement.  
2. Enlarge and/or increase the prominence of the storage warning, as this is an important statement. This can be achieved via boxing of the statement, and/or enlarging the font size of the statement.

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Thursday, August 16, 2012 2:59 PM  
**To:** Strongin, Brian K  
**Subject:** 202-811 LINZESS Carton/Container Labels with MedGuide statement

Hi Brian:

Attached please find the carton/container labels with the addition of the Medication Guide statement. In order to accommodate this change, a few modifications were made in regards to spacing, font size and prominence. Please let me if you have any questions or would like for us to make any edits. Sorry for the delay.

Thanks.

LK

Linda Kunka  
Senior Manager, Regulatory Affairs  
Forest Research Institute  
Harborside Financial Center  
Plaza V, Suite 1900  
Jersey City, NJ 07311  
A Division of Forest Laboratories, Inc.  
Phone: 201.386.2124  
Fax: 201.524.9711/9712  
linda.kunka@frx.com

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/s/  
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BRIAN K STRONGIN  
08/22/2012

**From:** Strongin, Brian K  
**Sent:** Thursday, August 18, 2011 9:33 AM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Information Request for NDA 202-811 Linaclotide

Please submit a response to the following information request as soon as possible:

Did you submit a "coding dictionary" containing a list of all investigator verbatim terms and the preferred terms to which they were mapped? If so please provide the location(s). We prefer this as a SAS file.

Thanks.

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/s/  
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BRIAN K STRONGIN  
08/18/2011

**Strongin, Brian K**

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**From:** Strongin, Brian K  
**Sent:** Friday, August 17, 2012 9:14 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Carton/Container Labels with MedGuide statement - FDA Comments

Here are our comments on the revised carton/container labeling that you sent yesterday. Please respond to these ASAP, no later than Monday morning if possible. Also, please submit the carton/container labels that you e-mailed to me yesterday. Let me know if you have any questions. Thanks.

Comments on the revised c&c labels:

All Labels and Labeling:

1. The medication guide statement should be revised based on 21 CFR 208.24, to the following text: "ATTENTION PHARMACIST (or PRESCRIBER for the Professional Samples): Each patient is required to receive the enclosed Medication Guide" in bolded font. As it currently reads, it does not address an "authorized dispenser" as required in the regulation.

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Professional Sample Kit Tray (4 count)

1. Add the storage warning to this labeling to be consistent with the carton labeling and container label for this professional sample count.

All Container Labels and Carton Labeling (Professional Sample and Retail)

1. Relocate the net quantity statement to a location away from the strength statement.  
2. Enlarge and/or increase the prominence of the storage warning, as this is an important statement. This can be achieved via boxing of the statement, and/or enlarging the font size of the statement.

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Thursday, August 16, 2012 2:59 PM  
**To:** Strongin, Brian K  
**Subject:** 202-811 LINZESS Carton/Container Labels with MedGuide statement

Hi Brian:

Attached please find the carton/container labels with the addition of the Medication Guide statement. In order to accommodate this change, a few modifications were made in regards to spacing, font size and prominence. Please let me if you have any questions or would like for us to make any edits. Sorry for the delay.

Thanks.

LK

Linda Kunka  
Senior Manager, Regulatory Affairs  
Forest Research Institute  
Harborside Financial Center  
Plaza V, Suite 1900

Jersey City, NJ 07311  
A Division of Forest Laboratories, Inc.  
Phone: 201.386.2124  
Fax: 201.524.9711/9712  
linda.kunka@frx.com

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BRIAN K STRONGIN  
08/17/2012

**Strongin, Brian K**

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**From:** Strongin, Brian K  
**Sent:** Wednesday, August 15, 2012 10:49 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** FW: NDA 202 811 LINZESS PMRs - Clarification on the Clinical Pharmacology PMR

With regard to your question about the need for multiple dosing, the clinical pharmacology reviewers still recommend repeat dosing. The number of doses is uncertain at this time, and will be subject to discussion with the pediatric and maternal health staff at the time of your protocol development and submission. If after those discussions it is determined that even a single dose study would actually be adequate, we can revise our agreement as appropriate. Thanks.

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Monday, August 13, 2012 2:00 PM  
**To:** Strongin, Brian K  
**Subject:** NDA 202 811 LINZESS PMRs - Clarification on the Clinical Pharmacology PMR

Hi Brian:

As we discussed at the teleconference on August 2nd and in our phone call last Friday, the Sponsors seek clarification on the Clinical Pharmacology PMR. Please see below:

*Virtually no systemic exposure to linaclotide or its active metabolite is seen following administration of therapeutic (and supratherapeutic) doses of linaclotide, making PK characterization of linaclotide very challenging. In light of the fact that we have no evidence of accumulation following multiple-doses of linaclotide, the sponsor questions the need for multiple dosing of linaclotide in the proposed lactation study.*

Can you present this to the Clinical Pharmacology reviewer for their input? Let me know if you have any questions. Thank you.

LK

---

**From:** Kunka, Linda  
**Sent:** Monday, August 06, 2012 1:05 PM  
**To:** Strongin, Brian K  
**Subject:** RE: LINZESS PMRs

Hi Brian:

We have reviewed the recent PMR requests and the Sponsors agree to the NonClinical PMR as proposed with a minor change in the title:

NonClinical PMR:

A nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide.

Final Protocol Submission – January 30, 2013

Study Completion – October 30, 2013

Final Study Report Submission – April 30, 2014

The Sponsors agree to the Clinical Pharmacology PMR as the Agency suggested:

Clinical Pharmacology PMR:

Conduct a multiple-dose milk-only lactation study to assess concentrations of linaclotide and its active metabolite in the milk of healthy, lactating but non-nursing female volunteers, using a validated assay in order to appropriately inform the nursing mothers' subsection of the labeling

Final Protocol Submission – March 31, 2013

Study Completion – September 30, 2014

Final Study Report Submission – September 30, 2015

We would like to defer our response on the pediatric PMRs until the conclusion of today's labeling teleconference.

Please let me know if you have any questions or if you would like to discuss further.

Thank you.

LK

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]

**Sent:** Mon 8/6/2012 10:21 AM

**To:** Kunka, Linda

**Cc:** Strongin, Brian K

**Subject:** LINZESS PMRs

I hope you had a nice weekend. Please e-mail and follow-up with a submission to your NDA agreeing to the following PMRs **ASAP**:

A nonclinical study in neonatal and juvenile mice to determine the mechanism of lethality in neonatal and juvenile mice treated with linaclotide.

Final Protocol Submission – January 30, 2013

Study Completion – October 30, 2013

Final Study Report Submission – April 30, 2014

A safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months to 17 years.

Final Protocol Submission – April 30, 2015

Study Completion – October 30, 2017

Final Study Report Submission – October 30, 2018

A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years to 17 years.

Final Protocol Submission – April 30, 2015

Study Completion – October 30, 2017

Final Study Report Submission – October 30, 2018

Conduct a multiple-dose milk-only lactation study to assess concentrations of linaclotide and its active metabolite in the milk of healthy, lactating but non-nursing female volunteers, using a validated assay in order to appropriately inform the nursing mothers' subsection of the labeling.

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

If you would like to propose alternative timelines for these studies, please do so. **Also, please propose a timeline for the clinical pharmacology PMR. Please respond, at least by e-mail, by COB today and let me know if you have any questions.** Thanks.

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BRIAN K STRONGIN  
08/15/2012

**Strongin, Brian K**

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**From:** Strongin, Brian K  
**Sent:** Tuesday, August 14, 2012 3:22 PM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** FDA Comments on the LINZESS PI Sent to us 8-10-12

**Attachments:** LINZESS PI Sponsor Proposal Clean 08-10-2012 FDA Comments Added 8-14.doc

I've attached our comments on the PI that you sent to us 8/10/12. We can discuss these at the call today. Thanks.



.INZESS PI Sponsor  
Proposal Cl...

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

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BRIAN K STRONGIN  
08/14/2012

## Strongin, Brian K

---

**From:** Strongin, Brian K  
**Sent:** Tuesday, August 14, 2012 9:25 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Package Insert Comments

Please respond ASAP to the following comments regarding the proposed package insert:

1. Table of Contents: The same title for the Boxed Warning that appears in the Highlights and Full Prescribing Information must also appear at the beginning of the Table of Contents in UPPER-CASE letters and **bolded**.
2. Full Prescribing Information: The MedGuide must appear at the end of the Full Prescribing Information upon approval.

Thanks.

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/s/  
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BRIAN K STRONGIN  
08/14/2012

**From:** Strongin, Brian K  
**Sent:** Tuesday, August 07, 2012 4:21 PM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS: Information Request/Advice Concerning the Package Insert

Please respond to the following information request/advice ASAP regarding Section 14.1, Irritable Bowel Syndrome with Constipation:

1. Combine Tables 3 and 4 in Section 14.1. Include only primary endpoints for the 9 out of 12 week responders and primary and secondary endpoints in the 6 out of 12 week responders. Please clearly explain that the 6/12 primary endpoint responder is not constructed the same as the 9/12 responder. For the 9/12 (APC3+1), a weekly responder needs at least 3 CSBM and an increase of 1 from baseline and a decrease of 30% in pain score. For the 6/12 (APC+1) you only needed an increase of 1 CSBM from baseline and the 30% decrease in pain to qualify.
2. Remove Figure 1 and substitute text describing it.
3. Please remove the following sentence from the last paragraph in Section 14.1:

"There was no evidence of rebound worsening compared to baseline".

Please let me know if you have any questions. Thanks.

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/s/  
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BRIAN K STRONGIN  
08/07/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

MEMORANDUM

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

DATE: August 2, 2012

TO: NDA 202-811, LINZESS (linaclotide) Capsules

FROM: Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products

SUBJECT: Teleconference Regarding Non-Clinical and Clinical Post-Marketing Requirements

**FDA Attendees:**

Victoria Kusiak, M.D.  
Deputy Director  
Office of Drug Evaluation III

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Joyce Korvick, M.D.  
Deputy Director for Safety  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Ruyi He, M.D.  
Medical Team Leader  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Robert Fiorentino, M.D.  
Medical Team Leader  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Erica Wynn, M.D.  
Medical Officer  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

David Joseph, Ph.D.  
Pharmacology/Toxicology Team Leader  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Yuk-Chow Ng, Ph.D.  
Pharmacology/Toxicology Reviewer  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

**Sponsor Attendees:**

Forest Laboratories Inc.

June Bray, RPh, MBA  
Senior Vice President, FRI Regulatory Affairs

James DeMartino, PhD  
Senior Director, Regulatory Affairs

Linda Kunka, MA  
Senior Manager, Regulatory Affairs

Harvey Schneier, MD  
Executive Director, Clinical Development Internal Medicine & GI

Steven Shiff, MD  
Director, Clinical Development  
Stephan Ortiz, RPh, PhD

Associate Director, Clinical Pharmacology and Drug Dynamics

Anne Gilson  
Principal Scientist, Toxicology

Ironwood Pharmaceuticals

Mark Currie, PhD  
Senior VP R&D, Chief Scientific Officer

Gwyn Reis  
Vice President, Regulatory Affairs

Sarah Lieber, MS  
Associate Director, Regulatory Affairs

Caroline Kurtz, PhD  
Vice President, Program Management

Jeff Johnston, MD  
Vice President, Clinical Development, and Chief Medical Officer

Joseph Lavins, MD  
Senior Director, Clinical Research

Alex Bryant, PhD  
Vice President, Drug Metabolism and Pharmacokinetics

Adeline Smith PhD  
Director, Toxicology

**Background**

NDA 202-811 for LINZESS (linaclotide) Capsules was submitted August 9, 2011 for the treatment of constipation (b) (4) irritable bowel syndrome and chronic constipation. Linaclotide was lethal at 10 mcg/kg/day orally in neonatal mice after administration of 1 or 2 daily doses, starting on post partum day 7. Lethality was also observed in juvenile mice after a single oral administration on post partum day 14 (100 mcg/kg) and post partum day 21 (600 mcg/kg).

In a July 3, 2012 teleconference with the sponsor, the Division requested the following non-clinical post-marketing studies (PMRs):

Study 1. A nonclinical study in neonatal mice (b) (4) to determine the mechanism of mortality.

Study 2. A nonclinical study to explore the tolerability of older juvenile mice to linaclotide.

On July 31, 2012, the PMR request was revised, via e-mail to the sponsor, to the following study:

A nonclinical study in neonatal and juvenile mice to determine the mechanism of lethality in neonatal and juvenile mice treated with linaclotide

The following additional PMRs were also requested via e-mail to the sponsor on July 31, 2012:

A safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months to (b) (4) years.

A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years to (b) (4) years.

On August 1, 2012 the sponsor requested a teleconference to discuss their preference to conduct two separate studies as originally discussed and the PMRs in pediatric patients.

### **Today's Call**

The sponsor opened by stating their preference to conduct two studies, as originally requested, to fulfill the revised non-clinical PMR. The Division responded that it was generally acceptable to conduct two studies to fulfill a PMR and that they would review and provide comment on the draft protocols when they have been received. The Division explained that they did not want to limit the mechanistic studies to 7 – 9 day old mice and that studies in four week old mice may be necessary.

The discussion then turned to the pediatric PMRs. The sponsor asked if the age ranges requested in the PMRs were correct. The Division responded that the correct older age should be 17 years and that the PMRs would be revised to reflect this. The sponsor asked if it was acceptable to conduct dose-ranging studies in addition to safety and efficacy studies. The Division replied that this was acceptable and that more specific aspects of the protocols would be discussed when draft protocols had been submitted. The call then concluded.

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/s/  
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BRIAN K STRONGIN  
08/16/2012

**From:** Strongin, Brian K  
**Sent:** Thursday, July 26, 2012 4:02 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** FW: NDA 202-811 LINZESS Information Request  
 Please submit to your IND, draft protocols for these PMR studies by October 30, 2012. We will proposed revised PMR due dates (final protocol, study completion and final report submission) based on receiving the draft protocols by October 30, 2012. We will also review them and provide comments. Thanks and let me know if you have questions.

---

**From:** Kunka, Linda [<mailto:Linda.Kunka@frx.com>]  
**Sent:** Tuesday, July 24, 2012 3:05 PM  
**To:** Strongin, Brian K  
**Subject:** RE: NDA 202-811 LINZESS Information Request

Hi Brian:

Below please find the proposed dates for the nonclinical PMR studies in response to your July 18<sup>th</sup> request.

1. A nonclinical study in neonatal mice (b) (4) to determine the mechanism of mortality by exploring the effects of linaclotide (b) (4).

Final Protocol Submission – October 30, 2012  
 Study Completion – April 30, 2013  
 Final Study Report Submission – June 30, 2013

2. A nonclinical study (b) (4)

Final Protocol Submission – October 30, 2012  
 Study Completion – July 30, 2013  
 Final Study Report Submission – September 30, 2013

Let me know if you need anything further. Would you like me formally submit this to the NDA?  
 Thanks.

LK

---

**From:** Strongin, Brian K [<mailto:Brian.Strongin@fda.hhs.gov>]  
**Sent:** Wednesday, July 18, 2012 6:47 PM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** FW: NDA 202-811 LINZESS Information Request

Hi. I hope you're doing well. After our 7/3/12 teleconference, I believe you were going to submit a revised pediatric plan including non-clinical studies investigating the mechanism of mouse deaths in the juvenile mice studies and how the sensitivity to linaclotide lethality changes with age. Can you give me an update on this? Thanks.

---

ongin, Brian K  
day, June 19, 2012 1:59 PM  
a, Linda'  
jin, Brian K  
NDA 202-811 LINZESS Information Request

We have the following comments and information request. Please respond to the information request ASAP:

1. On further consideration, we will be changing the (b) (4) related to pediatric use to a Boxed Warning and a Warning and Precaution. A revised marked-up package insert will be sent soon.
2. Change the FDA Approved Patient Labeling section of the package insert to a Medication Guide. Prominently include information on the risks of LINZESS use in the pediatric population.
3. We would like to schedule a teleconference the week of July 2 to discuss the following post-marketing requirements: a study to determine the mechanism of the deaths in juvenile mouse studies and a study to obtain a more complete understanding of how sensitivity to linaclotide lethality changes with age in juvenile mice and to inform about the potential risk in older pediatric patients (i.e. younger than two years of age). Please let me know if either of the following dates and times are acceptable: July 3 from 2PM - 3PM or July 5 from 3:30PM - 4:30PM.

Thanks.

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/s/  
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BRIAN K STRONGIN  
07/26/2012

**Strongin, Brian K**

---

**From:** Strongin, Brian K  
**Sent:** Friday, July 13, 2012 1:11 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS FDA Marked-Up and Clean Package Insert and MedGuide

**Attachments:** Linaclotide PI FDA Clean 7-13-12.doc; Linaclotide PI FDA Mark-UP.doc

Here is a marked-up and clean copy of the package insert and MedGuide in preparation for our t-con on Monday afternoon. Thanks and sorry for the delay.



Linaclotide PI FDA Clean 7-13-...  
Linaclotide PI FDA Mark-UP.doc...

54 Page(s) 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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BRIAN K STRONGIN  
07/17/2012

MEMORANDUM

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

**DATE:** July 3, 2012

**TO:** NDA 202-811; LINZESS (linaclotide) Capsules

**FROM:** Brian Strongin, R.Ph., MBA  
Chief Project Management Staff  
Division of Gastroenterology and Inborn Errors Products

**SUBJECT:** Non-Clinical Post-Marketing Requirements

**Sponsor Attendees:**

Forest Laboratories Inc.

June Bray, RPh, MBA	Senior Vice President, FRI Regulatory Affairs
James DeMartino, PhD	Senior Director, Regulatory Affairs
Linda Kunka, MA	Senior Manager, Regulatory Affairs
Donato Forlenza, PharmD, MBA	Post-Doctoral Fellow, Regulatory Affairs
Gavin Corcoran, MD	Executive Vice President, R&D Clinical & Early Development
Harvey Schneier, MD	Executive Director, Clinical Development Internal Medicine & GI
Steven Shiff, MD	Director, Clinical Development
Charles Lindamood III, Ph.D., D.A.B.T.	Executive Director, Early Development
Anne Gilson	Principal Scientist, Toxicology
Christina Carruthers	Principal Scientist, Toxicology
George Zhang	Senior Principal Scientist
Carrie Furin	Project Manager III

Ironwood Pharmaceuticals

Mark Currie, PhD	Senior VP R&D, Chief Scientific Officer
Gwyn Reis	Vice President, Regulatory Affairs
Sarah Lieber, MS	Associate Director, Regulatory Affairs
Caroline Kurtz, PhD	Vice President, Program Management
Jeff Johnston, MD	Vice President, Clinical Development, and Chief Medical Officer

Joseph Lavins, MD  
Alex Bryant, PhD

Adeline Smith PhD

Senior Director, Clinical Research  
Vice President, Drug Metabolism and  
Pharmacokinetics  
Director, Toxicology

**FDA Attendees:**

Vickie Kusiak, M.D.  
Donna Griebel, M.D.

Andrew Mulberg, M.D.,  
Joyce Korvick, M.D.  
Ruyi He, M.D.  
Rob Fiorentino, M.D.  
Erica Wynn, M.D.  
Lara Dimick M.D.  
David Joseph, Ph.D.  
Yuk-Chow Ng, Ph.D.  
Melissa Tassinari, M.D.

Elizabeth Durmowicz, M.D.  
Matt Bacho  
Brian Strongin, R Ph, M.B.A.

Deputy Director, Office of Drug Evaluation III  
Director, Division of Gastroenterology and Inborn  
Errors Products (DGIEP)  
Deputy Director, DGIEP  
Deputy Director for Safety, DGIEP  
Medical Team Leader, DGIEP  
Medical Team Leader, DGIEP  
Medical Reviewer, DGIEP  
Medical Reviewer, DGIEP  
Pharmacology Team Leader  
Pharmacology Reviewer  
Senior Clinical Analyst, Pediatric and Maternal  
Health Staff (PMHS)  
Medical Officer, PMHS  
Senior Regulatory Health Project Manager, PMHS  
Chief, Project Management Staff, DGIEP

Background

NDA 202-811, sponsor Forest Laboratories, for LINZESS (linaclotide) Capsules, submitted and received August 9, 2011 provides for the treatment of IBS-C and chronic constipation. Sponsorship changed from Ironwood Pharmaceuticals to Forest Laboratories after the NDA was submitted. Linaclotide is an NME.

Linaclotide was lethal in two separate toxicology studies in juvenile mice. The mechanism for this lethality is unknown.

Linaclotide was lethal at 10 mcg/kg/day in neonatal mice after oral administration of 1 or 2 daily doses, starting on post partum day 7. Lethality was also observed in juvenile mice after a single oral administration on post partum day 14 (100 mcg/kg) and post partum day 21 (600 mcg/kg). The deaths were identified in mice with ages approximately equivalent to human infants and children age 1 to 23 months. There were no deaths in the control groups. There is currently no data for mice between ages of 21 days and 6 weeks. Linaclotide was not lethal in a study in juvenile mice age 6 weeks (approximately equivalent to humans age 12 to 16 years) at a dose of 20,000 mcg/kg/day for 28 days. The maximum recommended dose in adults is approximately 5 mcg/kg/day, based on a 60-kg body weight.

At today's teleconference, we discussed the following non-clinical post-marketing requirements related to the deaths in juvenile mouse studies:

1. A study to determine the mechanism of lethality
2. A study to obtain a more complete understanding of how sensitivity to linaclotide lethality changes with age in juvenile mice and to inform about the potential risk in older pediatric patients (i.e. older than 2 years).

### Teleconference Discussion

The sponsor provided an overview of a position paper submitted to the NDA June 25, 2012. They contended that the totality of evidence supports exaggerated pharmacology manifested as an increased fluid secretion in juvenile mice. Mice are uniquely sensitive to increased fluid secretion in the gastrointestinal tract. The gastrointestinal tract is undeveloped in neonatal mice, which is the key difference between neonatal mice and human neonates. Mice have an underdeveloped capacity for water absorption. Neonatal mice have a higher level of intestinal GC-C receptors.

The FDA responded that this hypothesis was well presented and reasonable. Concern was expressed that there was no evidence in support of the sponsor's hypothesis, based on the Agency's review of the neonatal/juvenile mouse toxicity studies. The actual cause of lethality was not determined in the macroscopic and microscopic examinations, although it is clear from previous studies that the lethal dose levels were pharmacologically active in neonatal mice. There was no indication in the data about the exact cause of death, although the deaths were clearly drug related. GC-C receptors are found in other parts of the body, not just in the gastrointestinal tract, so it is possible that systemic effects were involved in the lethality in neonatal/juvenile mice. The active metabolite was detected in one plasma sample from neonatal mice, which is suggestive of systemic absorption.

The sponsor contended that a significant body of evidence in support of exaggerated pharmacology exists. They will submit more data to demonstrate this.

The FDA asked if the sponsor had ideas about further studies to investigate the mechanism of juvenile mouse deaths. The sponsor stated that they believe that the deaths were linked to a fluid shift into the intestine and will evaluate this in neonatal mice. Fluid secretion and its link to mortality will be a major endpoint in these studies and diarrhea and electrolyte shift will also be important. They added that intestinal weight is a possible endpoint. The FDA suggested that the sponsor investigate systemic exposure as well as intestinal fluid shift. The Agency is looking for assurance that the deaths were not due to unexpected systemic exposure, and stated that detection of drug or its active metabolite in plasma would evoke more concern and questions.

The sponsor stated that evidence exists that GC-C is expressed in other tissues, but there are very low levels outside the gastrointestinal tract and that GC-C outside the gastrointestinal tract has

little role in physiologic function. The FDA requested a study to investigate the mechanism of lethality in neonatal/juvenile mice. The sponsor responded that they will attempt to demonstrate an exaggerated pharmacological effect (i.e. excessive fluid secretion in the intestine), and a lack of systemic absorption as the first step. The agency stated that the next step is to generate data in age groups not explored, looking at lethality and general toxicity as mice mature.

The sponsor contended that they need to study mice with a more fully developed gastrointestinal tract. Neonatal mice are not representative of the human gastrointestinal tract and a dramatic maturation occurs after about 3 weeks of age, post-weaning.

The FDA stated that the sponsor's approach appears to be reasonable. Testing mice at age 4 weeks is a reasonable place to start. Doses up to 20,000 mcg/kg were tolerated at 6 weeks of age in mice. If deaths occur in 4 week-old mice, then 5-week old mice should be studied. If no deaths occur in 4-week old mice, then no more study is needed.

FDA suggested a high dose of 20,000 mcg/kg/day in 4-week old mice, since the same dose was used in 6-week old mice. The sponsor stated that a 20,000 mcg/kg dose is dramatically higher than the clinical dose. They asked if a smaller dose was acceptable, and proposed 500 mcg/kg/day (given for one week) as the high dose, which is 100-fold greater than the intended adult human dose.

The FDA stated that in the context of the existing lethality data, the use of 500 mcg/kg/day was not adequate, given that 100% mortality was seen at 600 mcg/kg in 21-day old mice. The Agency requested a higher dose in 28-day old mice (i.e. 1000 or 1200 mcg/kg as the high dose), to allow for evaluation of a shift in the lethality curve in 4-week old mice. The FDA and sponsor agreed that 1000 mcg/kg was reasonable for use as the high dose.

The sponsor stated that the first study will look at fluid shift as a mechanism of mortality. They will also look at other clinical parameters and evaluate the systemic exposure in neonatal mice.

They stated that their second study will look at 4-week old mice dosed for 7 days with 1000 mcg/kg as the high dose.

The discussion then turned to the sponsor's proposed pediatric plan. (b) (4)

The FDA responded that the requested animal data are needed before any human studies in pediatrics may proceed. The sponsor responded that they will submit a revised pediatric plan including nonclinical studies.

The call then concluded.

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/s/  
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BRIAN K STRONGIN  
08/01/2012

**Strongin, Brian K**

---

**From:** Strongin, Brian K  
**Sent:** Tuesday, June 19, 2012 5:18 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** RE: NDA 202-811 LINZESS Information Request

One more correction: the study should inform about the potential risk in patients older than 2 years of age, not younger. Thanks.

---

**From:** Strongin, Brian K  
**Sent:** Tuesday, June 19, 2012 5:13 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** RE: NDA 202-811 LINZESS Information Request

I wanted to add two clarifications about the second study: "a study to obtain a more complete understanding of how sensitivity to linaclotide lethality changes with age in juvenile mice and to inform about the potential risk in older pediatric patients (i.e. younger than two years of age)." This study should be conducted in mice between 3 - 6 weeks of age. Also, at the teleconference, please be prepared to discuss your ideas about the types of studies that can address these PMRs. Thanks.

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Tuesday, June 19, 2012 4:23 PM  
**To:** Strongin, Brian K  
**Subject:** RE: NDA 202-811 LINZESS Information Request

Hi Brian:

July 3<sup>rd</sup> at 2PM – 3PM will work for us. Please use the number below.

Toll-free dial-in number (U.S. and Canada):

(b) (6)

Conference code:

(b) (6)

Thanks.

LK

---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Tuesday, June 19, 2012 1:59 PM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** NDA 202-811 LINZESS Information Request

We have the following comments and information request. Please respond to the information request ASAP:

1. On further consideration, we will be changing the (b) (4) related to pediatric use to a Boxed Warning and a Warning and Precaution. A revised marked-up package insert will be sent soon.
2. Change the FDA Approved Patient Labeling section of the package insert to a Medication Guide. Prominently include information on the risks of LINZESS use in the pediatric population.
3. We would like to schedule a teleconference the week of July 2 to discuss the following post-marketing requirements: a study to determine the mechanism of the deaths in juvenile mouse studies and a study to obtain a more complete understanding of how sensitivity to linaclotide lethality changes with age in juvenile mice and to inform about the potential risk in older pediatric patients (i.e. younger than two years of age). Please let me know if either of the following dates and times are acceptable: July 3 from 2PM - 3PM or July 5 from 3:30PM - 4:30PM.

Thanks.

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/s/  
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BRIAN K STRONGIN  
06/19/2012

## Strongin, Brian K

---

**From:** Strongin, Brian K  
**Sent:** Tuesday, June 19, 2012 1:59 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** NDA 202-811 LINZESS Information Request

We have the following comments and information request. Please respond to the information request ASAP:

1. On further consideration, we will be changing the (b) (4) related to pediatric use to a Boxed Warning and a Warning and Precaution. A revised marked-up package insert will be sent soon.
2. Change the FDA Approved Patient Labeling section of the package insert to a Medication Guide. Prominently include information on the risks of LINZESS use in the pediatric population.
3. We would like to schedule a teleconference the week of July 2 to discuss the following post-marketing requirements: a study to determine the mechanism of the deaths in juvenile mouse studies and a study to obtain a more complete understanding of how sensitivity to linaclotide lethality changes with age in juvenile mice and to inform about the potential risk in older pediatric patients (i.e. younger than two years of age). Please let me know if either of the following dates and times are acceptable: July 3 from 2PM - 3PM or July 5 from 3:30PM - 4:30PM.

Thanks.

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/s/  
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BRIAN K STRONGIN  
06/19/2012

**Strongin, Brian K**

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**From:** Strongin, Brian K  
**Sent:** Monday, June 11, 2012 12:50 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** FW: LINZESS: Marked-UP Package Insert

**Attachments:** LINZESS Marked-Up PI 6-11-12.PDF; LINZESS Mark-Up 6-8-12.doc

I forgot to tell you that I removed the section titled FDA Approved Patient Labeling from this mark-up. We will receive comments from the patient labeling team on this section in about two weeks. I'll send those comments after I receive them and our review team has had a chance to discuss them. Thanks.

---

**From:** Strongin, Brian K  
**Sent:** Monday, June 11, 2012 9:10 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS: Marked-UP Package Insert

Please see the attached package insert with initial labeling comments from the review team. As review of the label continues, additional recommendations will be provided during labeling discussions. In addition to the PDF label, an identical copy of the label is provided in WORD format for your convenience.



.INZESS Marked-Up LINZESS Mark-Up  
PI 6-11-12.P... 6-8-12.doc (47...

44 Page(s) 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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BRIAN K STRONGIN  
06/11/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

MEMORANDUM

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

DATE: June 8, 2012

TO: NDA 202-811, LINZESS (linaclotide) Capsules

FROM: Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products

SUBJECT: Teleconference Regarding Labeling Mark-Up

**FDA Attendees:**

Victoria Kusiak, M.D.  
Deputy Director  
Office of Drug Evaluation III

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Ruyi He, M.D.  
Medical Team Leader  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Robert Fiorentino, M.D.  
Medical Team Leader  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Erica Wynn, M.D.  
Medical Officer  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

David Joseph, Ph.D.  
Pharmacology/Toxicology Team Leader  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Yuk-Chow Ng, Ph.D.  
Pharmacology/Toxicology Reviewer  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

Maria Walsh, M.S.N.  
Associate Director of Regulatory Affairs  
Office of Drug Evaluation III

Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and Inborn Errors Products  
Office of Drug Evaluation III

**Sponsor Attendees:**

Forest Laboratories Inc.

Marco Taglietti, MD  
Sr. VP, R&D and President, FRI

June Bray, RPh, MBA  
Senior Vice President, FRI Regulatory Affairs

James DeMartino, PhD  
Senior Director, Regulatory Affairs

Linda Kunka, MA  
Senior Manager, Regulatory Affairs

Gavin Corcoran, MD  
Executive Vice President, R&D Clinical & Early Development

Harvey Schneier, MD

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Vice President, Biometrics

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Director, Toxicology

Ada Silos-Santiago PhD  
Director, Clinical Pharmacology

## **Background**

NDA 202-811 for LINZESS (linaclotide) Capsules was submitted August 9, 2011 for the treatment of constipation (b) (4) irritable bowel syndrome and chronic constipation. The sponsor proposed 145 mcg and 290 mcg doses for the chronic constipation indication. Linaclotide was lethal at 10 mcg/kg/day orally in neonatal mice after administration of 1 or 2 daily doses, starting on post partum day 7. Lethality was also observed in juvenile mice after a single oral administration on post partum day 14 (100 mcg/kg) and post partum day 21 (600 mcg/kg). The Division had prepared substantially complete, marked-up labeling and requested this teleconference to discuss two issues: (b) (4) (b) (4) and the addition of language regarding deaths in juvenile mouse studies.

## **Today's Call**

After introductions, Dr. Fiorentino stated that the Division had (b) (4) (b) (4). He added that the efficacy difference between the 145 mcg and 290 mcg doses was small. The Division tried to identify a subgroup with a clear benefit from the higher dose, but couldn't find one.

Dr. Griebel added that this issue could be discussed more in the future.

The discussion then turned to the issue of deaths in juvenile mouse studies. Dr. Griebel expressed concern about the unknown safety of the product in the pediatric population. The Division added a Contraindication in pediatrics until more information was obtained about the mechanism of toxicity. Dr. Griebel added that the sponsor could present their side during labeling negotiations.

The sponsor asked if the deaths in juvenile mouse studies would impact the conduct of pediatric studies. Dr. Griebel responded that the Division did not want pediatric studies in patients 17 years and younger until this issue is clarified with non-clinical data.

In response to the sponsor's question, Dr. Griebel stated that the Division was not ready to discuss post-marketing requirements/commitments related to this issue at that time.

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/s/  
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BRIAN K STRONGIN  
06/13/2012

**From:** Strongin, Brian K  
**Sent:** Wednesday, May 23, 2012 12:23 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Statistical Information Request  
Please respond to this statistical information request ASAP. Thanks.

- A. Please refer to “Table 14.4.3.18 D” for Studies LIN-MD-01 and MCP-103-303. We are unable to reproduce these tables by deriving the CSBM monthly responder rate using the CSBM weekly responder data, PARAMCD=“OCSBMRESP”, provided in SAS transport file ADEFF. Please provide the SAS codes used to obtain the CSBM monthly responder data
- B. For Studies MCP-103-303 and LIN-MD-01 please perform the following:
1. Perform subgroup analyses of primary efficacy endpoint by BMI ( $\geq 30$  kg/m<sup>2</sup> vs.  $< 30$  kg/m<sup>2</sup>) and baseline constipation severity per study.
  2. Perform observed case analyses of monthly responder for CSBM by month per study; monthly responders are defined as subjects who are weekly responders for at least 3 weeks in a month.
  3. Perform observed case analyses of overall responder analyses for CSBM only per study; overall responders are defined subjects who are monthly responders for all three months.
  4. Provide a SAS transport file for monthly data for CSBM per study for observed data (no imputation).
  5. Provide numbers of patients with at least one AE, at least one TRAE, withdrawn due to AE, at least one episode of diarrhea, and discontinued due to TRAE of Diarrhea for pooled data
- C. For Studies MCP-103-302 and LIN-MD-31, please perform the following:
1. Perform a subgroup analysis of abdominal pain and CSBM by BMI ( $\geq 30$  kg/m<sup>2</sup> vs.  $< 30$  kg/m<sup>2</sup>) per study.
  2. Provide a SAS transport file for monthly data for abdominal pain and CSBM, abdominal pain alone, and CSBM alone per study for observed data (no imputation)

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/s/  
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BRIAN K STRONGIN  
05/23/2012

**Strongin, Brian K**


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**From:** Strongin, Brian K  
**Sent:** Tuesday, May 22, 2012 4:44 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** RE: FDA Mark-Up of a Few Sections of the LINZESS Package Insert  
**Attachments:** LINZESS Partial PPI Mark-Up 5-22-12.doc

Thanks for catching it. I've attached a more clear document.

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Friday, May 18, 2012 10:43 AM  
**To:** Strongin, Brian K  
**Subject:** RE: FDA Mark-Up of a Few Sections of the LINZESS Package Insert

Hi Brian:

On printing the document you sent me I noticed that there were additional pages that included some comments on other sections. I am not distributing the document you sent me to the team here. I am only circulating the sections listed below. (I went through the document and accepted/deleted the other comments and deletions).

I just wanted you to know in case you needed to make any adjustments. Thanks.

LK

---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Friday, May 18, 2012 8:48 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** FDA Mark-Up of a Few Sections of the LINZESS Package Insert

I've attached out mark-up of the following sections of your proposed package insert:

Dosage Forms and Strengths  
Drug Interactions  
Overdosage  
Description  
Clinical Pharmacology  
How Supplied/Storage and Handling

I anticipate being able to send more marked-up sections on May 29 or May 30. Thanks.

Also: I'm on leave today and Monday, but will be checking e-mails. Thanks.

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4 Page(s) 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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BRIAN K STRONGIN  
05/22/2012

**From:** Strongin, Brian K  
**Sent:** Monday, May 07, 2012 8:51 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** May 4, 2012 Response to Clinical Information Request for NDA 202811, LINZESS  
[Please respond to this information request ASAP.](#)

For Figures 3.1 and 3.2, please provide the absolute values that correspond with bar graphs .

[Thanks.](#)

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Friday, May 04, 2012 5:10 PM  
**To:** Strongin, Brian K  
**Subject:** RE: Clinical Information Request for NDA 202811, LINZESS

Hi Brian:

The attached files provide our response to your May 2nd request listed below. FDA's request is in [blue text](#) and the Sponsor response follows in black text.

We will follow this e-mail communication with a formal gateway submission.

Please let me know if you have any questions. Thanks.

LK

---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Wednesday, May 02, 2012 11:08 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for NDA 202811, LINZESS

[Please respond to this information request ASAP.](#) Thanks.

We are assessing the treatment benefit patients may achieve with the 145ug dose and the 290ug dose of Linaclotide. As a part of this, we are exploring patient's perception of disease severity at baseline and the treatment difference achieved with the 145ug and 290ug doses. We are characterizing the population of patients enrolled in your trial to attempt to identify a patient population for which the 290ug may offer an additional benefit.

1) For each of the treatment groups (placebo, 145ug and 290ug) please tabulate average weekly SBM (and CSBM) at baseline and at each week over the 12 weeks of the Treatment Period.

You should present this information descriptively and graphically.

2) In addition, for the 145ug and 290 ug doses, please present descriptively (and graphically if possible) the treatment difference (treatment - placebo) with 95%CIs for the primary efficacy response variable by average weekly SBM (and CSBM) at baseline. The results of the SBM and CSBM tabulations should be presented separately.

3) For each baseline patient reported constipation severity levels (i.e. none, mild, moderate, severe, very severe) please tabulate the proportion of patients that had 0, 1, 2, 3,...n SBMs (and CSBMs). Again this information should be presented descriptively (and graphically if possible).

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/s/  
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BRIAN K STRONGIN  
05/07/2012



NDA 202811

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Blake Burrell, MS, RAC  
Senior Manager, Regulatory Affairs-CMC  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Mr. Burrell:

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

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

1. All methods for drug product (b) (4)  

  2. All methods for drug product (b) (4)  

  3. Method for the analysis of linaclotide by SEC for Ironwood Pharmaceuticals, Inc. (MOA-0091-01): (b) (4)  

  4. Method for the analysis of identification, assay and purity of Linaclotide by HPLC (MOA-0093-04): (b) (4)  

- c. In section 8.8, calculation should be for %Impurity not %Purity.

- d. In section 8.8, relative retention times should be listed for identification of specified impurities.
5. Method for the analysis of identification, assay and purity of Linaclotide by HPLC (MOA-0094-03):

Please refer to all comments for method MOA-0093-04 above.

6. [Redacted] (b) (4)
7. [Redacted] (b) (4)
8. Identification, assay and content uniformity (by [Redacted] (b) (4)) for Linaclotide capsules, 145µg and 290µg (PRD-TM-ANL-00770):

- a. [Redacted] (b) (4)
- b. [Redacted] (b) (4)

9. [Redacted] (b) (4)

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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CATHERINE A TRAN-ZWANETZ  
05/03/2012

MOO JHONG RHEE  
05/03/2012  
Chief, Branch IV

**From:** Strongin, Brian K  
**Sent:** Wednesday, May 02, 2012 11:08 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for NDA 202811, LINZESS  
[Please respond to this information request ASAP. Thanks.](#)

We are assessing the treatment benefit patients may achieve with the 145ug dose and the 290ug dose of Linaclotide. As a part of this, we are exploring patient's perception of disease severity at baseline and the treatment difference achieved with the 145ug and 290ug doses. We are characterizing the population of patients enrolled in your trial to attempt to identify a patient population for which the 290ug may offer an additional benefit.

1) For each of the treatment groups (placebo, 145ug and 290ug) please tabulate average weekly SBM (and CSBM) at baseline and at each week over the 12 weeks of the Treatment Period. You should present this information descriptively and graphically.

2) In addition, for the 145ug and 290 ug doses, please present descriptively (and graphically if possible) the treatment difference (treatment - placebo) with 95%CIs for the primary efficacy response variable by average weekly SBM (and CSBM) at baseline. The results of the SBM and CSBM tabulations should be presented separately.

3) For each baseline patient reported constipation severity levels (i.e. none, mild, moderate, severe, very severe) please tabulate the proportion of patients that had 0, 1, 2, 3,...n SBMs (and CSBMs). Again this information should be presented descriptively (and graphically if possible).

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BRIAN K STRONGIN  
05/02/2012

**From:** Wilkins Parker, Jamie  
**Sent:** Wednesday, April 25, 2012 10:08 AM  
**To:** Strongin, Brian K  
**Cc:** Maslov, Yelena  
**Subject:** Revised Linzess Labels  
Good Morning Brian  
The revised Carton and Container Labels for Linzess are acceptable.

Thank you!

Jamie Wilkins Parker

**Jamie Wilkins Parker, Pharm.D.**  
Safety Evaluator  
Division of Medication Error Prevention and Analysis  
FDA/CDER/OSE/OMEPRM  
WO22-4443  
301.796.6113 (p)

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BRIAN K STRONGIN  
04/26/2012



NDA 202-811

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Forest Laboratories, Inc.  
Attention: Linda Kunka  
Senior Manager, Regulatory Affairs  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Ms. Kunka

Please refer to your August 8, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LINZESS (linaclotide).

On April 18, 2012, we received your April 17, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 9, 2012

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 11, 2012.

If you have any questions, call me at (301) 796-1008

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., MBA  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
04/19/2012

## Strongin, Brian K

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**From:** Strongin, Brian K  
**Sent:** Wednesday, April 18, 2012 10:28 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Clinical Information Request

**Attachments:** AEs over 65 subset.doc; 4.19.12.AEDECODE.doc

Please respond to this information request ASAP. Thanks.



AEs over 65  
subset.doc (82 KB)..



4.19.12.AEDECODE  
.doc (35 KB)

Please refer to "Table 11.1.1.1.1-1 Incidence of Treatment-Emergent Adverse Events in  $\geq 2\%$  and  $\geq 2$  Patients in Either Age Category who Received Linacotide in the Phase 3 CC Placebo-Controlled Trials Combined (Group 1)—Safety Population"

We are unable to reproduce this table. For example our analysis for the data show that for the  $\geq 65$  year old age group, there were 31 total incidences of diarrhea (16 in the 145ug group, 6 in the 290ug and 9 in the Placebo group). Please advise how this data was generated and a reason for the discrepancies. (A subset of the data we generated for the  $\geq 65$  year old age group in attached for your convenience.)

**Table 11.1.1.1-1. Incidence of Treatment-Emergent Adverse Events in  $\geq 2\%$  and  $\geq 2$  Patients in Either Age Category who Received Linaclootide in the Phase 3 CC Placebo-Controlled Trials Combined (Group 1)—Safety Population**

	<b>&lt; 65 Years</b>										<b><math>\geq 65</math> years</b>				
	<i>Linaclootide</i>					<i>Linaclootide</i>									
	<i>Placebo</i> (N = 369)	<i>145 ug</i> (N = 379)	<i>290 ug</i> (N = 373)	<i>Total</i> (N = 752)	<i>Placebo</i> (N = 55)	<i>145 ug</i> (N = 51)	<i>290 ug</i> (N = 49)	<i>Total</i> (N = 100)							
<b>Patients with at least one TEAE</b>	<b>186 (50.5)</b>	<b>229 (60.4)</b>	<b>207 (55.5)</b>	<b>436 (58.0)</b>	<b>36 (65.5)</b>	<b>33 (64.7)</b>	<b>28 (57.1)</b>	<b>61 (61.0)</b>							
Diarrhea	16 (4.3)	54 (14.2)	54 (14.5)	108 (14.4)	4 (7.3)	15 (29.4)	6 (12.2)	21 (21.0)							
Flatulence	20 (5.4)	19 (5.0)	15 (4.0)	34 (4.5)	2 (3.6)	5 (9.8)	6 (12.2)	11 (11.0)							
Abdominal pain	11 (3.0)	15 (4.0)	17 (4.6)	32 (4.3)	2 (3.6)	2 (3.9)	3 (6.1)	5 (5.0)							
Upper respiratory tract infection	14 (3.8)	21 (5.5)	13 (3.5)	34 (4.5)	3 (5.5)	1 (2.0)	0	1 (1.0)							
Nausea	13 (3.5)	15 (4.0)	16 (4.3)	31 (4.1)	2 (3.6)	0	2 (4.1)	2 (2.0)							
Headache	17 (4.6)	13 (3.4)	16 (4.3)	29 (3.9)	2 (3.6)	2 (3.9)	1 (2.0)	3 (3.0)							
Abdominal distension	10 (2.7)	13 (3.4)	13 (3.5)	26 (3.5)	0	2 (3.9)	2 (4.1)	4 (4.0)							
Urinary tract infection	12 (3.3)	13 (3.4)	10 (2.7)	23 (3.1)	3 (5.5)	2 (3.9)	2 (4.1)	4 (4.0)							
Nasopharyngitis	13 (3.5)	5 (1.3)	16 (4.3)	21 (2.8)	0	4 (7.8)	1 (2.0)	5 (5.0)							
Sinusitis	6 (1.6)	12 (3.2)	11 (2.9)	23 (3.1)	2 (3.6)	1 (2.0)	0	1 (1.0)							
Abdominal pain upper	7 (1.9)	12 (3.2)	5 (1.3)	17 (2.3)	0	1 (2.0)	0	1 (1.0)							
Back pain	9 (2.4)	6 (1.6)	7 (1.9)	13 (1.7)	1 (1.8)	1 (2.0)	1 (2.0)	2 (2.0)							
Bronchitis	7 (1.9)	3 (0.8)	4 (1.1)	7 (0.9)	2 (3.6)	2 (3.9)	1 (2.0)	3 (3.0)							
Hypertension	1 (0.3)	2 (0.5)	2 (0.5)	4 (0.5)	1 (1.8)	2 (3.9)	1 (2.0)	3 (3.0)							
Fatigue	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.4)	0	3 (5.9)	0	3 (3.0)							
Pain in extremity	1 (0.3)	1 (0.3)	3 (0.8)	4 (0.5)	1 (1.8)	0	2 (4.1)	2 (2.0)							
Hematuria	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (1.8)	2 (3.9)	0	2 (2.0)							
Abdominal pain lower	5 (1.4)	0	1 (0.3)	1 (0.1)	0	1 (2.0)	1 (2.0)	2 (2.0)							
Orthostatic hypotension	0	0	1 (0.3)	1 (0.1)	0	1 (2.0)	1 (2.0)	2 (2.0)							

Source: After-text Table 4.1.3.1B.

AEDECODE	N (Placebo)	N (Linaclotide 133ug)	N (Linaclotide 266ug)	N Rows
Diarrhoea	9	16	6	31
Flatulence	3	6	6	15
Urinary tract infection	5	5	4	14
Abdominal pain	2	3	4	9
Nasopharyngitis	0	5	2	7
Upper respiratory tract infection	4	1	2	7
Abdominal distension	1	3	2	6
Bronchitis	2	3	1	6
Headache	2	3	1	6
Nausea	2	2	2	6
Sinusitis	2	2	1	5
Atrial fibrillation	2	2	0	4
Fatigue	0	3	1	4

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/s/  
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BRIAN K STRONGIN  
04/19/2012

**Strongin, Brian K**

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**From:** Strongin, Brian K  
**Sent:** Tuesday, April 17, 2012 1:10 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Clinical Information Request - Additional Request  
**Attachments:** FDA Apr 10 #2.zip; Final Response April 10 IR.pdf

Please respond to this information request ASAP.

Chronic constipation patients rated their symptoms as mild, moderate, or severe at baseline. Please reanalyze the data submitted, stratifying by baseline severity as indicated by the patients.

Thanks.

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Monday, April 16, 2012 2:42 PM  
**To:** Strongin, Brian K  
**Subject:** LINZESS Clinical Information Request

Hi Brian:

The attached pdf file provides our response to your April 10th request listed below. FDA's request is in blue text and the Sponsor response follows in black text. Tables generated to support Question 2 are located in the attached zip file.

We will follow this e-mail communication with a formal gateway submission.

Please let me know if you have any questions. Thanks.

LK

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**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Tuesday, April 10, 2012 10:44 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Clinical Information Request

Please respond to this information request ASAP. Thanks.

1) In your application you state, "...the difference in efficacy between the 145-ug and the 290-ug doses suggests that there are patients who are more likely to benefit from the 290-ug dose." However, the data from the pivotal Phase 3 double blind, chronic constipation trials demonstrated that the primary response efficacy of the 145-ug and the 290-ug doses were comparable (20.3% and 19.4% respectively in Study MCP-103-303; 15.5% and 20.5% in Study LIN- MD-01). We have been unable to identify a subgroup of patients that are "more likely to benefit" from the 290ug than the 145ug dose. Please provide subgroup analyses

(using the primary endpoint as a response variable) that identify which patients (based on baseline disease characteristics and demographics) would be "more likely" to benefit from the 290 ug dose compared to the 145ug dose. Please provide additional rationale for use of the 290ug dose in the chronic constipation population.

2) Please provide a demographic analysis of the Long-term safety trial data on the dose reduced group, divided by those who stayed on the reduced dose and those who were discontinued, by age, sex, race, ethnicity, BMI (i.e. a sub analysis of Table 2.4.1) from the 120-day safety update. Also analyze the dose reduced groups, divided by those who stayed on the reduced dose and those who were discontinued, by concomitant medication and associated other baseline characteristics.

Thanks.

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**FDA Inquiry 1:**

In your application you state, "...the difference in efficacy between the 145-ug and the 290-ug doses suggests that there are patients who are more likely to benefit from the 290-ug dose." However, the data from the pivotal Phase 3 double blind, chronic constipation trials demonstrated that the primary response efficacy of the 145-ug and the 290-ug doses were comparable (20.3% and 19.4% respectively in Study MCP-103-303; 15.5% and 20.5% in Study LIN- MD-01). We have been unable to identify a subgroup of patients that are "more likely to benefit" from the 290ug than the 145ug dose. Please provide subgroup analyses (using the primary endpoint as a response variable) that identify which patients (based on baseline disease characteristics and demographics) would be "more likely" to benefit from the 290 ug dose compared to the 145ug dose. Please provide additional rationale for use of the 290ug dose in the chronic constipation population.

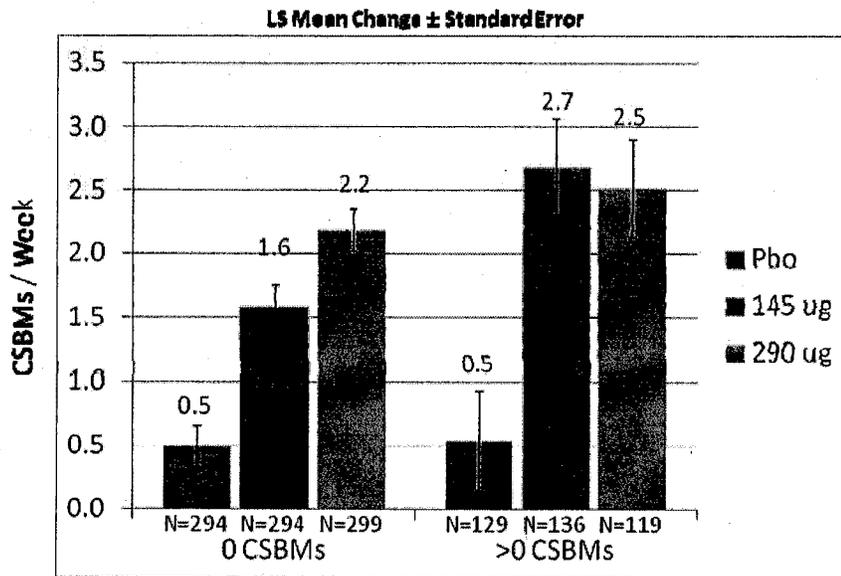
**Sponsor Response 1:**

To examine the effect of the 290 ug dose compared with the 145 ug dose, subgroup analyses of the primary efficacy parameter (12-week CSBM Overall Responder) were performed based on baseline disease characteristics and demographics using the Pooled CC Phase 3 ITT Population. We have not identified a subgroup based on demographics that had meaningful differences in response between the 145 and 290 ug doses for the primary responder endpoint. However, the results indicate that patients with severe constipation symptoms are more likely to respond to the 290 ug dose than the 145 ug dose. Specifically, among patients who had no CSBMs/week at baseline, a greater percentage of those who received the 290 ug dose met the 12-week CSBM Overall Responder criterion than those who received the 145 ug dose (18.7% vs. 13.3%,  $p=0.0734$ ).

The benefit of the 290 ug dose over the 145 ug dose for patients with severe constipation symptoms was more clearly demonstrated when subgroup analyses were performed on Change from Baseline in 12-week CSBM Frequency Rate, a secondary efficacy parameter that is based on the primary efficacy assessment but represents a more sensitive measure than a dichotomous responder endpoint. Analyses show that among patients who had no CSBMs/week at baseline, those who received the 290 ug dose had a least-squares (LS) mean change of 2.2 CSBMs/week from baseline, compared with an LS mean change of 1.6 CSBMs/week for those who received the 145 ug dose ( $p=0.0014$ , see the figure below). Additionally, among patients who had  $<1$  SBMs/week at baseline, those who received the 290 ug dose had an LS mean change of 1.8 CSBMs/week from baseline, compared with an LS mean change of 1.3 CSBMs/week for those who received the 145 ug dose ( $p=0.0439$ ). For patients who suffer from severe constipation symptoms, an improvement of 0.5-0.6 CSBMs/week with the 290 ug dose over and above the  $\sim 1$  CSBM/week treatment effect (difference between active and placebo) with the 145 ug dose is important and clinically meaningful. Similar results were observed for subgroups based on severity of straining, while the subgroup based on stool consistency showed a trend favoring treatment with 290 ug dose compared to the 145 ug dose in the more severe subgroup. The detailed results of these subgroup analyses are presented in the table below.

In conclusion, patients with more severe constipation symptoms are likely to experience more benefit from the 290 ug dose.

**Figure: 12-Week Change from Baseline in CSBMs Stratified by Baseline CSBMs  
(Pooled CC Phase 3 ITTT Population)**



**Unacloctide 145ug vs. 290 ug p-value =0.0014      Unacloctide 145 ug vs. 290 ug p-value =0.6646**

**Note: Results are based on an ANCOVA model with treatment group and geographic region as factors and baseline value as a covariate.**

**Table: Subgroup Analyses based on Baseline Constipation Symptoms**

Subgroup Variable	Subgroup	12-week CSBM Overall Responder						Change from Baseline in 12-week CSBM Frequency Rate					
		145 ug		290 ug		p-Value	145 ug		290 ug		p-Value		
		N	n (%)	N	n (%)		N	Mean (Std Err)	N	Mean (Std Err)			
Baseline CSBM Frequency Rate	0*	294	39 (13.3)	299	56 (18.7)	0.0734	294	1.587 (0.165)	299	2.186 (0.163)	0.0014		
	>0	136	41 (30.1)	119	29 (24.4)	0.2044	136	2.680 (0.387)	119	2.518 (0.385)	0.6646		
Baseline SBM Frequency Rate	<1*	160	15 (9.4)	159	23 (14.5)	0.2096	160	1.323 (0.210)	159	1.809 (0.205)	0.0439		
	≥1	270	65 (24.1)	259	62 (23.9)	0.9057	270	2.244 (0.218)	259	2.571 (0.223)	0.1601		
Baseline Stool Consistency	<2*	126	22 (17.5)	127	22 (17.3)	0.9313	126	1.739 (0.327)	127	2.292 (0.339)	0.0896		
	≥2	247	56 (22.7)	235	57 (24.3)	0.8138	247	2.232 (0.219)	235	2.584 (0.216)	0.1423		
Baseline Severity of Straining	<3.5	229	51 (22.3)	205	47 (22.9)	0.7742	229	2.249 (0.217)	205	2.377 (0.218)	0.6026		
	≥3.5*	144	27 (18.8)	157	32 (20.4)	0.7520	144	1.843 (0.337)	157	2.603 (0.349)	0.0174		

• \* indicates more severe subgroup within the subgroup variable

• P-values for the responder endpoint are obtained from Cochran-Mantel-Haenszel (CMH) tests controlling for trial and geographic region.

• P-values for the change-from-baseline endpoint are obtained from analysis of covariance (ANCOVA) models with fixed-effect terms for trial, geographic region, and treatment group and baseline value as a covariate.

• All means are least-squares (LS) means.

**FDA Inquiry 2:**

Please provide a demographic analysis of the Long-term safety trial data on the dose reduced group, divided by those who stayed on the reduced dose and those who were discontinued, by age, sex, race, ethnicity, BMI (i.e. a sub analysis of Table 2.4.1) from the 120-day safety update. Also analyze the dose reduced groups, divided by those who stayed on the reduced dose and those who were discontinued, by concomitant medication and associated other baseline characteristics.

**Sponsor Response 2:****Demographic Analysis**

Demographic profiles are provided for the dose-reduced group of patients who participated in the long-term safety (LTS) studies, i.e., those who had their dose of linaclotide adjusted downward to 145 ug from the 290 ug dose. For clarity, the dose reduced group was defined as those pts whose final dose was 145 ug (before discontinuing or upon completing or reaching the cut-off date). This includes 11 patients who after a dose reduction to 145 ug, had a subsequent increase to 290 ug, but whose final dose was 145 ug. Those patients who had a dose reduction and whose final dose was 290 ug were excluded. Table 2.4.1A shows the demographics of the dose-reduced group of patients who completed participation or remained active in an LTS study as of 11-June-2011, the 120-day safety update cutoff date, and Table 2.4.1B shows the demographics of the dose-reduced group of patients who prematurely discontinued before the cutoff date. Patients were eligible to enter the LTS studies from either a preceding CC or IBS-C study, so the tables display the demographic data for both the CC and IBS-C subpopulations as well as for the two combined ("Overall"). Numerical differences in demographic variables between the subgroup of CC patients who remained active or completed by the data cutoff date, and the subgroup of CC patients who dropped out are observed but none appears to be clinically meaningful. The same conclusion appears to be justified to describe the differences also present in the IBS-C subpopulation and overall population.

**Concomitant Medications Analysis**

The concomitant medications used by the dose-reduced group of patients who completed participation or remained active in an LTS study as of the cutoff date are shown in Table 3.1.2A, and those used by the dose-reduced group of patients who prematurely discontinued in Table 3.1.2B.

**Associated Other Baseline Characteristics Analysis**

In the NDA, the only baseline characteristics of the safety population pre-specified were hypertension, diabetes mellitus, and certain cardiovascular disorders. Numbers of patients with these conditions at baseline were relatively small (In the CC Safety Population of Group 1 studies, 268 patients had hypertension, 67 patients had diabetes mellitus, and 37 patients had cardiovascular disorders, See ISS in-text table 6.1--1). In these small subpopulations, incidence rates of adverse events, and potentially clinically significant laboratory values, vital signs, and ECG parameters were compared to rates in the total Safety Population of the Group 1 studies. These analyses supported a conclusion that there were no meaningful differences between the

subgroups consisting of patients with the baseline characteristics of interest and patients in the overall Safety Population. The above analyses were not carried out in the LTS studies of Group 3.

In this submission, we have not provided analyses of the effect of the above-mentioned associated other baseline characteristics. This is because the small number of patients who would have these conditions in the dose-reduced group, which consists of only about one-third of the Safety Population of the LTS studies, would be insufficient for drawing conclusions.

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/s/  
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BRIAN K STRONGIN  
04/17/2012

**From:** Strongin, Brian K  
**Sent:** Tuesday, April 10, 2012 10:44 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS Clinical Information Request

Please respond to this information request ASAP. Thanks.

1) In your application you state, "...the difference in efficacy between the 145-ug and the 290-ug doses suggests that there are patients who are more likely to benefit from the 290-ug dose." However, the data from the pivotal Phase 3 double blind, chronic constipation trials demonstrated that the primary response efficacy of the 145-ug and the 290-ug doses were comparable (20.3% and 19.4% respectively in Study MCP-103-303; 15.5% and 20.5% in Study LIN- MD-01). We have been unable to identify a subgroup of patients that are "more likely to benefit" from the 290ug than the 145ug dose. Please provide subgroup analyses (using the primary endpoint as a response variable) that identify which patients (based on baseline disease characteristics and demographics) would be "more likely" to benefit from the 290 ug dose compared to the 145ug dose. Please provide additional rationale for use of the 290ug dose in the chronic constipation population.

2) Please provide a demographic analysis of the Long-term safety trial data on the dose reduced group, divided by those who stayed on the reduced dose and those who were discontinued, by age, sex, race, ethnicity, BMI (i.e. a sub analysis of Table 2.4.1) from the 120-day safety update. Also analyze the dose reduced groups, divided by those who stayed on the reduced dose and those who were discontinued, by concomitant medication and associated other baseline characteristics.

Thanks.

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/s/  
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BRIAN K STRONGIN  
04/10/2012

**From:** Strongin, Brian K  
**Sent:** Tuesday, March 27, 2012 4:30 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** FW: NDA 202811 Linzess - Information Request from the Office of Scientific Investigations

Please verify the following contact information about the CRO responsible for the IVRS system:

Mark Penland  
Associate Director  
ICON Clinical Research  
Suite 500  
320 Seven Springs Way  
Brentwood TN 37027  
Telephone (615) 309-4253  
Fax (615) 309-4337

If this is not correct, please provide us with the correct contact information (including name of contact at the organization, telephone, fax, and e-mail).

Thanks,

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/s/  
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BRIAN K STRONGIN  
03/27/2012

**From:** Strongin, Brian K  
**Sent:** Monday, March 26, 2012 3:09 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** NDA 202811 Linzess - Information Request from the Office of Scientific Investigations

**Importance:** High  
Please respond to this information request ASAP.

Based on the protocols, our understanding is that patients enrolled in Studies LIN-MD-01, LIN-MD-31, MCP-103-302, and MCP-103-303 were required to telephone an IVRS to report on their daily bowel habits. These diary responses were used in determining the primary efficacy endpoint.

Please describe procedures related to data handling once the information was entered into the IVRS. Your response should include but not be limited to:

- Who had access to the data once it was entered into the IVRS
- Was the access limited to read-only capability
- What happened to the data once it was collected
- Where is archived data stored
- Did the clinical investigator get a copy of each subject's diary information and derived primary efficacy endpoint for the clinical trial record and if so, is there a record of when this was sent?

Thanks.

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/s/  
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BRIAN K STRONGIN  
03/26/2012

**From:** Strongin, Brian K  
**Sent:** Thursday, March 15, 2012 10:08 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS, NDA 202-811, Information Request Regarding the Proposed Package Insert

Please respond to this request as soon as possible.

Regarding section 6.1, Adverse Events, Clinical Trials Experience, in your proposed package insert, we have concerns about pooling safety data across indications and studies. Please separate the information in Section 6.1 by indication (i.e. IBS-C and chronic constipation).

Thanks.

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BRIAN K STRONGIN  
03/15/2012



NDA 202-811

**DISCIPLINE REVIEW LETTER**

Forest Laboratories, Inc.  
Attention: Linda Kunka  
Senior Manager, Regulatory Affairs  
Haborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Ms. Kunka:

Please refer to your August 8, 2010 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LINZESS (linaclotide) Capsules, 145 mcg and 290 mcg.

Our review of your proposed carton and container labeling is complete, and we have identified the following deficiencies:

Package Insert

1. Warnings and Precautions section, Highlights and Full Prescribing Information:

We recommend the addition of the statement, "Keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles closed tightly in a dry place." Linaclotide is sensitive to moisture and formaldehyde, therefore the proposed expiration dating is only valid if the drug remains in the proposed commercial container closure system during the entire shelf life. A prominent warning of this type is needed to prevent transferring the capsules to a pharmacy bottle.

2. How Supplied/Storage and Handling and Instructions for Patients within the Patient Counseling Information sections:

Increase the prominence of the statement "Keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles closed tightly in a dry place." Linaclotide is sensitive to moisture and formaldehyde, therefore the proposed expiration dating is only valid if the drug remains in the proposed commercial container closure system during the entire shelf life. A prominent warning of this type is needed to prevent transferring the capsules to a pharmacy bottle or pill box.

Container Labels (4 count [REDACTED] (b) (4); 30 count trade bottle)

1. [REDACTED] (b) (4)
2. Relocate the graphic that is currently directly adjacent to the proprietary name. In its current placement, it appears as part of the proprietary name and could be misinterpreted as a modifier or extra letter.
3. Increase the size and prominence of the strength statement.
4. Revise the storage statement to read “Keep LINZESS in the original container to protect from moisture. Do not remove the desiccant from inside the bottle.” Move this statement to the principal display panel, in prominent text. Since linaclotide is sensitive to moisture and formaldehyde, the proposed expiration dating is only valid if the drug remains in the proposed commercial container closure system during the entire shelf life. A prominent warning of this type is needed to prevent the capsules from being transferred to a pharmacy bottle or pill box. On the 4 count sample bottle, we recommend relocating the net quantity statement to the top right corner of the principal display panel to allow space for the above statement on the principal display panel of the label.

Carton Labeling (4 count [REDACTED] (b) (4); 30 count trade)

1. See Comments 2-4 regarding the container label.
2. Remove the blue shading from the lower portion of the panels on the carton labeling. This color is used on both strengths, and makes the bottles look similar, which can lead to product selection errors.

[REDACTED] (b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BRIAN K STRONGIN  
03/06/2012

## Strongin, Brian K

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**From:** Strongin, Brian K  
**Sent:** Friday, February 17, 2012 9:37 AM  
**To:** 'linda.kunka@frx.com'  
**Cc:** Strongin, Brian K  
**Subject:** Linaclotide Information Request

Please provide the following information for the studies proposed in your pediatric plan submitted October 7, 2011:

- a. Final Protocol Submission:
- b. Study Completion:
- c. Final Study Report Submission

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BRIAN K STRONGIN  
02/17/2012

**From:** Strongin, Brian K  
**Sent:** Monday, February 13, 2012 4:43 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** FW: Clinical Information Request for NDA 202-811, LINZESS  
*The plan you propose is acceptable. Thanks.*

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Thursday, February 09, 2012 11:25 AM  
**To:** Strongin, Brian K  
**Subject:** RE: Clinical Information Request for NDA 202-811, LINZESS

Hi Brian:

We would like to provide a response to this request below and also seek some further clarification on Question 2b. FDA's request is in *blue italic text* and the Sponsor response follows in black text.

Please let me know if you have any questions. Thanks.

LK

*It is our understanding that in the phase 3 long-term open-label safety trials more than 25% of patients had dose reductions as per the table from the ISS Section 8.5 pg 113. We are interested in the timing of the dose reductions as well as the reason for the dose adjustment.*

**FDA Request 1:**

*Please provide a reanalysis of the safety data in the ISS for the long-term trials (group 3) by the dose of study drug administered, separating out the patients with dose reductions (i.e. by 145ug, 290ug and dose-reduced groups in the CC patients and by 290ug and dose-reduced groups in the IBS trials).*

**Sponsor's Response to Request 1:**

Additional pooled ISS analysis tables for the long-term trials (ie, ISS Group 3) will be provided for all adverse-event endpoints included in the 120-Day Safety Update (ie, Treatment-emergent AE (TEAE), Serious AE, and AEs associated with premature discontinuation from the study) for the CC indication, IBS-C indication, and Overall (CC+IBS-C). These analysis tables will present the incidence summaries for the following two mutually exclusive groups of Group 3 patients\*:

- Patients who stayed on the open-label LIN 290 ug dose
- Patients who had a dose reduction (including also those whose LIN 290 ug dose was temporarily suspended in the study)

\*all patients entering the long term safety studies began treatment with LIN 290, so patients receiving LIN 145 ug are part of the dose-reduction group

**Due to additional analyses required for this request, we will be able to provide this information on or before March 9<sup>th</sup>.**

**FDA Request 2a:**

*Please provide summary data tables and analyses for the patients with dose reductions. Please present the following according to category of dose adjustment pattern and indication (IBS vs. CC):*

- a) *The mean and median length of time patients were on initial drug prior to dose reduction*

**Sponsor Response to Request 2a:**

The 120-Day Safety Update (**Seq0016**) included an analysis table, **Table 1.5.6** (APPENDIX III AFTER-TEXT TABLES), which presents the mean and median length of time patients were on the initial open-label LIN 290 ug dose prior to dose reduction.

Does this analysis table satisfy the Division's request?

***FDA Request 2b:***

*b) The AE that prompted dose reduction (with temporal association to dose adjustment). If diarrhea was the reason for dose reduction, provide an analysis of the severity of the diarrhea as it relates to frequency and presence of associated AEs (dehydration, hemodynamic changes, etc.).*

**Sponsor Response to Request 2b:**

The AE that prompted dose reduction (with temporal association to dose adjustment). The 120-Day Safety Update (**Seq0016**) included an analysis table, **Table 6.1.3.5** (APPENDIX III AFTER-TEXT TABLES), which presents the incidence summaries of all AEs that caused/led to dose reductions.

Does this analysis table satisfy the Division's request?

For diarrhea AEs that were the reason for dose reduction, an analysis summarizing the number and percent of patients who also experienced the following associated AEs (with preferred terms) will be provided for each indication:

- Blood pressure systolic decreased
- Blood pressure diastolic decreased
- Syncope
- Presyncope
- Loss of consciousness
- Dizziness
- Dehydration
- Orthostatic Hypotension
- Hypotension

Is this plan acceptable? If yes, the timeline for this deliverable will also be **on or before March 9<sup>th</sup>**.

---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Friday, February 03, 2012 10:50 AM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for NDA 202-811, LINZESS

[Please respond to this information request ASAP. Thanks.](#)

It is our understanding that in the phase 3 long-term open-label safety trials more than 25% of patients had dose reductions as per the table from the ISS Section 8.5 pg 113. We are interested in the timing of the dose reductions as well as the reason for the dose adjustment.

1) Please provide a reanalysis of the safety data in the ISS for the long-term trials (group 3) by the dose of study drug administered, separating out the patients with dose reductions (i.e.. by 145ug, 290ug and dose-reduced groups in the CC patients and by 290ug and dose-reduced groups in the IBS trials).

- 2) Please provide summary data tables and analyses for the patients with dose reductions. Please present the following according to category of dose adjustment pattern and indication (IBS vs CC):
- a) The mean and median length of time patients were on initial drug prior to dose reduction, and
  - b) The AE that prompted dose reduction (with temporal association to dose adjustment). If diarrhea was the reason for dose reduction, provide an analysis of the severity of the diarrhea as it relates to frequency and presence of associated AEs (dehydration, hemodynamic changes, etc.).

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BRIAN K STRONGIN  
02/13/2012

**Strongin, Brian K**

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**From:** Strongin, Brian K  
**Sent:** Wednesday, February 08, 2012 12:31 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS NDA 202811 Clinical Information Request

[Please respond to this information request ASAP.](#) Thanks.

We are reviewing your Submission dated February 3, 2012.

The following patients were identified from the list of previously submitted case report forms as cases for which the diagnosis of ischemic colitis could not definitively be ruled in or out and for which another cause of rectal bleeding could not be identified.

Please assess the following patients for ischemic colitis using the same adjudication process outlined in your submission.

If you feel these cases are not justified as "cases of interest", please provide a rationale for your conclusion.

Pt 0053035 is a 30 year old white female who developed diarrhea that required a reduction of the Linaclotide dose from 290mcg to 145 mcg. During this time, she also developed bright red blood per rectum which was defined as mild in nature and resolved following the dose reduction. Although, this patient appears to have no risk factors for IC, there have been cases of IC in younger adults following treatment with laxatives.

Pt 0393021 is a 45 year old white female who was initially on 145mcg of linaclotide in the pivotal trials. She was subsequently rolled over into the long-term trial and began taking 290 mcg of the study drug. Approximately 32 days after the study drug, the patient developed diarrhea which resulted in a dose reduction. The patient developed right upper quadrant abdominal pain (moderate intensity), diarrhea and intermittent black stools. It was also noted that during this time there was an increased blood pressure and pulse reading (which in the absence of additional data may have been indicative of an occult bleed).

Pt 0145001 (also referred to as pt 0061002 in trial MCP-103-201) is a 60 year old white female. Past medical history appeared otherwise insignificant for cardiovascular disease, however her age places her at increased risk of IC. The patient was taking 290 mcg of study drug when she experienced abdominal discomfort described as moderate intensity. This resulted in a dose reduction. Approximately 28 days later the patient developed mild blood in her stool. During this time it appears that she also complained of moderate incomplete evacuation which lasted from 12/6/08 until 1/1/09. Treatment was temporarily held and subsequently the dose of the study drug was decreased. These events were assessed as possibly related to study drug.

Pt 0870101 is a 66 year old white female who was status post myocardial infarction receiving 290 mcg of linaclotide. On 7/14/2009, 139 days after starting the study drug, she developed a moderate gastroenteritis. From 7/14/09 - 7/28/09, she also experienced black tarry stools. On 7/30/2009 the patient experienced watery diarrhea which resulted in a reduction of the study drug dosage. The patient has risk factors for IC.

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BRIAN K STRONGIN  
02/08/2012

**From:** Strongin, Brian K  
**Sent:** Friday, February 03, 2012 10:50 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for NDA 202-811, LINZESS  
[Please respond to this information request ASAP. Thanks.](#)

It is our understanding that in the phase 3 long-term open-label safety trials more than 25% of patients had dose reductions as per the table from the ISS Section 8.5 pg 113. We are interested in the timing of the dose reductions as well as the reason for the dose adjustment.

1) Please provide a reanalysis of the safety data in the ISS for the long-term trials (group 3) by the dose of study drug administered, separating out the patients with dose reductions (i.e., by 145ug, 290ug and dose-reduced groups in the CC patients and by 290ug and dose-reduced groups in the IBS trials).

2) Please provide summary data tables and analyses for the patients with dose reductions. Please present the following according to category of dose adjustment pattern and indication (IBS vs CC):

- a) The mean and median length of time patients were on initial drug prior to dose reduction, and
- b) The AE that prompted dose reduction (with temporal association to dose adjustment).  
If diarrhea was the reason for dose reduction, provide an analysis of the severity of the diarrhea as it relates to frequency and presence of associated AEs (dehydration, hemodynamic changes, etc.).

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/s/  
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BRIAN K STRONGIN  
02/03/2012

**From:** Strongin, Brian K  
**Sent:** Wednesday, February 01, 2012 6:00 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS - NDA 202-811 Clinical Information Request  
Please either submit a copy or tell us the location of the study reports for the long-term safety trials in NDA 202-811.

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BRIAN K STRONGIN  
02/01/2012



NDA 202-811

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Linda Kunka  
Senior Manager, Regulatory Affairs  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Ms. Kunka:

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

We are reviewing the Statistical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For Studies MCP-103-302, MCP-103-303, LIN-MD-01, and LIN-MD-31, please perform the following:

1. Plot mean abdominal discomfort during the treatment period by week and treatment group;
2. Plot mean bloating during the treatment period by week and treatment group;
3. Perform observed case analysis of weekly responders for abdominal pain and complete spontaneous bowel movement (CSBM), abdominal pain alone, and CSBM alone by week on IBS-C studies; for CSBM by week only on CC studies;
4. Perform observed case analyses of monthly responder for abdominal pain and CSBM, abdominal pain alone, and CSBM alone by month on IBS-C studies; for CSBM by month only on CC studies (monthly responders are defined as subjects who are weekly responders for at least 2 weeks in a month);
5. Perform observed case analysis of overall responder analyses for abdominal pain and CSBM, abdominal pain alone, and CSBM alone on IBS-C studies; for CSBM only on CC studies (overall responders are defined subjects who are monthly responders for at least two out of any three months (MCP103-303, LIN-MD-01, and LIN-MD-31) and at least four of any six months (MCP-103-302);

6. Provide SAS transport file for weekly and monthly data for abdominal pain and CSBM, abdominal pain alone, and CSBM alone per study for observed data (no imputation) for IBS-C studies; for CSBM only per study for CC studies;
7. Perform analysis of primary efficacy endpoint for population excluding duplicate patients for each study;
8. Explain the differences in number of responders between your analysis and worst case 1 analysis for primary efficacy endpoint by treatment group;
9. Perform statistical analysis for number of patients with at least one AE, at least one treatment-related AE (TRAE), withdrawn due to AE, at least one episode of diarrhea, and discontinued due to TRAE of diarrhea by treatment group for each study and combined studies for each indication;
10. Provide information regarding the usage of rescue medication by week and treatment group.

If you have any questions, call me at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III

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/s/  
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BRIAN K STRONGIN  
01/30/2012

**From:** Strongin, Brian K  
**Sent:** Tuesday, January 24, 2012 9:19 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** FW: Response to January 20th Statistical Request  
 Hi. [We have a follow-up question:](#)

Regarding the first portion of the response: How was the investigator instructed to answer the question "Did the patient complete the study?" on the termination page of the study eCRF?

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Monday, January 23, 2012 5:30 PM  
**To:** Strongin, Brian K  
**Subject:** Response to January 20th Statistical Request

Hi Brian:

Please see our response to the Statistical portion of this request below. FDA's request is in blue italic text and the Sponsor response follows in black text.

Please let me know if you have any additional questions. The team is reviewing the Biopharmaceutics portion of this request and we will respond shortly.

Thanks.

LK

#### FDA Statistical Request

*For the two phase 3 Studies MCP-103-303 and LIN-MD-01, please clarify how a subject was identified as a study completer. Also for Study MCP-103-303, we noticed that the subjects discontinued during the 12-week treatment period and those discontinued during the 4-week random-withdrawal period are not readily separable to us. Please either add a variable/index to facilitate the separation of these subjects and/or entries, or help locate such a variable/index in the datasets.*

#### Sponsor Response

- For studies MCP-103-303 and LIN-MD-01, study completers are defined as patients for whom the question "Did the patient complete the study?" on the termination page of the study eCRF was checked "Yes". These patients are identified in the ADSL study datasets by selecting patients where the variable *COMPLFL*='Y'.

For study MCP-103-303, CSR Table 14.1.3B lists the number of study completers by randomized-withdrawal treatment sequence and overall (N= 533 total patients). For study LIN-MD-01, CSR Table 14.1.3 lists the number of study completers by treatment group and overall (N=533 total patients).

- For study MCP-103-303, patients who were in the ITT population and re-randomized to study drug at the Week 12 study visit were counted as Treatment Period completers in CSR Table 14.1.3A (N=540 patients total). These patients would be identified in the MCP-103-303 ADSL study dataset by selecting those patients where *ITTFLL*="Y" and the variable *RAND2DT* is non-missing.

- In study MCP-103-303:
  - Patients who discontinued during the 12-week Treatment Period would have a missing value for the variable *RAND2DT* and a value of “N” for the variable *COMPLFL* in the ADSL dataset.
  - Patients who discontinued during the 4-week Randomized Withdrawal Period would have a non-missing value for the variable *RAND2DT* and a value of “N” for the variable *COMPLFL* in the ADSL dataset.

---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Friday, January 20, 2012 6:16 PM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:**

Please e-mail and follow with a submission of the responses to these comments and requests ASAP. Thanks.

#### Statistical

For the two phase 3 Studies MCP-103-303 and LIN-MD-01, please clarify how a subject was identified as a study completer. Also for Study MCP-103-303, we noticed that the subjects discontinued during the 12-week treatment period and those discontinued during the 4-week random-withdrawal period are not readily separable to us. Please either add a variable/index to facilitate the separation of these subjects and/or entries, or help locate such a variable/index in the datasets.

#### Biopharmaceutics

1. It appears that paddle speed does not affect the dissolution profile of your proposed product; therefore, revise your proposed dissolution method to reflect a paddle speed of 50 rpm.
2. The following dissolution acceptance criterion is recommended:  $Q = \text{(b) (4)}$  at 15 minutes. This recommendation is based on the mean in-vitro dissolution profiles for all strengths at release and under 15 months stability studies. Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.

Thanks.

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/s/  
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BRIAN K STRONGIN  
01/24/2012



NDA 202-811

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Jane L. Watts, MS (RAC)  
Senior Manager, Regulatory Affairs  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Ms. Watts:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linzess (linaclotide) Capsules, 145 µg and 290 µg.

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

1. Regarding drug substance specification:

- a. Please provide an updated drug substance specification in Section 3.2.S Linaclotide – All Manufacturers to include analytical procedure numbers for (b) (4).  
(b) (4) The drug substance specification provided in this section is the regulatory specification for linaclotide drug substance.
- b. Provide analytical procedures and method validation data for determination of (b) (4) contents under Section 3.2.S Linaclotide – All Manufacturers if non-compendial procedures are used.
- c. Include residue on ignition with an acceptance criterion of NMT (b) (4).
- d. (b) (4) the acceptance criteria for specific optical rotation based on data from only the nine primary stability batches because these batches are most representative of the commercial processes. Furthermore, please clarify the discrepancy for specific optical rotation data for the primary stability batches. The data presented in the NDA are inconsistent with those in DMF (b) (4).
- e. Revise the acceptance criteria for linaclotide assay to (b) (4).  
(b) (4). In this context, (b) (4).
- f. Revise the acceptance criterion of linaclotide content on “as-is” basis to “report value”.

2. Revise the retest period for linaclotide drug substance to (b) (4) months. Per ICH Q1E, the retest period should be based on long-term data for drug substances intended for storage in a freezer. Extrapolation to extend the retest period is not applicable for storage in a freezer.
3. Regarding the manufacture of linaclotide capsules:
  - a. Please provide the sampling protocol, i.e. sample size and location for linaclotide bead assay.
  - b. Include content uniformity test of stratified in-process dosage unit. Stratified in-process dosage units from at least 10 locations and 3 capsules for each location during capsule filling should be analyzed for assay. The assay results should meet the following criteria:
    - i. RSD of all individual results (b) (4)
    - ii. Mean of all results: (b) (4) of target assay.
  - c. Establish a hold time of linaclotide beads to be not more than (b) (4). This recommendation is based on the hold time of linaclotide beads for the manufacture of the primary stability batches, which ranged from one to five months. Because there are no stability data of linaclotide beads, the stability of linaclotide beads is inferred based on the stability of linaclotide capsules. Thus, only one month of hold time could be justified.
  - d. Please clarify the size of commercial scale for encapsulation of 145 µg and 290 µg capsules.
4. Please (b) (4) the acceptance criteria for linaclotide assay to (b) (4) and total impurities to (b) (4) in the drug product release specification to ensure that your product will meet the stability specification at the end of the expiration dating period. Furthermore, (b) (4) the acceptance criterion of total impurities for stability to (b) (4) unless data (e.g. clinical batches) are provided to justify the proposed limit of (b) (4).
5. Please clarify whether the release and stability tests of the primary and supporting batches of linaclotide capsules were conducted using the regulatory analytical procedures. The test numbers listed in Appendix V (PRD-RPT-ANL-00335) are different from those of the regulatory procedures in Section 3.2.P.5.1. If non-regulatory procedures were used, please provide a summary of the differences as compared to the respective regulatory procedures.
6. Regarding the expiration dating period of the drug product:
  - a. Revise the expiration dating period of linaclotide capsules, 145 µg and 290 µg to 15 months. Your proposed expiration dating period of (b) (4) months is not acceptable. The long-term data of supporting batches, L0004295 (145 µg, both bottle configurations) and L0004261 (30-count), appear to show a significantly greater decrease in assay than the predicted values derived from linear regression analyses of primary batches. For example, assay for batch L0004295 in the 4-count bottle changed from (b) (4) at the initial time point to (b) (4) after 6 months, which is significantly lower than the predicted value of (b) (4). Given the observed stability trend and limited batch history, extrapolation to extend the expiration dating period is not acceptable.
  - b. Computation of expiration dating period of the drug product should begin with the date of encapsulation, not packaging.

7. Please provide a statement to certify that the components of the drug product container closure system comply with the current federal regulations for contact with food products.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.  
Branch Chief, Branch IV  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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MOO JHONG RHEE  
01/20/2012  
Chief, Branch IV

**From:** Strongin, Brian K  
**Sent:** Tuesday, January 03, 2012 12:35 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** FW: NDA 202-811 LINZESS Statistical Information Request  
[Please see our response to your questions below:](#)

[A 2-stage submission is preferred and the sensitivity analyses proposal in the attached email is acceptable.](#)

---

**From:** Kunka, Linda [mailto:Linda.Kunka@frx.com]  
**Sent:** Wednesday, December 28, 2011 3:00 PM  
**To:** Strongin, Brian K  
**Subject:** RE: NDA 202-811 LINZESS Statistical Information Request

Dear Brian,

Thank you for your email of December 22, 2011 requesting additional statistical analyses of chronic constipation studies MCP-103-303 and LIN-MD-01. Addressing items 1, 3, 4, 5 and 7 and aspects of item 2 which are similar in scope to your October 21, 2011 request for analyses of the IBS-C studies will be straightforward; we will be able to provide you with the results of these analyses in approximately 3 weeks. However, sensitivity analyses for the change-from-baseline secondary efficacy endpoints (as opposed to responder endpoints), will require additional programming time; we estimate an additional 3 weeks will be required to provide updated SAS transport files (item 6) and the corresponding sensitivity analyses (assuming the proposal outlined below is acceptable).

We would like to offer 2 options for providing these additional analyses to FDA and would like to know which of these options the FDA statisticians would prefer:

1. A 2-staged approach where we would first submit the results of all analyses except the secondary efficacy endpoint sensitivity analyses (in approximately 3 weeks) and secondly, in another 3 weeks, provide the secondary-efficacy-endpoint sensitivity results and SAS transport files.
2. A single-stage approach where we would delay the submission of the all results until the secondary efficacy endpoint sensitivity results are available (therefore, approximately 6 weeks for the full submission).

Also, we would like to receive input from the FDA statisticians as to whether the proposal outlined below for the sensitivity analyses of the change-from-baseline secondary efficacy endpoints is an acceptable approach.

**FDA Request: Item 2.**

*Perform the following sensitivity analyses for the primary and secondary efficacy endpoints for each study MCP-103-303 and LIN-MD-01 and two studies combined:*

- *Observed case: exclude subjects from the analysis at a specific time point if the patients have insufficient data at that time point.*
- *Complete case: exclude subjects from the analysis at all time points if they have insufficient data at any of the time points of analysis.*
- *Worst case: (1) subjects with missing observations at any of the time points of analysis are assume to be "failed"; (2) subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be a responder, and subjects receiving treatment with missing observations at any of the time points of analysis are assumed to be a non-responder.*
- *Imputation using LOCF*
- *Imputation using a model-based, multiple imputation approach (model should be described in the response)*

**Proposal for Addressing Sensitivity Analyses for the Secondary Efficacy Endpoints in Item 2**

We propose that, for the sensitivity analyses of the 7 change-from-baseline secondary efficacy endpoints, consistent with the primary efficacy endpoint sensitivity analyses, data be excluded at the weekly level, using as the exclusion criterion a patient having less than 4 complete IVRS calls in a week. (Note: This criterion of a minimum of 4 complete IVRS calls was also applied for the October 21, 2011 statistical analysis request for IBS-C studies MCP-103-302 and LIN-MD-31.) For the sensitivity analyses, a patient's 12-week value will be the score averaged over the 12-week Treatment Period; consistent with the secondary efficacy endpoint analyses, the 12-week value will be a weighted average of the 12 Treatment Period weeks, with the weights determined by the number of days in that week.

We don't believe that the Worst Case responder/non-responder imputation proposal (bullet 3 in item 2) is directly applicable for the change-from-baseline secondary efficacy endpoints. Instead, for these endpoints, we propose to apply a baseline-observation-carried-forward (BOCF) imputation method for the missing observations (similar to imputation using LOCF except using BOCF).

Is this proposal for the sensitivity analyses of the secondary efficacy endpoints for studies MCP-103-303 and LIN-MD-01 acceptable?

Please let me know if you have any questions.

Thanks.

LK

---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Thursday, December 22, 2011 3:29 PM  
**To:** Kunka, Linda  
**Cc:** Strongin, Brian K  
**Subject:** NDA 202-811 LINZESS Statistical Information Request

Please respond to the attached information request letter ASAP. Thanks.

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BRIAN K STRONGIN  
01/03/2012



NDA 202-811

## INFORMATION REQUEST

Forest Laboratories, Inc.  
Attention: Linda Kunka  
Senior Manager, Regulatory Affairs  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Ms. Kunka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LINZESS (linaclotide) Capsules, 145 mcg and 290 mcg.

We are reviewing the statistical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide subgroup analyses for the primary and secondary efficacy endpoints for each study MCP-103-303 and Lin-MD-01 for the following subgroups: gender, age, race, and geographic region.
2. Perform the following sensitivity analyses for the primary and secondary efficacy endpoints for each study MCP-103-303 and Lin-MD-01 and two studies combined:
  - Observed case: exclude subjects from the analysis at a specific time point if the patients have insufficient data at that time point.
  - Complete case: exclude subjects from the analysis at all time points if they have insufficient data at any of the time points of analysis.
  - Worst case: (1) subjects with missing observations at any of the time points of analysis are assumed to be “failed”; (2) subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be a responder, and subjects receiving treatment with missing observations at any of the time points of analysis are assumed to be a non-responder.
  - Imputation using LOCF
  - Imputation using a model-based, multiple imputation approach (model should be described in the response)
3. For each study MCP-103-303 and Lin-MD-01, and the two studies combined, please perform an analysis of weekly responders for complete spontaneous bowel movement (CSBM) by week.

4. For each study MCP-103-303 and Lin-MD-01, and the two studies combined, please perform analyses of monthly responder for CSBM by month. Monthly responders here are defined as subjects who are weekly responders for at least two weeks in a month.
5. For each study MCP-103-303 and Lin-MD-01, and the two studies combined, please perform an overall responder analyses for CSBM. Overall responders here are defined as subjects who are monthly responders for at least two out of the three months.
6. Please provide SAS transport files for weekly and monthly data for CSBM for each study MCP-103-303 and Lin-MD-01, and two studies combined, along with appropriate data definition files.
7. Clarify if having less than four IVRS responses per week is treated as missing/non-responding for that week in the chronic constipation studies. If not, a sensitivity analysis should be performed for the primary endpoint treating subjects with fewer than four IVRS responses per week as non-responders for that weekl.

If you have any questions, call me at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., MBA  
Chief, Project Management Staff  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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BRIAN K STRONGIN  
12/22/2011

**From:** Strongin, Brian K  
**Sent:** Tuesday, December 20, 2011 1:00 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** NDA 202-811 LINZESS Clinical Information Request  
Please send the patient ID numbers, site number, narratives and CRF's for the Terms listed below for all linaclotide patients:

Immune system - hypersensitivity, drug hypersensitivity, Anaphylactic reaction.  
Skin and subq - Urticaria

Thanks.

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BRIAN K STRONGIN  
12/20/2011

**From:** Strongin, Brian K  
**Sent:** Friday, December 16, 2011 9:43 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** LINZESS NDA 202-811 Clinical Information Request  
[Please submit case report forms and narratives for the IBS-C patients in the list below ASAP.](#)

STUDYID	USUBJID	AEDECOD	AETERM
LIN-MD-31	LIN-MD-31.0133110	Anaemia	ANEMIA
LIN-MD-31	LIN-MD-31.0133110	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.0253134	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.0353112	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.0383104	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.0733119	Anaemia	SEVERE ANEMIA
LIN-MD-02	LIN-MD-31.0933101	Anaemia	ANEMIA
LIN-MD-31	LIN-MD-31.0953176	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.0993111	Anaemia	ANEMIA
LIN-MD-31	LIN-MD-31.1163108	Anaemia	ANEMIA
LIN-MD-31	LIN-MD-31.1163108	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.1163112	Anaemia	ANEMIA
LIN-MD-02	LIN-MD-31.1213115	Anaemia	WORSENING ANEMIA
MCP-103-305	MCP-103-202.208024	Anaemia	ANEMIA
MCP-103-202	MCP-103-202.238012	Anaemia	ANEMIA
MCP-103-302	MCP-103-302.0362015	Anaemia	ANEMIA
MCP-103-305	MCP-103-302.0362041	Anaemia	ANEMIA
MCP-103-305	MCP-103-302.0502003	Anaemia	WORSENING OF ANEMIA
MCP-103-305	MCP-103-	Anaemia	WORSENING OF

	302.0622011		ANEMIA (LOWERING OF HCT AND HGB)
MCP-103-302	MCP-103- 302.0762007	Anaemia	MILD ANEMIA
MCP-103-302	MCP-103- 302.0942002	Anaemia	WORSENING ANEMIA
MCP-103-302	MCP-103- 302.1282015	Anaemia	ANEMIA
LIN-MD-02	LIN-MD- 31.0393101	Faeces discoloured	DARK STOOLS
LIN-MD-31	LIN-MD- 31.0873104	Faeces discoloured	BLACK STOOLS
MCP-103-202	MCP-103- 202.224011	Faeces discoloured	BLACK STOOLS
LIN-MD-02	LIN-MD- 31.0363132	Haematochezia	BLOODY STOOLS
LIN-MD-02	LIN-MD- 31.0463117	Haematochezia	BLOOD IN STOOL
LIN-MD-02	LIN-MD- 31.0673145	Haematochezia	BLOODY STOOL
LIN-MD-02	LIN-MD- 31.1343107	Haematochezia	INTERMITTENT BLOOD WITH STOOL
MCP-103-202	MCP-103- 202.503003	Haematochezia	HEMATOCHEZIA
MCP-103-302	MCP-103- 302.0582008	Haematochezia	BLOOD IN STOOL
MCP-103-305	MCP-103- 302.0632015	Haematochezia	BLOOD IN STOOL
MCP-103-305	MCP-103- 302.0692037	Haematochezia	BLOOD IN STOOL
MCP-103-305	MCP-103- 302.0722013	Haematochezia	BLOOD ON STOOL
MCP-103-302	MCP-103- 302.0302004	Haematocrit decreased	LOW HEMATOCRIT LEVEL
MCP-103-305	MCP-103- 302.0602007	Haematocrit decreased	LOW HEMATOCRIT
MCP-103-305	MCP-103- 302.0852021	Haematocrit decreased	DECREASE IN HCT
MCP-103-305	MCP-103- 302.0742002	Haematocrit increased	ELEVATED HEMATOCRIT
LIN-MD-02	LIN-MD- 31.1233119	Ileus	ILEUS SECONDARY TO NARCOTICS

MCP-103-305	MCP-103-202.260001	Ileus	ILEUS
MCP-103-305	MCP-103-302.0382010	Melaena	MELENA
LIN-MD-31	LIN-MD-31.0173102	Occult blood positive	OCCULT BLOOD IN STOOL
MCP-103-305	MCP-103-202.207003	Occult blood positive	HEMOCULT POSITIVE STOOLFOR OCCULT BLOOD
MCP-103-305	MCP-103-202.256014	Occult blood positive	HEME POSITIVE STOOLS (FECAL OCCULT POSITIVE)
LIN-MD-31	LIN-MD-31.0043117	Rectal haemorrhage	BRIGHT RED BLOOD BLOOD PER RECTUM
LIN-MD-02	LIN-MD-31.0083137	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-02	LIN-MD-31.0563110	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-31	LIN-MD-31.0723102	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-31	LIN-MD-31.0723109	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-02	LIN-MD-31.0733119	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-02	LIN-MD-31.0983109	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-02	LIN-MD-31.1043102	Rectal haemorrhage	RECTAL BLEEDING
LIN-MD-02	LIN-MD-31.1223110	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-305	MCP-103-202.220019	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-202	MCP-103-202.266015	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-202	MCP-103-202.279010	Rectal haemorrhage	RECTAL BLEEDING AFTER BOWEL MOVEMENTS
MCP-103-202	MCP-103-202.287013	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-305	MCP-103-302.0362011	Rectal haemorrhage	RECTAL BLEEDING (WORSENING)

MCP-103-305	MCP-103-302.0472011	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-305	MCP-103-302.0622012	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-305	MCP-103-302.0642010	Rectal haemorrhage	WORSENING RECTAL BLEEDING RELATED TO DIARRHEA
MCP-103-302	MCP-103-302.0672013	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-302	MCP-103-302.0672013	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-302	MCP-103-302.0692010	Rectal haemorrhage	BLOOD FROM RECTUM
MCP-103-305	MCP-103-302.0802001	Rectal haemorrhage	WORSENING OF RECTAL BLEEDING
MCP-103-305	MCP-103-302.0872024	Rectal haemorrhage	BLOOD PER RECTUM
MCP-103-302	MCP-103-302.1282015	Rectal haemorrhage	RECTAL BLEEDING
MCP-103-305	MCP-103-302.0852021	Red blood cell count decreased	DECREASE IN RBC

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/s/  
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BRIAN K STRONGIN  
12/16/2011

**From:** Strongin, Brian K  
**Sent:** Friday, December 09, 2011 12:58 PM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for NDA 202-811 LINZESS  
Please respond to the following information request ASAP. Thanks.

The ADAE data set that you submitted was subdivided into two groups:

- Group 1 were trials conducted and submitted in support of the Chronic Constipation indication
- Group 2 were trials conducted and submitted in support of the IBS-C indication.

In Group 1, there was 1 person in the 145µg group, 8 people in the 290 µg, and 1 person in the placebo group who had “blood in stool”. We also noted that study subjects in the 290µg group tended to be younger. Increasing age is thought to be a risk factor for the development of ischemic colitis. We have identified the following AE terms in your ADAE dataset which may represent potential cases of ischemic colitis. Please provide a listing for each of the patients with adverse events that correspond to these terms. Please provide patient ID number, site number, trial, treatment group (i.e. placebo or dose of linaclotide), number of days on drug, date of onset of AE, evaluation of possibility of AE being related to ischemic colitis. Please provide narrative summaries for all cases. Please provide a summary analysis of all the data and an evaluation of the possibility of ischemic colitis being induced by linaclotide. We request that you combine the adverse events as we have outlined below in the section titled "COMBINE THE FOLLOWING AE TERMS FOR REPEAT ANALYSIS" and then analyze the occurrence of events by treatments. We also request that you combine the adverse events as we have outlined below and then analyze the occurrence of events by treatments group.

<b>STUDYID</b>	<b>USUBJID</b>	<b>AETERM</b>	<b>AEDECOD</b>
LIN-MD-01	LIN-MD-01.0060102	ANEMIA	Anaemia
LIN-MD-01	LIN-MD-01.0100112	BLOOD IN STOOL	Haematochezia
LIN-MD-01	LIN-MD-01.0250101	BLOOD IN STOOL	Haematochezia
LIN-MD-01	LIN-MD-01.0460104	BLOOD IN STOOL	Haematochezia
LIN-MD-01	LIN-MD-01.0460104	BLOOD IN STOOL	Haematochezia
LIN-MD-01	LIN-MD-01.0570141	HEMATOCHEZIA	Haematochezia
LIN-MD-01	LIN-MD-01.0370104	RECTAL BLEEDING	Rectal haemorrhage
LIN-MD-01	LIN-MD-01.0540111	RECTAL BLEEDING	Rectal haemorrhage

LIN-MD-01	LIN-MD-01.0980101	RECTAL BLEEDING	Rectal haemorrhage
LIN-MD-02	LIN-MD-01.0070103	ANEMIA	Anaemia
LIN-MD-02	LIN-MD-01.0070113	ANEMIA	Anaemia
LIN-MD-02	LIN-MD-01.0380101	ANEMIA	Anaemia
LIN-MD-02	LIN-MD-01.0430109	ANEMIA	Anaemia
LIN-MD-02	LIN-MD-01.0520107	ANEMIA	Anaemia
LIN-MD-02	LIN-MD-01.0740101	ANEMIA	Anaemia
LIN-MD-02	LIN-MD-01.0110102	BLACK STOOL	Faeces discoloured
LIN-MD-02	LIN-MD-01.0870101	BLACK STOOL	Faeces discoloured
LIN-MD-02	LIN-MD-01.0610117	BLOOD IN STOOL	Haematochezia
LIN-MD-02	LIN-MD-01.0170101	DECREASED HEMATOCRIT LEVEL	Haematocrit decreased
LIN-MD-02	LIN-MD-01.0740101	DECREASED HEMOGLOBIN LAB VALUE	Haemoglobin decreased
LIN-MD-02	LIN-MD-01.0170101	DECREASED HEMOGLOBIN LEVEL	Haemoglobin decreased
LIN-MD-02	LIN-MD-01.0960102	MELANOSIS COLI	Melanosis coli
LIN-MD-02	LIN-MD-01.0370104	RECTAL BLEEDING	Rectal haemorrhage
LIN-MD-02	LIN-MD-01.0980109	RECTAL BLEEDING	Rectal haemorrhage
LIN-MD-02	LIN-MD-01.0370104	RECTAL BLEEDING SECONDARY TO HEMORRHOID	Haemorrhoidal haemorrhage
LIN-MD-02	LIN-MD-01.0100103	TENDER WHOLE ABDOMINAL AREA	Abdominal tenderness
LIN-MD-02	LIN-MD-01.0240104	WORSENING ANEMIA	Anaemia
MCP-103-201	MCP-103-201.008006	DECREASED HEMOGLOBIN	Haemoglobin decreased
MCP-103-201	MCP-103-	ISCHEMIC COLITIS	Colitis ischaemic

	201.020007		
MCP-103-201	MCP-103-201.031011	LOW HGB	Haemoglobin decreased
MCP-103-303	MCP-103-303.0133011	ANEMIA	Anaemia
MCP-103-303	MCP-103-303.0713002	BLOOD IN STOOL	Haematochezia
MCP-103-303	MCP-103-303.0713002	BLOOD IN STOOL	Haematochezia
MCP-103-303	MCP-103-303.0713002	BLOOD IN STOOL	Haematochezia
MCP-103-303	MCP-103-303.0723011	BLOOD IN STOOL	Haematochezia
MCP-103-303	MCP-103-303.0913006	BLOOD IN STOOL	Haematochezia
MCP-103-303	MCP-103-303.0153009	BLOOD WITH STOOL	Haematochezia
MCP-103-303	MCP-103-303.0583005	DARK STOOL	Faeces discoloured
MCP-103-303	MCP-103-303.0093006	INCREASED RECTAL BLEEDING	Rectal haemorrhage
MCP-103-303	MCP-103-303.0063008	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-303	MCP-103-303.0243007	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-303	MCP-103-303.0803002	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-303	MCP-103-303.0873006	RECTAL BLEEDING SECONDARY TO HEMORRHOIDS	Haemorrhoidal haemorrhage
MCP-103-303	MCP-103-303.0693003	SMALL ANAL BLEEDING	Anal haemorrhage
MCP-103-303	MCP-103-303.0913007	SMALL BLOOD DROPLET WITH BOWEL MOVEMENT	Haematochezia
MCP-103-305	MCP-103-303.0103029	ANEMIA	Anaemia
MCP-103-305	MCP-103-303.0253001	ANEMIA	Anaemia
MCP-103-305	MCP-103-303.0673007	ANEMIA	Anaemia
MCP-103-305	MCP-103-303.1003001	ANEMIA	Anaemia

MCP-103-305	MCP-103-303.1073017	ANEMIA	Anaemia
MCP-103-305	MCP-103-303.1103005	BLACK TARRY STOOL	Melaena
MCP-103-305	MCP-103-303.0393029	BLOOD IN STOOL	Haematochezia
MCP-103-305	MCP-103-303.0723026	BLOOD IN STOOL	Haematochezia
MCP-103-305	MCP-103-201.061002	BLOOD IN STOOL (SCANT AMOUNT)	Haematochezia
MCP-103-305	MCP-103-303.0343015	DECREASED HEMOGLOBIN 10.0 (NORMAL RANGE 11.5-15.5)	Haemoglobin decreased
MCP-103-305	MCP-103-303.0453013	LOW HEMAGLOBIN	Haemoglobin decreased
MCP-103-305	MCP-103-303.0583007	LOW HEMATOCRIT	Haematocrit decreased
MCP-103-305	MCP-103-303.0583007	LOW HEMOGLOBIN	Haemoglobin decreased
MCP-103-305	MCP-103-303.0043007	MELANOSIS COLI	Melanosis coli
MCP-103-305	MCP-103-303.0103029	POSITIVE HEMOCCULT STOOLS	Occult blood positive
MCP-103-305	MCP-103-303.0943017	POSITIVE HEMOCULT	Occult blood positive
MCP-103-305	MCP-103-004.02003	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-201.051009	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-303.0033039	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-303.0743015	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-303.0743016	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-303.0943012	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-303.1013007	RECTAL BLEEDING	Rectal haemorrhage
MCP-103-305	MCP-103-303.0043005	WORSENERD ANEMIA	Anaemia
MCP-103-305	MCP-103-303.0253001	WORSENING ANEMIA	Anaemia

**COMBINE THE FOLLOWING AE TERMS FOR REPEAT ANALYSIS**

Group 1) Black Stool, Blacks Stools, Black Tarry Stools, Dark Stools, Dark Stool, Intermittent Black Stool, Melena,

Group 2) Bloody Stools, Bloody Stool, Blood in Stool, Blood on Stool, Heme Positive Stools, Hemocult Positive Stool for Occult, Intermittent Blood in Stool, Intermittent Blood with Stool, Occult Blood in Stool, Positive Hemocult Stools, Positive Hemocult, Small Blood Droplet in Bowel Movement

Group 3) Bleeding Hemorrhoid,

Group 4) Blood in Rectum, Blood Per Rectum, Blood From Rectum, Bright Red Blood per Rectum, Hematochezia, Rectal Bleeding, Rectal Bleeding (Worsening), Rectal Bleeding After Bowel Movements, Worsening of Rectal Bleeding, Increased Rectal Bleeding

Group 5) Bowel Obstruction

Group 6) Decrease in HCT, Decrease in Hemoglobin, Decrease HGB, Decreased Hematocrit. Decreased Hematocrit level, Decreased Hemoglobin, Decreased Hemoglobin 10, Decrease Hemoglobin Lab Value, Decreased Hemoglobin Level, Low Hemocrit, low Hemaglobin, Low Hematocrit, Low Hematocrit Level, Low Hemoglobin, Low HGB, Worsening Low Hematocrit, Worsening Low Hemoglobin,

Group 7) Gastroenteritis, Gastroenteitis

Group 8) Ischemic Colitis

Group 9) Melanosis Coli

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/s/  
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BRIAN K STRONGIN  
12/09/2011

**From:** Strongin, Brian K  
**Sent:** Wednesday, December 07, 2011 10:47 AM  
**To:** 'Kunka, Linda'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for LINZESS  
[Please see the attached clinical information request.](#)

Thank you for your December 5th response to our November 18th information request letter. We appreciate the information, however, in light of the large number of cases of rectal bleeding and hospital admissions for GI related illness; we are requesting that you analyze this information. Please provide a listing of each patient with the following information; patient ID number, site number, trial, treatment group (i.e. placebo or dose of linaclotide), number of days on drug, date of onset of AE, evaluation of possibility of AE being related to ischemic colitis. Please provide narrative summaries for all cases that are possibly or likely related to linaclotide, and any cases of probable ischemic colitis in the placebo group. Please provide a summary analysis of all the data and an evaluation of the possibility of ischemic colitis being induced by linaclotide.

[Thank you,](#)

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/s/  
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BRIAN K STRONGIN  
12/07/2011

**From:** Strongin, Brian K

**Sent:** Monday, December 05, 2011 9:36 AM

**To:** 'Kunka, Linda'

**Cc:** Strongin, Brian K

**Subject:** NDA 202811 Clinical Information Request

During a previous conversation regarding your NDA, the Division was informed that you have produced a chronic constipation white paper in April of 2009. Please e-mail a copy of that paper and follow with a submission to your application. Thanks.

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/s/  
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BRIAN K STRONGIN  
12/05/2011

**From:** Strongin, Brian K  
**Sent:** Wednesday, November 30, 2011 11:32 AM  
**To:** 'linda.kunka@frx.com'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical and Statistical Information Requests for NDA 202-811, LINZESS  
Please respond to these information requests ASAP. Thanks.

1. During the review of the Chronic Constipation indication of your application, datasets from the pivotal trials submitted in support of your application were combined to generate the following table. (Please refer to Table 1 below.) There appeared to be an imbalance in the number of study participants in the 145µg and 290µg linaclotide groups relative to the placebo group who either were 1) lost to follow-up; 2) withdrew consent; or 3) experienced an adverse event. There was also a discrepancy the numbers generated from the dataset and the numbers reported.

Table 1 Subject Disposition Pivotal Constipation Trials Combined\*

<b>Reason for Withdrawal</b>	<b>Placebo</b>	<b>145 µ</b>	<b>290 µg</b>
Adverse Event	19 (18)	32	31
Insufficient Therapeutic Response	12	1	3
Lost to Follow-Up	4	14 (13)	16
Other Reasons	5 (4)	3 (2)	2
Protocol Violation	8	6 (5)	8 (7)
Withdrawal of Consent	10	18	18

\*Numbers in parentheses are a combination of those reported in the clinical study reports

There does not appear to be a rationale in the clinical study reports for the imbalances in those who were lost to follow-up or withdrew consent. Please provide a rationale for the imbalances.

2. Please provide an update on the status of your response to the statistical issues included in the Filing Communication letter dated October 28, 2011.

Thanks.

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/s/  
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BRIAN K STRONGIN  
11/30/2011



NDA202811

**METHODS VALIDATION  
MATERIALS RECEIVED**

Forest Research Institute Inc.  
Attention: Jane L. Watts (RAC)  
Director, Regulatory Affairs-CMC

Dear Ms. Jane L. Watts:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Linzess (linaclotide) capsules, 145 mcg and to our 10/26/2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 11/10/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
11/22/2011



NDA 202811

**INFORMATION REQUEST**

Forest Laboratories, Inc.  
Attention: Linda Kunka  
Senior Manager, Regulatory Affairs  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311

Dear Ms. Kunka:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LINZESS (linaclotide) Capsules, 145 mcg and 290 mcg.

We also refer to the attached table, containing a list of selected Safety Reports submitted to IND 63,290 for linaclotide capsules.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In order to adequately assess the potential adverse events related to Ischemic Colitis, please provide the following information ASAP, but no later than December 5, 2011.

1. Provide a summary of premarketing or post-marketing Safety Reports (if your product is marketed overseas) for those patients with Ischemic Colitis and Other Forms of Intestinal Ischemia. The case definition may be based on either of the following:
  - a. The term "ischemic colitis" is explicitly used in the Safety Report as a possible diagnosis, or
  - b. The report contains any endoscopic or histologic evidence of ischemic change or necrosis. The case definition for intestinal ischemia may also include cases where an occlusive process of the proximal large vessel was suggested. The Agency will consider proposals for alternative definitions
2. Please provide narrative summaries and any available case report forms for the cases listed above.
3. Provide a listing and case report forms for all patients with the following:

- a. Rectal hemorrhage identified from AE datasets within your clinical studies. For Rectal Hemorrhage you should search for the following terms: rectal bleeding, rectal hemorrhage, bloody stool, hematochezia, lower gastrointestinal bleeding, or melena.
  - b. Ileus, bowel obstruction (small or large), colitis, enteritis, gastroenteritis and any other GI related diagnoses.
  - c. Hospital admissions or emergency room visits, indicating which ones were for GI related complaints or diagnosis.
4. Please review the cases listed in the table in the attachment below, and provide updated narratives, CRF's and follow-up on these patients. Also provide an opinion about the likelihood that each case represented a case of ischemic colitis and provide an assessment of the possibility that it was drug related.

If you have any questions, call Brian Strongin, Chief, Regulatory Project Management Staff, at (301) 796-1008

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ATTACHMENT

Table A – Safety Report Submissions

Table A: Safety Report Submissions

<b>Trial/ Site/</b>	<b>Patient ID#</b>	<b>Diagnosis/ Dose</b>	<b>Initial Safety report Date</b>	<b>Comments</b>
MCP103-305/ 028	0542012	IBS-C 300mg	9/30/11	Sponsor diagnosis ischemic colitis
LIN-MD-02/ 003	0033120	IBS-C 150mg	5/12/11	Reported as ileus, but c/w ischemic colitis, biopsy shows ischemia
LIN-MD-02/ 076	0763138	IBS-C & CC 300mg	7/22/11and 6/7/11	Reported as ileus but appears to be recurrent distal SBO in patient with no prior surgical Hx. Why?
MCP103-305 008	0085006	IBS-C 300mg	5/29/2009	Small bowel ileus. ? drug related
MCP-103-305 026	0262004	IBS-C 300mg	11/10/2009	Bloody diarrhea, dx. viral gastroenteritis, did flex sig really visualize entire left colon to splenic flexure

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/s/  
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DONNA J GRIEBEL  
11/18/2011



NDA 202811

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Ironwood Pharmaceuticals, Inc.  
301 Binney Street  
Cambridge, MA 02142

ATTENTION: Sarah Lieber  
Associate Director, Regulatory Affairs

Dear Ms. Lieber:

Please refer to your New Drug Application (NDA), dated and received August 9, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linaclotide Capsules, 145 mcg and 290 mcg.

We also refer to your correspondence, dated August 22, 2011, received August 22, 2011, requesting review of your proposed proprietary name, Linzess. We have completed our review of the proposed proprietary name, Linzess, and have concluded that it is acceptable.

The proposed proprietary name, Linzess, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 22, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology (OSE), at (301) 796-5412. For any other information regarding this application, contact Brian Strongin, R.Ph., MBA, Chief of Project Management Staff for the Division of Gastroenterology and Inborn Errors Products (DGIEP), at (301) 796-1008.

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  
11/17/2011

**From:** Strongin, Brian K  
**Sent:** Monday, October 31, 2011 9:50 AM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request

Please clarify the data cut off date that will be used for the 120-day safety update.

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/s/  
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BRIAN K STRONGIN  
10/31/2011



NDA 202811

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Ironwood Pharmaceuticals, Inc.  
Attention: Mark Currie  
VP R&D, Chief Scientific Officer  
301 Binney Street  
Cambridge, MA 02142

Dear Mark Currie:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Linzess (linaclotide) capsules, 145 mcg and 290 mcg.

We will be performing methods validation studies on Linzess (linaclotide) capsules, 145 mcg, as described in NDA 202811

In order to perform the necessary testing, we request the following sample materials and equipments:

Samples

325 Linzess (linaclotide) capsules, 145 mcg  
390 mg Linaclotide drug substance

Standards

60 Linaclotide Working Standard (vials)  
150 mg Linaclotide Primary Standard  
125 mg Linaclotide system suitability material

(b) (4)

(b) (4)

HPLC Columns

(b) (4)

(b) (4)

Please include the MSDSs and certificates of analysis for the samples and standards.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: James F. Allgire  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
10/26/2011



NDA 202-811

**FILING COMMUNICATION**

Ironwood Pharmaceuticals, Inc.  
Attention: Sarah Lieber, M.S.  
Associate Director, Regulatory Affairs  
301 Binney Street  
Cambridge, MA 02142

Dear Ms. Lieber:

Please refer to your New Drug Application (NDA) dated August 8, 2011, received August 9, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for LINZESS (linaclotide) Capsules, 145 mcg and 290 mcg.

We also refer to your amendments dated August 10, August 22, August 23, and October 7, 2011.

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 June 9, 2011.

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 April 20, 2012.

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

Clinical

We could not locate information in your application regarding immunogenicity testing performed on LINZESS. Please clarify what immunogenicity testing has been performed on LINZESS or provide the location of this information in your application.

### Statistical

The following statistical information could not be located in your application:

1. Provide subgroup analyses for primary efficacy endpoints by study for studies MCP-103-302-CSR-01 and Lin-MD-31.
2. Perform the following sensitivity analyses for studies MCP-103-302-CSR-01 and Lin-MD-31.  
Sensitivity analyses for the primary efficacy endpoint should also include:
  - Observed case: exclude subjects from the analysis at a specific time point if the patients have insufficient data at that time point.
  - Complete case: exclude subjects from the analysis at all time points if they have insufficient data at any of the time points of analysis.
  - Worst case: (1) subjects with missing observations at any of the time points of analysis are assume to be “failed”; (2) subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be a responder, and subjects receiving treatment with missing observations at any of the time points of analysis are assumed to be a non-responder.
  - LOCF analysis
  - Multiple imputation
3. Please perform analysis of weekly responders for abdominal pain and complete spontaneous bowel movement (CSBM), abdominal pain alone, and CSBM alone by week.
4. For studies MCP-103-302-CSR-01 and Lin-MD-31, please perform analyses of monthly responder for abdominal pain and CSBM, abdominal pain alone, and CSBM alone by month. Monthly responders are defined as subjects who are weekly responders for at least 2 weeks in a month.
5. For studies MCP-103-302-CSR-01 and Lin-MD-31, please perform overall responder analyses for abdominal pain and CSBM, abdominal pain alone, and CSBM alone. Overall responders are defined subjects who are monthly responders for at least two out of any three months (Lin-MD-31) and at least four of any six months (MCP-103-302-CSR-01).
6. Please provide SAS transport file for weekly and monthly data for abdominal pain and CSBM, abdominal pain alone, and CSBM alone per study for studies MCP-103-302-CSR-01 and Lin-MD-31.

### Quality - Biopharmaceutics

The following biopharmaceutics information could not be located in your application:

1. Provide information on the pH solubility profile of Linaclotide. The report should include solubility data for the drug substance covering the entire physiological pH range.
2. Conduct testing and provide data to demonstrate the discriminating capability of the selected dissolution method. The provided data do not support the discriminating ability of the selected method.

3. Submit the report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method.
4. Provide the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value).

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.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for constipation (b)(4) irritable bowel syndrome (IBS-C) patients younger than 6 years of age and for chronic constipation (CC) patients younger than six months of age. Once we have reviewed your request, we will notify you if the partial waiver requests are denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for IBS-C patients ages (b)(4) to 17 years and CC patients ages (b)(4) to 17 years. Once we have reviewed your requests, we will notify you if the partial deferral requests are denied.

If you have any questions, call Brian Strongin, R.Ph., MBA, Chief, Regulatory Project Management Staff, at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.  
Director  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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BRIAN K STRONGIN  
10/21/2011  
Signing for Donna Griebel

**From:** [Strongin, Brian K](#)  
**To:** ["Sarah Lieber";](#)  
**cc:** [Strongin, Brian K;](#)  
**Subject:** FW: Site selection for NDA 202-811 linaclotide  
**Date:** Thursday, October 20, 2011 11:18:17 AM

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Please provide Dr. Horn's CV, phone number and fax for his clinical trial site at the address below. Please send the phone number and fax ASAP. Thanks.

---

Site 95 in trial LIN-MD-31  
Horn, Curtis  
303 West Sunset Road  
Suite 102  
San Antonio, TX 78209  
US

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/s/  
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BRIAN K STRONGIN  
10/20/2011

**From:** Strongin, Brian K  
**Sent:** Monday, October 17, 2011 1:48 PM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** FW: Information Request for NDA 202-811 LINZESS

[We have the following information request in response to your October 14, 2011 e-mail below:](#)

Given your response, the discrepancy between the ISS datasets patient number and the reported safety patient number cannot be explained. In the ADSL data, there is 4803 records for safety population and 4752 if excluding the duplicate subjects. However, in the ISS reports, you claim that only 4370 patients are included in the safety data. Please address the difference and help us identify the patients included in the reports.

**From:** Sarah Lieber [mailto:slieber@ironwoodpharma.com]  
**Sent:** Friday, October 14, 2011 4:53 PM  
**To:** Strongin, Brian K  
**Subject:** RE: Information Request for NDA 202-811 LINZESS - Response to Item#4 of October 12, 2011 Request

Hi Brian,

Here is our response to your October 12, 2011 email request item #4. I hope this response addresses the reviewer's request. Feel free to contact me if you need any additional information.

Thank you.

Best regards,

Sarah

***FDA Request #4: We noticed that the duplicate subjects have multiple entries in the ISE and ISS datasets. Those entries are not readily identifiable to us. Please either add a variable/index to facilitate the identification of these subjects and/or entries, or help locate such a variable/index in the datasets.***

***Sponsor Response:*** Within each of the ISS/ISE datasets, there is a variable called DUPPATID that identifies records that are associated with duplicate patients. The possible values of DUPPATID are 1 to 25 (with each number representing a duplicate patient) and null (representing non-duplicate patients).

For example, Duplicate Patient 6 (DUPPATID=6) originally enrolled in Study MCP-103-202 with a unique subject identifier (USUBJID) of MCP-103-202.281002, and later enrolled in Study LIN-MD-01 with a USUBJID of LIN-MD-01.0160101. In any given ISS dataset, some records are associated with USUBJID MCP-103-202.281002, and the rest are associated with USUBJID LIN-MD-01.0160101. However, all records for this patient are flagged with a DUPPATID=6. Detailed mapping of DUPPATID numbers and USUBJID numbers in the individual linaclotide studies can be found in Section 16.6 of

the ISS SAP (Amendment 2, dated April 6, 2011).

To select data in an ISS/ISE dataset for patients who **are not** duplicate patients, one can simply subset the data using this SAS code: “Where DUPPATID=.”. To view all data for duplicate patients, subset the data using this SAS code: “Where DUPPATID ^=.”.

In order to implement the rules for handling data of the duplicate patients specified in the ISS and ISE SAPs, we used a set of 10 variables to identify duplicate-patient data to be included in the integrated efficacy/safety analyses of various groups. These variables are DG1CCFL, DG1IBSFL, DG1OAF, DG2FL, DG3CCFL, DG3IBSFL, DG3OAF, DG4CCFL, DG4IBSFL, and DG4OAF. Please refer to sections 6.1 and 16.6 of the ISS SAP (Amendment 2, dated April 6, 2011), Section 8.0 of the CC ISE SAP (Amendment 2, dated May 13, 2011), and Section 8.0 of the IBS-C ISE SAP (Amendment 1, dated May 13, 2011) for data handling of duplicate patients. Provided in the following table are explanations of these 10 variables used for handling data of the duplicate patients in the ISS/ISE datasets. Further information about these variables can be found in the Data Definition Tables (define.pdf) of the ISS and ISE.

Variable Name	Label	Values
CCFL	Duplicate Patient Group 1 CC Analysis Flag	DG1CCFL = Y if the duplicate patient data entry was included in the Group 1 CC ISS/ISE analyses; DG1CCFL = N if the duplicate patient data entry was not included in the Group 1 CC ISS/ISE analyses; DG1CCFL = null if the data entry does not belong to a duplicate patient.
IBSFL	Duplicate Patient Group 1 IBS-C Analysis Flag	DG1IBSFL = Y if the duplicate patient data entry was included in the Group 1 IBS-C ISS/ISE analyses; DG1IBSFL = N if the duplicate patient data entry was not included in the Group 1 IBS-C ISS/ISE analyses; DG1IBSFL = null if the data entry does not belong to a duplicate patient.
OAF	Duplicate Patient Group 1 Overall Analysis Flag	DG1OAF = Y if the duplicate patient data entry was included in the Group 1 CC+IBS-C ISS/ISE analyses; DG1OAF = N if the duplicate patient data entry was not included in the Group 1 CC+IBS-C ISS/ISE analyses; DG1OAF = null if the data entry does not belong to a duplicate patient.
FL	Duplicate Patient Group 2 Analysis Flag	DG2FL = Y if the duplicate patient data entry was included in the Group 2 ISS analyses; DG2FL = N if the duplicate patient data entry was not included in the Group 2 ISS analyses; DG2FL = null if the data entry does not belong to a duplicate patient.
CCFL	Duplicate Patient Group 3 CC Analysis Flag	DG3CCFL = Y if the duplicate patient data entry was included in the Group 3 CC ISS/ISE analyses; DG3CCFL = N if the duplicate patient data entry was not included in the Group 3 CC ISS/ISE analyses;

		DG3CCFL = null if the data entry does not belong to a duplicate patient.
SFL	Duplicate Patient Group 3 IBS-C Analysis Flag	DG3IBSFL = Y if the duplicate patient data entry was included in the Group 3 IBS-C ISS/ISE analyses; DG3IBSFL = N if the duplicate patient data entry was not included in the Group 3 IBS-C ISS/ISE analyses; DG3IBSFL = null if the data entry does not belong to a duplicate patient.
AFL	Duplicate Patient Group 3 Overall Analysis Flag	DG3OAFL = Y if the duplicate patient data entry was included in the Group 3 CC+IBS-C ISS/ISE analyses; DG3OAFL = N if the duplicate patient data entry was not included in the Group 3 CC+IBS-C ISS/ISE analyses; DG3OAFL = null if the data entry does not belong to a duplicate patient.
CFL	Duplicate Patient Group 4 CC Analysis Flag	DG4CCFL = Y if the duplicate patient data entry was included in the Group 4 CC ISS analyses; DG4CCFL = N if the duplicate patient data entry was not included in the Group 4 CC ISS analyses; DG4CCFL = null if the data entry does not belong to a duplicate patient.
SFL	Duplicate Patient Group 4 IBS-C Analysis Flag	DG4IBSFL = Y if the duplicate patient data entry was included in the Group 4 IBS-C ISS analyses; DG4IBSFL = N if the duplicate patient data entry was not included in the Group 4 IBS-C ISS analyses; DG4IBSFL = null if the data entry does not belong to a duplicate patient.
AFL	Duplicate Patient Group 4 Overall Analysis Flag	DG4OAFL = Y if the duplicate patient data entry was included in the Group 4 CC+IBS-C ISS analyses; DG4OAFL = N if the duplicate patient data entry was not included in the Group 4 CC+IBS-C ISS analyses; DG4OAFL = null if the data entry does not belong to a duplicate patient.

Chronic Constipation; IBS-C = Irritable Bowel Syndrome with Constipation; ISE = Integrated Summary of Efficacy; ISS = Integrated Summary of Safety; please refer to Section 5.0 of the ISS SAP Amendment 2 for the definition of groups 1-4.

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**From:** Strongin, Brian K  
**Sent:** Wednesday, October 12, 2011 5:02 PM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Information Request for NDA 202-811 LINZESS

Here is another statistical information request:

1. Please submit separate IBS and CC data sets for all data sets.
2. Please add values of "Weekly Number of Days with Complete Diary" and "Weekly

Number of Days with Diary Entries” in the efficacy datasets adefeff.xpt.

3. Please transpose the efficacy datasets adefeff.xpt by subjects so each study subject only has one row entry in the dataset.
4. We noticed that the duplicate subjects have multiple entries in the ISE and ISS datasets. Those entries are not readily identifiable to us. Please either add a variable/index to facilitate the identification of these subjects and/or entries, or help locate such a variable/index in the datasets.
5. To facilitate our review, please submit programs used to generate derived datasets and those for the primary and key secondary analyses.

Thanks and let me know if you have any questions.

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BRIAN K STRONGIN  
10/17/2011

**From:** Strongin, Brian K  
**Sent:** Friday, October 14, 2011 7:00 PM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** FW: Information Request for NDA 202-811 LINZESS  
[Here are our responses to your questions. Thanks.](#)

1. Do the item 2 and 3 requests apply to only the ISE ADEFF dataset or to the ISE ADEFF **and** to the four individual Phase 3 efficacy ADEFF datasets?

[They apply to both ISE and individual study ADEFF datasets.](#)

2. Additionally, a version of ADEFF that has only one row entry per subject, as requested in item 3, would require between 1500 and 2000 variables. Because of the large number of variables, we are considering two conventions for naming variables and would like to know which approach you prefer.

The first approach would be to follow the current standard of a maximum of 8 characters for variable names. The second approach would employ variable names longer than 8 characters. The disadvantage to the first approach is that the variable names would be difficult to interpret, although there would be descriptive variable labels. Using the second approach the variable names would be readily interpretable, but a non-standard method for creating and extracting the SAS datasets (proc cport/cimport) would be necessary. The specific conventions for the variable--naming using approach 1 and the general method for approach 2 are attached in a Word document (options for naming conventions for ADEFFSL.doc).

[We prefer the first approach with shorter variable names. Please make sure to explain the variables in the define.pdf file.](#)

---

**From:** Sarah Lieber [mailto:[slieber@ironwoodpharma.com](mailto:slieber@ironwoodpharma.com)]  
**Sent:** Thursday, October 13, 2011 5:51 PM  
**To:** Strongin, Brian K  
**Subject:** RE: Information Request for NDA 202-811 LINZESS

Dear Brian,

We are happy to provide the datasets requested in the e-mail below. We would like to confirm certain aspects of two of the items (item 2 and 3) in the request:

Do the item 2 and 3 requests apply to only the ISE ADEFF dataset or to the ISE ADEFF **and** to the four individual Phase 3 efficacy ADEFF datasets?

Additionally, a version of ADEFF that has only one row entry per subject, as requested in item 3, would require between 1500 and 2000 variables. Because of the large number of variables, we are considering two conventions for naming variables and would like to know which approach you prefer.

The first approach would be to follow the current standard of a maximum of 8 characters for variable names. The second approach would employ variable names longer than 8 characters. The disadvantage to the first approach is that the variable names would be difficult to interpret, although there would be descriptive variable labels. Using the second approach the variable names would be readily interpretable, but a non-standard method for creating and extracting the SAS datasets (proc cport/cimport) would be necessary. The specific conventions for the variable--naming using approach 1 and the general method for approach 2 are attached in a Word document (options for naming conventions for ADEFFSL.doc).

The ISS datasets requested in item 1 (which provided clarification of your request from September 28<sup>th</sup>) is being prepared for submission and will be sent within a week. The additional requested datasets will be prepared based on your response to this email. When we receive your input, we will provide you with an estimated timeline for the submission of these additional datasets.

Feel free to contact me if you have any questions.

Best regards,  
Sarah

Sarah Rhee Lieber, MS  
Associate Director, Regulatory Affairs  
Ironwood Pharmaceuticals 301 Binney Street Cambridge, MA 02142  
Office: 617-621-8405  
Cell: (b) (6)  
Fax: 617-812-5946  
[slieber@ironwoodpharma.com](mailto:slieber@ironwoodpharma.com)

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**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
**Sent:** Wednesday, October 12, 2011 5:02 PM  
**To:** Sarah Lieber  
**Cc:** Strongin, Brian K  
**Subject:** Information Request for NDA 202-811 LINZESS

Here is another statistical information request:

1. Please submit separate IBS and CC data sets for all data sets.
2. Please add values of "Weekly Number of Days with Complete Diary" and "Weekly Number of Days with Diary Entries" in the efficacy datasets adefx.xpt.
3. Please transpose the efficacy datasets adefx.xpt by subjects so each study subject only has one row entry in the dataset.
4. We noticed that the duplicate subjects have multiple entries in the ISE and ISS datasets. Those entries are not readily identifiable to us. Please either add a variable/index to facilitate the identification of these subjects and/or entries, or help locate such a variable/index in the datasets.
5. To facilitate our review, please submit programs used to generate derived datasets and those for the primary and key secondary analyses.

Thanks and let me know if you have any questions.

This email message and any attachments are intended for the exclusive use of the addressee(s) and may contain confidential or privileged information. If you are not the intended recipient, please notify Ironwood Pharmaceuticals immediately - by either replying to this message or calling (617) 621-7722 - and destroy all copies of this message and any attachments.

Thank you for your cooperation.

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BRIAN K STRONGIN  
10/14/2011

**From:** Strongin, Brian K  
**Sent:** Wednesday, October 12, 2011 5:02 PM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Information Request for NDA 202-811 LINZESS

Here is another statistical information request:

1. Please submit separate IBS and CC data sets for all data sets.
2. Please add values of "Weekly Number of Days with Complete Diary" and "Weekly Number of Days with Diary Entries" in the efficacy datasets adefeff.xpt.
3. Please transpose the efficacy datasets adefeff.xpt by subjects so each study subject only has one row entry in the dataset.
4. We noticed that the duplicate subjects have multiple entries in the ISE and ISS datasets. Those entries are not readily identifiable to us. Please either add a variable/index to facilitate the identification of these subjects and/or entries, or help locate such a variable/index in the datasets.
5. To facilitate our review, please submit programs used to generate derived datasets and those for the primary and key secondary analyses.

Thanks and let me know if you have any questions.

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BRIAN K STRONGIN  
10/12/2011

From: Strongin, Brian K  
Sent: Monday, October 03, 2011 9:36 AM  
To: 'Sarah Lieber'  
Cc: Strongin, Brian K  
Subject: Clinical Information Request for NDA 202811 Linzess

I have another information request:

Subject level data was submitted only for the double-blind, phase 2 chronic constipation studies. Please submit these data for the phase 2 IBS-C dose ranging studies, or tell us where it is located.

Also, I'm still trying to fine the answer to your question below. I'll get back to you as soon as I can.

Thanks.

---

From: Sarah Lieber [mailto:slieber@ironwoodpharma.com]  
Sent: Wednesday, September 28, 2011 1:10 PM  
To: Strongin, Brian K  
Subject: RE: Clinical Information Request for NDA 202811 Linzess

Dear Brian,

We are happy to provide divided ADAE datasets as requested in your email. We would like, however, to highlight that the ISS ADAE dataset (located in Module 5.3.5.3) contains an indicator variable named DISEASE. For every record in ADAE, this variable indicates whether a patient enrolled as an IBS-C patient or as a patient with chronic constipation. The 2 values for DISEASE are "IBS-C" and "Chronic Constipation". This variable is included in all 10 ISS safety datasets: ADAE, ADCM, ADEG\_TRI, ADEGG1, ADEGG3, ADLBG1, ADLBG3, ADMH, ADSL and ADVS.

Please let us know whether this variable will be sufficient for the Agency's needs, or whether you would prefer to have us proceed with dividing the ADAE dataset into two datasets, one for IBS-C, and another for chronic constipation. If would prefer to have us divide ADAE into two datasets, would you like each of the 10 ISS safety datasets divided into 2 datasets?

Please let me know the Agency's preference. If you would like the datasets to be separated, we will prepare the datasets and submit as soon as possible.

Thank you.

Best regards,

Sarah

Sarah Rhee Lieber, M.S.  
Associate Director, Regulatory Affairs  
Ironwood Pharmaceuticals 320 Bent Street Cambridge, MA 02141

T: 617.621.8405 F: 617.494.0908 [www.ironwoodpharma.com](http://www.ironwoodpharma.com)

From: Strongin, Brian K [mailto:[Brian.Strongin@fda.hhs.gov](mailto:Brian.Strongin@fda.hhs.gov)]  
Sent: Wednesday, September 28, 2011 9:43 AM  
To: Sarah Lieber  
Cc: Strongin, Brian K  
Subject: Clinical Information Request for NDA 202811 Linzess

The ADAE dataset located in Module 5.3.5.3.25.3.1 contains efficacy and safety study data for both the IBS-C and chronic constipation(CC) indications combined.

Please submit safety datasets that contains only data from efficacy and safety studies for IBS-C and CC individually. If these data sets have been submitted, please provide the location.

This email message and any attachments are intended for the exclusive use of the addressee(s) and may contain confidential or privileged information. If you are not the intended recipient, please notify Ironwood Pharmaceuticals immediately - by either replying to this message or calling (617) 621-7722 - and destroy all copies of this message and any attachments. Thank you for your cooperation.

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BRIAN K STRONGIN  
10/03/2011

**From:** Strongin, Brian K  
**Sent:** Wednesday, September 28, 2011 9:43 AM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Clinical Information Request for NDA 202811 Linzess

The ADAE dataset located in Module 5.3.5.3.25.3.1 contains efficacy and safety study data for both the IBS-C and chronic constipation(CC) indications combined.  
Please submit safety datasets that contains only data from efficacy and safety studies for IBS-C and CC individually. If these data sets have been submitted, please provide the location.

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BRIAN K STRONGIN  
09/28/2011



NDA 202-811

**NDA ACKNOWLEDGMENT**

Ironwood Pharmaceuticals, Inc.  
Attention: Mark Currie  
Vice President Research and Development  
Chief Scientific Officer  
301 Binney Street  
Cambridge, MA 02142

Dear Mr. Currie:

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: LINZESS (linaclotide) Capsules, 145 mcg and 290 mcg

Date of Application: August 9, 2012

Date of Receipt: August 9, 2012

Our Reference Number: NDA 202-811

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 October 8, 2011, 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 Gastroenterology and Inborn Errors 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) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., MBA  
Division of Gastroenterology and  
Inborn Errors Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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BRIAN K STRONGIN  
09/01/2011

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. 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.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

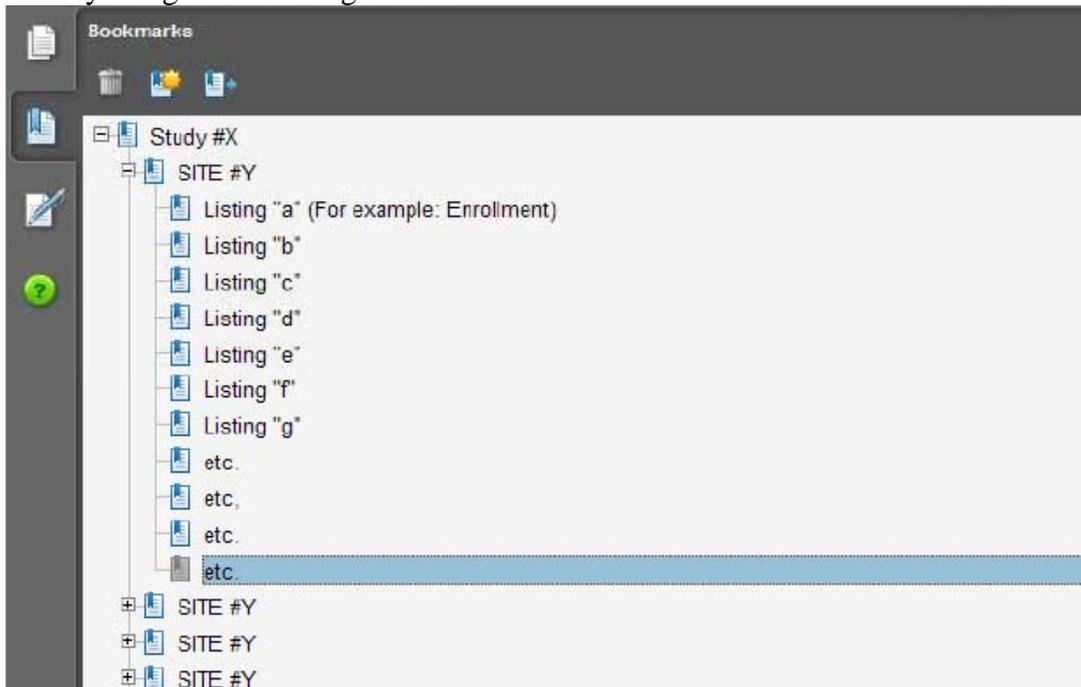
**I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Number of subjects screened for each site by site
  - b. Number of subjects randomized for each site by site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
  - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
  - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
  - c. 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
  - d. 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.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### **III. Request for Site Level Dataset:**

OSI 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 Attachment 1, “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 a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## **Attachment 1**

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

#### **1.1 Introduction**

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

#### **1.2 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 to facilitate the evaluation of the application. 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 Standard Deviation (TRTEFFS) – the standard deviation 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 Standard Deviation (SITEEFFS) – the standard deviation 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: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. 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).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	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
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	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
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	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: Example for Clinical Site Data Elements Summary Listing (Table 1)**

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

## Attachment 2

### Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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/s/  
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MAUREEN D DEWEY  
08/24/2011

## Dewey, Maureen

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**From:** Dewey, Maureen  
**Sent:** Tuesday, August 23, 2011 3:42 PM  
**To:** 'slieber@ironwoodpharma.com'  
**Cc:** Strongin, Brian K  
**Subject:** NDA 202-811 Linaclotide Information Request

**Attachments:** NDA 202811 IR Instructions.pdf; NDA 202-811 meeting minutes.pdf

Ms. Lieber,

Please refer to your August 9, 2011, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linaclotide.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your supplemental application.

We refer to the meeting minutes dated April 21, 2011, in which we requested summary level clinical site data sets be provided in the data set files under the name "DSI Site Level DataSet". We are unable to locate these data sets. If you have provided this data please inform us of the location of the "define.pdf" and the SAS transport (.xpt) file in the ECTD.

If you have not included this data please use the instructions attached to this email to construct these SAS files.

Please respond to the above requests for additional information by August 31, 2011.

If you have any questions about this request, please feel free to call me at (301) 796-0845.



NDA 202811 IR  
Instructions.pdf...



NDA 202-811  
meeting minutes.pdf

Sincerely,

Maureen Dewey, M.P.H.  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products  
CDER/FDA

(301) 796-0845 (office)  
(301) 796-9905 (fax)

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From: Strongin, Brian K  
Sent: Friday, August 19, 2011 8:13 AM  
To: 'Sarah Lieber'  
Cc: Strongin, Brian K  
Subject: RE: Information Request for NDA 202-811 Linaclotide

In regard to response #1: the statement of Good Clinical Practice for each study is sufficient.

Also, the proposal for the coding dictionary in SAS is acceptable.

From: Sarah Lieber [mailto:slieber@ironwoodpharma.com]  
Sent: Thursday, August 18, 2011 6:21 PM  
To: Strongin, Brian K  
Subject: RE: Information Request for NDA 202-811 Linaclotide

Dear Brian,

Here are our responses to your August 18, 2011 4:34 pm email requests;

FDA Request 1: Please provide a statement of Good Clinical Practice or its location in the application; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures.

Response 1: A statement of Good Clinical Practice for the each study is provided in the clinical study report. The IRB information and inform consent procedures of each studies as well as the study specific GCP statements are provided in the CSR. See Table 1 for the summary of the location of each CSR and relevant ethics sections. In addition, if the Division is looking for a single statement of GCP for all clinical studies included in the NDA, the Sponsor is prepared to provide such document of GCP statement.

Table 1: Locations of GCP statements for the Clinical Studies in NDA 202811

Clinical Study Report Number	NDA Module	Location	CSR PDF Page	Information	Page of GCP
MCP-103-103-CSR-01	m5-3-1	1pg 3:	Cover Page	pg 18: Section 5. Ethics Section	
MCP-103-001-CSR-03	m5-3-3	1pg 4:	Cover Page	pg 25: Section 5. Ethics Section	
MCP-103-002-CSR-02	m5-3-3	1pg 4:	Cover Page	pg 17: Section 5. Ethics Section	
MCP-103-004-CSR-01	m5-3-5-1 (Chronic Constipation)	pg 4:	Cover Page	pg 20: Section 5. Ethics Section	
MCP-103-201-CSR-01	m5-3-5-1 (Chronic Constipation)	pg 4:	Cover Page	pg 24: Section 5. Ethics Section	
MCP-103-303-CSR-01	m5-3-5-1 (Chronic Constipation)	pg 7:	Cover Page	pg 27: Section 5. Ethics Section	
LIN-MD-01	m5-3-5-1 (Chronic Constipation)	pg 1:	Cover Page	pg 29: Section 5. Ethics Section	
MCP-103-005-CSR-01	m5-3-5-1 (Irritable Bowel Syndrome with Constipation)	pg 294:	Cover Page	pg 304: Section 5. Ethics Section	

MCP-103-202-CSR-01m5-3-5-1 (Irritable Bowel Syndrome with Constipation )pg 4: Cover Page  
pg 22: Section 5. Ethics Section  
MCP-103-302-CSR-01m5-3-5-1 (Irritable Bowel Syndrome with Constipation )pg 8: Cover Page  
pg 26: Section 5. Ethics Section  
LIN-MD-31m5-3-5-1 (Irritable Bowel Syndrome with Constipation )pg 1: Cover Page  
pg 37: Section 5. Ethics Section

FDA Request 2: In your e-mail of August 18, 2011 at 12:00PM, in response to my information request of 9:33AM that day, you state that the AE databases for the phase 2 and 3 studies were created using different versions of MedDRA. Please identify the version of MedDRA used for each clinical trial.

Response 2: The versions of MedDRA used in Phase 2 and Phase 3 studies are provided in Table 2.

Table 2

Clinical Study Report Number	MedDRA Version Used
MCP-103-201-CSR-01	Version 9.1
MCP-103-303-CSR-01	Version 12.0
LIN-MD-01	Version 12.0
MCP-103-202-CSR-01	Version 9.1
MCP-103-302-CSR-01	Version 13.0
LIN-MD-31	Version 13.0

Also please let us know if our proposal (e-mail of August 18, 2011 at 12:00PM) for the requested coding dictionary is acceptable to the Division. Upon the confirmation, we will submit the requested SAS file to the NDA.

Feel free to contact me if you have any other questions. Thanks.

Best regards,  
Sarah

Sarah Rhee Lieber, MS  
Associate Director, Regulatory Affairs  
Ironwood Pharmaceuticals 301 Binney Street Cambridge, MA 02142  
Office: 617-621-8405  
Cell: (b) (6)  
Fax: 617-812-5946  
slieber@ironwoodpharma.com

From: Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]  
Sent: Thursday, August 18, 2011 4:34 PM  
To: Sarah Lieber  
Cc: Strongin, Brian K  
Subject: Information Request for NDA 202-811 Linaclotide

Sorry about having another request so soon. Please submit a response to these requests as soon as you can:

1. Please provide a statement of Good Clinical Practice or its location in the application; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures.

2. In your e-mail of August 18, 2011 at 12:00PM, in response to my information request of 9:33AM that day, you state that the AE databases for the phase 2 and 3 studies were created using different versions of MedDRA. Please identify the version of MedDRA used for each clinical trial.

This email message and any attachments are intended for the exclusive use of the addressee(s) and may contain confidential or privileged information. If you are not the intended recipient, please notify Ironwood Pharmaceuticals immediately - by either replying to this message or calling (617) 621-7722 - and destroy all copies of this message and any attachments. Thank you for your cooperation.

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/s/  
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BRIAN K STRONGIN  
08/19/2011

**From:** Strongin, Brian K  
**Sent:** Thursday, August 18, 2011 4:34 PM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Information Request for NDA 202-811 Linaclotide

Sorry about having another request so soon. Please submit a response to these requests as soon as you can:

1. Please provide a statement of Good Clinical Practice or its location in the application; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures.
2. In your e-mail of August 18, 2011 at 12:00PM, in response to my information request of 9:33AM that day, you state that the AE databases for the phase 2 and 3 studies were created using different versions of MedDRA. Please identify the version of MedDRA used for each clinical trial.

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/s/  
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BRIAN K STRONGIN  
08/18/2011

**From:** Strongin, Brian K  
**Sent:** Thursday, August 18, 2011 9:33 AM  
**To:** 'Sarah Lieber'  
**Cc:** Strongin, Brian K  
**Subject:** Information Request for NDA 202-811 Linaclotide  
Please submit a response to the following information request as soon as possible:

Did you submit a "coding dictionary" containing a list of all investigator verbatim terms and the preferred terms to which they were mapped? If so please provide the location(s). We prefer this as a SAS file.

Thanks.

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/s/

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BRIAN K STRONGIN  
08/18/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 63,290

**MEETING MINUTES**

Ironwood Pharmaceuticals, Inc.  
Attention: Sarah Lieber, M.S.  
Manager, Regulatory Affairs  
301 Binney Street  
Cambridge, MA 02142

Dear Ms. Lieber:

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

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on March 22, 2011.

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

If you have any questions, call me at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.  
Chief, Regulatory Project Management Staff  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** March 22, 2011, 4:00PM  
**Meeting Location:** White Oak Building #22, Conference Room 1311

**Application Number:** IND 63,290  
**Product Name:** Linaclotide  
**Indication:** Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Idiopathic Constipation  
**Sponsor/Applicant Name:** Forrest Laboratories and Ironwood Pharmaceuticals

**Meeting Chair:** Hugo Gallo-Torres, M.D., Ph.D.  
**Meeting Recorder:** Brian Strongin, R.Ph., M.B.A.

### FDA ATTENDEES

Donna Griebel, M.D. Director, Division of Gastroenterology Products (DGP)  
Andrew Mulberg, M.D., Deputy Director, DGP  
Hugo Gallo-Torres, M.D., Ph.D. Medical Team Leader, DGP  
Eric Wynn, M.D. Medical Reviewer, DGP  
David Joseph, Ph.D. Supervisory Pharmacologist, DGP  
Sue Chih Lee, Ph.D. Clinical Pharmacology Team Leader  
Insook Kim, Ph.D., Clinical Pharmacology Reviewer  
Mike Welch, Ph.D. Team Leader, Biometrics  
Brian Strongin, R Ph, M.B.A. Chief, Project Management Staff

### SPONSOR ATTENDEES

#### IRONWOOD

Alexander Bryant, Ph.D., Vice President, Pre-clinical Pharmacology and Toxicology  
Robert Busby, Ph.D., Vice President, Drug Metabolism and Pharmacokinetics  
Mark Currie, Ph.D., Sr. Vice President, Research and Development and Chief Scientific Officer  
Jeff Johnston, M.D., Vice President, Clinical Development, and Chief Medical Officer  
Caroline Kurtz, Ph.D., Vice President, Program Management  
Joe Lavins, M.D., Sr. Director, Clinical Research  
Sarah Lieber, M.S., Manager, Regulatory Affairs  
Jim MacDougall, Ph.D., Vice President, Biometrics  
Gwyn Reis, Vice President, Regulatory Affairs

Karel Van Loon, M.D., Senior Director, Drug Safety and Pharmacovigilance

#### FOREST LABORATORIES

Gavin Corcoran, MD, Sr. Vice President, Internal Medicine/Cardiovascular/Metabolism, Clinical Development

James DeMartino, Ph.D., Sr. Director, Regulatory Affairs

Robert Imani, MD, PhD, Associate Director, Pharmacovigilance and Risk Management

Daniel Jia, Ph.D., Sr. Director, Biostatistics

Linda Kunka, M.A., Sr. Manager, Regulatory Affairs

Stephan Ortiz, R.Ph., Ph.D., Sr. Principal Scientist, Clinical Pharmacology

Harvey Schneier, M.D., Executive Director, Clinical Development

Steven Shiff, M.D., Director, Clinical Development

### 1.0 BACKGROUND

IND 63,290 was submitted by Microbia, Inc. September 30, 2004 for Linaclotide for the treatment of IBS-C. Sponsorship of the IND changed to Ironwood Pharmaceuticals on April 14, 2008. An end-of-phase 2 meeting to discuss phase 3 chronic constipation protocols was held May 15, 2008.

A pre-NDA meeting request was submitted January 13, 2011 to discuss the clinical and non-clinical submission content of a planned NDA for Linaclotide for irritable bowel syndrome with constipation and chronic constipation.

Summaries of the following phase 3 studies were included in the background package submitted February 18, 2011:

MCP-103-302: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 26 weeks in Patients with Irritable Bowel Syndrome with Constipation

LIN-MD-31: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Irritable Bowel Syndrome with Constipation

LIN-MD-01: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks in Patients with Chronic Constipation

MCP-103-303: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Constipation

## 2. DISCUSSION

### Nonclinical Question

#### Question 1

Does the Agency agree that the nonclinical studies conducted are sufficient to support the planned filing and review of the linaclotide NDA?

#### **FDA Response:**

**From the nonclinical information provided in the meeting package it appears that you have conducted the appropriate studies for filing an NDA, however the final determination that the NDA is fileable will be determined within 60 days of the application receipt.**

### Clinical Pharmacology Question

#### Question 2

Does the Agency agree that the content of the clinical pharmacology program is sufficient to support the planned filing and review of the linaclotide NDA?

#### **FDA Response:**

**We recommend that the effects of linaclotide and the metabolite on induction of CYP enzymes be studied. Please submit the full study reports for in vitro transporter studies and CYP enzymes at the time of NDA submission. However, neither of these issues rises to the level of a refuse-to-file issue. The final determination that the NDA is fileable will be determined within 60 days of the application receipt.**

#### ***Discussion:***

***Linaclotide is a peptide drug with no measurable systemic exposure following maximum therapeutic doses in humans and is neither a substrate nor an inhibitor of CYPs or various transporters (including p-glycoprotein). The sponsor believes the likelihood of this drug being a CYP inducer is minimal. The sponsor will evaluate the requirements for an in vitro induction study.***

### **Clinical Efficacy and Safety Questions**

#### **Question 3**

Does the Agency agree that the clinical data from the four pivotal Phase 3 trials (MCP-103-302 and LIN-MD-31 for the IBS-C indication; MCP-103-303 and LIN-MD-01 and for the CC indication), in addition to data from the overall clinical development program, provide an adequate basis for the filing and review of the linaclotide NDA in support of the IBS-C and CC indications?

#### **FDA Response:**

**From the information provided in the meeting package it appears that you have adequate basis for filing an NDA, however the final determination that the NDA is fileable will be determined within 60 days of the application receipt.**

#### **Question 4**

Ironwood and Forest plan to include two separate Summaries of Clinical Efficacy (Section 2.7.3 of Module 2); one for the IBS-C indication and one for the CC indication. All efficacy data will be summarized within Section 2.7.3, Summary of Clinical Efficacy of the eCTD. The summaries in Section 2.7.3 will serve as the narrative portions of the full Integrated Summary of Effectiveness (ISE). Supporting source tables, listings, figures (TLFs) and datasets will reside in Section 5.3.5.3 of Module 5. Does the Agency agree that this approach is acceptable?

#### **FDA Response:**

**Yes**

#### **Question 5**

Does the Agency agree with the proposed analyses and the presentation of efficacy data in the planned ISEs for the IBS-C and CC indications?

#### **FDA Response:**

**Yes**

**This approach seems acceptable, you will still need to provide all of the information that is outlined in the Guidance for Industry—Guideline for the format and content of the clinical and Statistical Sections of an Application.**

Question 6

Ironwood and Forest plan to include one combined Summary of Clinical Safety for both IBS-C and CC indications. All safety data will be summarized within Section 2.7.4 of Module 2, Summary of Clinical Safety. The summary in Section 2.7.4 will serve as the narrative portion of the full Integrated Summary of Safety (ISS). Supporting TLFs and datasets will reside in Section 5.3.5.3 in Module 5. Does the Agency agree that this approach is acceptable?

**FDA Response:**

Yes.

Question 7

Does the Agency agree with the proposed analyses and presentation of safety data in the ISS?

- a. For the purpose of the ISS, all 13 clinical studies of linaclotide (six Phase 3, four Phase 2, and three Phase 1) have been organized into groups based on study phase, study design, and subject population. Does the Agency agree that the proposed ISS groupings are acceptable?

**FDA Response:**

**Yes. In addition you should provide integrated safety analysis of group 1 (pivotal trials) and group 3 (long-term safety trials) pooled together**

*Discussion:*

*The sponsor will provide an additional integrated safety analysis of linaclotide-treated group 1 (pivotal trials) and group 3 (long-term safety trials) patients pooled together. These analyses will not include data from the placebo-treated patients during double-blind treatment in group 1, but will include data from the point of initiation of open-label linaclotide for these patients if they rolled over into the long-term safety trials. These analyses will include demographics, drug exposure and adverse events, including TEAEs, SAEs, Adverse Events Associated with Study Discontinuation, and Deaths. This proposal is acceptable.*

- b. Two open-label long-term safety (LTS) studies are currently ongoing; therefore, a cut-off date (11 October 2010) was applied to these studies for the safety data to be included in the NDA submission. In addition, a listing of any serious adverse events (SAEs) which occur in the LTS studies and are reported to the Sponsors after the October 11, 2010 cutoff and up to 3 months prior to NDA submission will be included in the initial NDA submission. Does the Agency agree with the proposed safety data cut-off date for the two ongoing open-label LTS Studies?

**FDA Response:**

Yes

Question 8

During the course of the Phase 2 and 3 studies, 25 patients enrolled under more than one patient identification number, without knowledge by either the investigators or sponsors, in one or more linaclotide studies in violation of eligibility criteria. These patients will be referred to in this document and the NDA as “duplicate patients”. Does the Agency agree with the proposed approach for the handling of data from the duplicate patients in the ISE and ISS?

**FDA Response:**

**You should perform appropriate sensitivity analyses to determine that these patients do not bias study results. These analyses should include datasets with and without the duplicate patients. One efficacy analysis would be where the patient is only counted as initially randomized in the study. Please provide a list of these patients including their patient numbers, sites where they enrolled, studies enrolled in, and timing of enrollment in each study and site. Include the results for each patient.**

*Discussion:*

*Of the 25 duplicate patients, only 2 patients were randomized twice into the same Phase 3 efficacy trial (LIN-MD-31). In the pre-specified efficacy analyses for this trial, each duplicate patient was counted only once, as initially randomized.*

*As per the Agency’s request, for each of the 4 individual Phase 3 efficacy trials and the corresponding pooled data for each indication (CC and IBS-C), sensitivity analyses will be performed using the following 2 methods: 1) excluding all data from the 25 duplicate patients in the analyses, and 2) including all data from the 25 duplicate patients in the analyses. These sensitivity analyses will be performed for the set of primary and secondary efficacy parameters. Additionally, for each of the 4 efficacy trials, these sensitivity analyses will be performed using the pre-specified multiple comparison procedure. The results of these analyses will be included within NDA Section 2.7.3 for CC and IBS-C.*

*A list of the duplicate patients including their patient numbers, sites where they enrolled, studies enrolled in, and timing of enrollment in each study and site, and results for each patient will be included in the submission.*

Question 9

Ironwood and Forest plan to submit the study data in the CDISC-SDTM 3.1.2 format, and the analysis datasets in the CDISC ADaM format for each of the completed Phase 2 and Phase 3 studies in support of the linaclotide efficacy claims. Ironwood and Forest do not plan to submit the raw datasets for these studies. However, a define.xml will be provided that will include detailed specifications for the analysis variables as a standard part of the submission for the analysis datasets. The NDA will also include the raw datasets from Phase 1 studies, raw pharmacokinetics (PK) datasets, and ISS and ISE analyses datasets. Does the Agency agree with the proposal for submitting the electronic datasets?

**FDA Response:**

**This plan appears to be acceptable, but please clarify what is meant by “raw datasets”.**

***Discussion:***

***The term “raw datasets” refers to the original CRF or eCRF data (and non-CRF data such as laboratory results and ECGs) as captured during the trial and extracted to SAS datasets. These raw datasets are used in the creation of SDTM datasets and are not compliant with the CDISC SDTM format. These datasets represent clean and locked datasets and will include appropriate documentation. These datasets will be included in the initial NDA submission.***

Question 10

Clinical study reports (CSRs) for each of the 11 completed clinical studies will be provided in the NDA, including 10 full CSRs and 1 abbreviated CSR (Study MCP-103-005). Separate interim CSRs will not be provided for the ongoing LTS studies; however, interim results will be presented in detail within Section 2.7.4. Does the Agency agree that this plan for CSRs to be provided in the linaclotide NDA is acceptable?

**Yes.**

**FDA Response:**

**We note that you do not plan to submit the PD results of MCP-103-005. We request that you submit the PD results of the MCP-103-005 for our review, not just the publication.**

***Discussion:***

*The sponsor will provide for Agency review the MCP-103-005 pharmacodynamic SAS datasets as well as the tables, listings, and figures, as an addendum to the abbreviated CSR. This was a single-center clinical pharmacology study that was designed and conducted by Dr. Michael Camilleri at The Mayo Clinic to evaluate the effect of linaclotide on GI transit. The safety data from this study, which were captured in a 21 CFR Part 11 compliant manner, are included in the abbreviated CSR along with the safety-related datasets. However, the pharmacodynamic data were collected using standard procedures for the investigational site and were not captured in a 21 CFR Part 11 compliant manner; these data were published in Gastroenterology (Andresen, 2007). This publication is included in this correspondence and will also be provided in the NDA.*

Question 11

Ironwood and Forest plan to include case report forms (CRFs) and detailed narratives for deaths, other SAEs, and withdrawals for adverse events (AEs) that occurred in the completed studies and for the ongoing LTS studies (for events occurring prior to the October 11, 2010 cut-off date). For SAEs reported after the data cut-off date of October 11, 2010 in LTS studies, a summary listing of patients who experienced SAEs, instead of CRFs and narratives, will be provided. Does the Agency agree with this proposal for the reporting of deaths, other SAEs and withdrawals due to AEs within the NDA?

**FDA Response:**

Yes

**Additional Questions**

Question 12

Does the Agency have any comments regarding the proposed content and format of the NDA for linaclotide?

**FDA Comments:**

**Please see the requests from the Division of Scientific Investigations in Attachments A and B**

Question 13

Does the Agency agree with the proposed content for the 120-day safety update?

**FDA Response:**

**Yes**

**We note that you plan to submit brief summaries of in vitro studies for interaction with various transporters and inhibition of CYP enzymes in 120 day safety update. We are strongly committed to following the 21<sup>st</sup> Century Review process. Late submissions may not allow us to meet our timelines and for this reason may not be reviewed during the first review cycle. We request that full study reports for those studies be submitted at the submission of NDA.**

Question 14

Please comment on the likelihood of an Advisory Committee meeting being convened for review of the linaclotide NDA.

**FDA Response:**

**While we are encouraged to take all new molecular entities to advisory committee meetings, our decision is based on review issues identified during the course of review. We will notify you if and when we have determined that your product will go to an advisory committee.**

Question 15

Please comment on the proposed plan for the pediatric studies.

**FDA Response:**

**Your proposed plan may be reasonable but will require discussion and input from the Pediatric Review Committee. You will need validated patient-reported outcome (PRO) instruments for use in children in different age ranges to pursue your proposed pediatric development plan.**

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

**5.0 ACTION ITEMS**

Action Item/Description	Owner
Evaluate the requirements for an <i>in vitro</i> study on the effects of linaclotide and the metabolite on induction of CYP enzymes	Sponsor
Provide an additional integrated safety analysis of linaclotide-treated group 1 (pivotal trials) and group 3 (long-term safety trials) patients pooled together. These analyses will not include data from the placebo-treated patients during double-blind treatment in group 1, but will include data from the point of initiation of open-label linaclotide for these patients if they rolled over into the long-term safety trials. These analyses will include demographics, drug exposure and adverse events, including TEAEs, SAEs, Adverse Events Associated with Study Discontinuation, and Deaths.	Sponsor
<p>For each of the 4 individual Phase 3 efficacy trials and the corresponding pooled data for each indication (CC and IBS-C), sensitivity analyses will be performed using the following 2 methods: 1) excluding all data from the 25 duplicate patients in the analyses, and 2) including all data from the 25 duplicate patients in the analyses. These sensitivity analyses will be performed for the set of primary and secondary efficacy parameters. Additionally, for each of the 4 efficacy trials, these sensitivity analyses will be performed using the pre-specified multiple comparison procedure. The results of these analyses will be included within NDA Section 2.7.3 for CC and IBS-C.</p> <p>A list of the duplicate patients including their patient numbers, sites where they enrolled, studies enrolled in, and timing of enrollment in each study and site, and results for each patient will be included in the submission.</p>	Sponsor

Raw datasets (See the Discussion following Question #9) will be included in the initial NDA submission	Sponsor
Provide for Agency review, the pharmacodynamic SAS datasets as well as the tables, listings, and figures, as an addendum to the abbreviated clinical study report for MCP-103-005.	Sponsor

## 6.0 ATTACHMENTS AND HANDOUTS

### ATTACHMENT A

#### Requests from the Division of Scientific Investigations

##### 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 completed 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 completed 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 completed Phase 3 clinical trials:

1. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
2. Name, address and contact information of all CROs used in the conduct of the clinical trials
3. 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
4. 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 and case report data tabulations for the site with coding key
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.

## **ATTACHMENT B**

### **Requests from the Division of Scientific Investigations**

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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	FINLIDISC	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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BRIAN K STRONGIN  
04/21/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 63,290

Ironwood Pharmaceuticals  
Attention: Christine Pierce, Regulatory Affairs  
320 Bent St.  
Cambridge, MA 02141

Dear Ms. Pierce:

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

We also refer to the meeting between representatives of your firm and the FDA on August 7, 2008. The purpose of the meeting was to discuss the development program for linaclotide and the irritable bowel syndrome indication.

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

If you have any questions, call me at (301) 796-2247.

Sincerely,

*{See appended electronic signature page}*

Thomas Moreno, M.S.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2  
**Meeting Date and Time:** August 7, 2008, 2 PM  
**Meeting Location:** FDA, White Oak Campus  
**Application Number:** IND 63,290  
**Product Name:** Linaclotide  
**Received Briefing Package** July 2, 2008  
**Sponsor Name:** Ironwood Pharmaceuticals  
**Meeting Requestor:** Christine Pierce  
**Meeting Chair:** Dr. Joyce Korvick  
**Meeting Recorder:** Thomas Moreno

**Meeting Attendees:**

**FDA Attendees**

Division of Gastroenterology Products

Joyce Korvick, M.D., M.P.H., Deputy Director  
Nancy Snow, D.O., Medical Officer  
Sushanta Chakder, Ph.D., Acting Supervisory Pharmacologist  
David Joseph, Ph.D., Pharmacology Reviewer  
Yuk-Chow Ng, Ph.D, Pharmacology Reviewer  
Roland Girardet, Regulatory Project Manager  
Thomas Moreno, M.S., Regulatory Project Manager

Division of Biometrics III

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Paul Reed, M.D., Medical Reviewer

Study Endpoints and Label Development (SEALD) Team

Ann-Marie Trentacosti, M.D., Reviewer

**Sponsor Attendees**

Ironwood:

Rob Busby, Ph.D., Sr. Director, Analytical Pharmacology/DMPK  
Mark Currie, Ph.D., Sr. V.P., Research and Development and Chief Scientific Officer  
Jeff Johnston, M.D., V.P., Clinical, Biometrics and Regulatory Affairs, Chief Medical Officer  
Caroline Kurtz, Ph.D., Director, Program Management  
BJ Lavins, M.D., Sr. Director, Clinical Research  
Jim MacDougall, Ph.D., Sr. Director, Biostatistics & Data Management  
Ashley Milton, Ph.D., Director, Clinical Pharmacology  
Christine Pierce, M.S., Manager Regulatory Affairs  
Gwyn Reis, Sr. Director, Regulatory Affairs

Consultant to Ironwood:

(b) (4)

Forest Laboratories, Inc.:

John Castellana, Ph.D., Sr. VP Clinical Operations & Biometrics  
Haim Erder, Executive Director, Health Outcomes  
Stephan Ortiz, R.Ph., Ph.D., Senior Principal Scientist, Clinical Pharmacology  
Harvey Schneier, M.D., Executive Director, Clinical Development GI & Emerging Therapies  
Steven Shiff, M.D., Associate Director, Clinical Development GI  
Marco Taglietti, M.D., Executive VP FRI, Chief Medical Officer

**1 BACKGROUND**

Linacotide is being developed as an orally administered therapeutic for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Constipation (CC). This meeting is an End of Phase 2 meeting to discuss the Phase 3 program for IBS-C. A separate meeting for CC was held on May 15, 2008.

**2 SPONSOR'S QUESTIONS AND FDA PRELIMINARY RESPONSES**

The FDA responded with preliminary responses on August 5, 2008, to the questions submitted by Ironwood Pharmaceuticals. The following meeting minutes contain each sponsor question, the FDA preliminary response, and key points from the meeting discussion.

Because of the limited meeting time, Ironwood decided to limit discussion to question 1, 2, 4a, and 4b.

**2.1 Clinical Pharmacology**

**Question 1:**

Clinical data demonstrate that linaclotide has no systemically measurable levels after oral administration of clinically relevant doses. As recommended by the Agency, we performed a systemic clearance study in the rat and observed that even in the presence of complete renal artery ligation linaclotide was actively cleared from the plasma, albeit at a decreased rate compared to renal intact animals (see Section 7.2.4 of the briefing book). These data indicate that trace amounts of linaclotide, that will be found in the systemic circulation following oral doses, will be cleared by at least two pathways (renal and biliary). In light of these data and coupled with the no measurable amount present in human subjects at the therapeutic dose, we believe that there is no scientific rationale for specific clinical investigations to assess the effects of renal impairment on the pharmacokinetics of linaclotide. Likewise, as the metabolism of linaclotide occurs outside of the liver, changes in liver function in patients would not be expected to alter linaclotide clearance and, hence, a specific hepatic impairment study would also not be warranted. Does the Agency agree with this position?

**FDA Response to Question 1:**

We believe that there is not enough information to answer the question at this time. Without knowing the composition of the to-be-marketed and clinical formulations, we cannot rule out the need for hepatic and renal impairment studies. Changes in composition of the formulation may enhance systemic absorption. The Agency suggests that a mass balance/radiolabel study be conducted in order to determine the route of elimination.

**Discussion:**

If assumptions (the to-be-marketed formulation is same as current, or if the to-be-marketed formulation has no appreciable systemic exposure, and phase 3 efficacy and safety data are reviewed) are acceptable then it is reasonable not to perform special population studies in renal and hepatically impaired populations and nursing mothers.

**Question 2:**

While there is a theoretical possibility that any absorbed linaclotide that is not degraded to its amino acid constituents could be distributed to breast milk in lactating females, Ironwood and Forest consider this to be of very low likelihood. While some drug may be present in the plasma (though not detectable), subsequent distribution into breast milk would require this low-permeability drug to cross a second epithelial barrier, further reducing the already undetectable level of linaclotide. Testing this possibility either in a preclinical or clinical PK study would not be technically feasible. Therefore, Ironwood and Forest contend that this theoretical risk can be appropriately communicated in labeling. Does the Agency agree with this position?

**FDA Response to Question 2:**

We cannot advise you until we have adequate information on the systemic exposure that is associated with the final to-be-marketed formulation.

**Additional FDA Clinical Pharmacology Comments**

In the meeting held between Ironwood and FDA on May 15, 2008, the Agency provided the following response to Question 2 from that briefing package:

**“Question 2, May 15, 2008:**

We do not believe that it would be informative to conduct a battery of drug-drug interaction studies because linaclotide is not quantifiable in human plasma at anticipated therapeutic doses, because as a peptide, linaclotide does not interact with the cytochrome P-450 (CYP-450) enzyme system, and because the potential of linaclotide to affect the GI absorption of drugs such as digoxin, which are routinely monitored, can be adequately addressed through labeling. Does the GI Division agree with the plan for not conducting drug interaction studies?

**FDA Response to Question 2, May 15, 2008:**

This appears reasonable at this time.”

It is important that you thoroughly investigate whether linaclotide, a cyclic peptide, is a P-gp substrate or a P-gp modulator. For example, cyclosporine A was declared to have < 1% absorption, and later found to interact with P-gp and CYP 3A enzymes. CYP3A enzymes are also present in the intestine.

To assist you in your development program for maximizing the therapeutic benefit of linaclotide, the Agency recommends the following.

- Conduct in-vitro studies to determine whether linaclotide is a P-gp substrate or a P-gp modulator.
- Evaluate metabolism of linaclotide by intestinal mucosa and intestinal CYP enzymes. Based on the results of these in-vitro studies, you should conduct DDI studies in humans accordingly.

Please refer to the following guidance for conducting appropriate Drug Drug Interaction studies in humans: *Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006)*.

**Discussion**

Ironwood agreed to conduct the recommended studies.

**2.2 Biopharmaceutics**

**Question 3:**

In the Agency’s May 12, 2008 response to the questions posed for the linaclotide EOP2 meeting, the Agency recommended that the “Guidance for Industry/ Immediate Release Solid Oral Dosage Forms/ Scale-up and Post Approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation” be used as a guide to determine the types of formulation changes that would not require bioequivalence studies. To address formulation changes between two oral solid dosage

forms of linaclotide which would require a bioequivalence study, Ironwood and Forest proposed, and the Agency agreed in principle at the May 15, 2008 EOP2 meeting, with submitting *in vitro* dissolution data in combination with pharmacokinetic data. The *in vitro* dissolution data will provide a direct comparison of dosage form performance in terms of availability of the drug at the site of action, while the pharmacokinetic results will provide assurance that the formulation changes do not markedly alter the systemic exposure of the drug. Since linaclotide is immediately available at its site of action (the luminal surface of the epithelial cells in the intestine) upon dissolution, we believe the bioequivalence of rapidly dissolving formulations of the drug (b) (4) dissolved in <30 min) can be established based on *in vitro* dissolution data and *in vivo* pharmacokinetic data.

Can the Agency confirm agreement with this approach?

**FDA Response to Question 3:**

Ironwood Pharmaceuticals requested that this question be withdrawn. Therefore, there is no FDA response to question 3.

## 2.3 Clinical

**Question 4:**

We plan to conduct two Phase 3 adequate and well-controlled safety and efficacy trials in patients with IBS-C to support the following indication: "Linaclotide is indicated for the treatment of irritable bowel syndrome with constipation in adults." One trial will include a 26-week double-blind treatment period to assess safety and efficacy; the other will have a 12-week double-blind treatment period followed by a 4-week randomized withdrawal period (to demonstrate the lack of rebound following cessation of treatment with linaclotide). The primary efficacy endpoint in both trials will be 12-week CSBM Overall Responder. (A 12-week CSBM Overall Responder is a patient who is a CSBM Weekly Responder for 9 out of 12 treatment weeks. A CSBM Weekly Responder is a patient whose CSBM frequency during a particular treatment week is at least 3 CSBMs/week and increases by at least 1 CSBM/week from pretreatment.) The secondary efficacy endpoints in both efficacy studies are also based on the first 12 weeks of treatment. In the 26-week trial, we will examine these primary and secondary efficacy endpoints and use the full 26-week Treatment Period to assess whether linaclotide has sustained efficacy over 26 weeks.

**Question 4a:**

Does the Agency agree with the selection of 12-week CSBM Overall Responder as the primary efficacy endpoint and that positive results with this endpoint (in both the 12-week and 26-week pivotal efficacy studies) would support the approval of linaclotide for the treatment IBS-C?

**FDA Response to Question 4a:**

No, your choice of primary efficacy endpoint is not acceptable. Your overall endpoint model is based upon linaclotide's mechanism of action, rather than the clinically important content valid subconcepts. IBS-c is a composite concept that includes subconcepts or domains of abdominal pain or discomfort associated and change in bowels (e.g. stool frequency,

appearance, and form). In choosing an endpoint which evaluates only stool frequency (CSBM weekly overall responder), you are excluding all of the other subconcepts or manifestations of IBS-c. Other subconcepts including the symptoms of pain or discomfort, which according to the Rome III committee must be present to make a diagnosis of IBS are omitted. For the indication, "treatment of IBS-c", it is important for the primary endpoint to capture all, as opposed to one, of the important subconcepts.

We recommend that you consider developing an instrument, that based upon patient input, is shown to represent a complete, meaningful, appropriate, and interpretable instrument of the major manifestations of IBS-c to utilize as your primary endpoint.

**Discussion**

Based on FDA's comments, Ironwood plans to change their proposed indication from "treatment of IBS-c" to (b) (4)

(b) (4)

. In addition, Ironwood will submit information from their qualitative studies to support the use of their proposed PRO instruments.

FDA noted that they could not provide comments about this new indication at this time and would need to have further internal discussions as well as review Ironwood's new proposal when submitted.

**Question 4b:**

Does the Agency agree that achieving positive results for the 26-week efficacy endpoints in the 26-week trial in addition to achieving positive results for the primary endpoint, 12-week CSBM Overall Responder, in the 12-week and in the 26-week trials, would support our proposed indication statement, which does not include a limit on treatment duration? ("Linaclotide is indicated for the treatment of irritable bowel syndrome with constipation in adults.")

**FDA Response to Question 4b:**

No, your proposed primary endpoint does not support the proposed indication.

**Discussion**

Since Ironwood and the Agency are not in agreement on the primary endpoint, Ironwood will resubmit this question in a new meeting request to allow for further discussion.

**Question 4c:**

As discussed with the Agency at the CC EOP2 meeting on May 15, 2008, we plan to include a 4-week randomized withdrawal period in one of the two Phase 3 CC trials and also in the 12-week efficacy trial in IBS-C to meet the Agency's request to assess whether the cessation of linaclotide dosing is associated with a rebound worsening of symptoms (see FDA Type-C meeting minutes dated April 19, 2007). Does the Agency agree that including a randomized withdrawal period following the double-blind treatment period in the two Phase 3 trials (one

in CC patients and one in IBS-C patients) to assess patients for a rebound worsening of their IBS-C or CC symptoms is sufficient for this purpose?

**FDA Response to Question 4c:**

Yes we agree that including a randomized withdrawal period following the double-blind treatment period in the two Phase 3 trials (one in CC patients and one in IBS-C patients) to assess patients for a rebound worsening of their IBS-C or CC, or how sustainable the effect is. As we discussed at our May 15, 2008 meeting, including a randomized withdrawal phase in both trials will provide a replication of findings. We also recommended that you re-randomize your patients at the end of the treatment period.

**Question 5:**

[REDACTED] (b) (4)

**FDA Response to Question 5:**

[REDACTED] (b) (4)

**Question 6:**

Does the Agency agree that the inclusion and exclusion criteria for the Phase 3 trials adequately define a population of patients with IBS-C, in whom the safety and efficacy of linaclotide can reasonably be assessed?

**FDA Response to Question 6:**

Your inclusion and exclusion criteria are acceptable.

**Question 7:**

It may be possible that the US Phase 3 efficacy trials would support a European Marketing Authorization Application (MAA) for IBS-C. However, the efficacy endpoints to support the approval of a European MAA may be different than the efficacy endpoints that will support the US NDA. Would it be acceptable to the Agency for a study protocol to have two separate statistical analysis plans, one to meet the US regulatory requirements and one to meet the European regulatory requirements?

**FDA Response to Question 7:**

For U.S. requirements, the primary endpoints, hypotheses to be tested, detailed statistical methods relating to primary and key secondary variables, methods for handling missing data, multiplicity, sensitivity analyses, etc. should be pre-specified in the protocol prior to start of

study. The statistical analysis plan (SAP) is meant to provide more technical detail relating to execution of analyses already stated in the protocol. (Reference ICH E9). We would expect for you to submit a single protocol and accompanying SAP relevant to your proposed indication.

**Question 8:**

Does the Agency agree that the same modified Rome II criteria that were used for patient enrollment into the linaclotide Phase 2 clinical study for IBS-C are acceptable for patient enrollment into the Phase 3 clinical trials (rather than the recently published Rome III diagnostic criteria)?

**FDA Response to Question 8:**

Your approach of using Rome II rather than Rome III criteria is acceptable for the adult studies. However, with respect to pediatric trials, you should submit a justification for the choice of diagnostic criteria to be used. Additional PRO validation of the criteria for pediatric patients likely will be needed.

**Question 9:**

We estimate that approximately 70 patients enrolled into the two IBS-C Phase 3 confirmatory efficacy trials will be greater than 65 years of age and that approximately 65 patients will be male (similar numbers will also be enrolled into the two CC Phase 3 trials). Does the Agency agree that the efficacy results in these subpopulations, if they are favorable and at least similar to those in the overall population, would support the proposed indication in the labeling? ("Linaclotide is indicated for the treatment of irritable bowel syndrome with constipation in adults.")

**FDA Response to Question 9:**

As we responded at our May 15, 2008 meeting, if the results for the subpopulations of patients >65 years, and male patients, are similar to those obtained in the general population, they would likely support an indication that would not exclude males or patients >65 years. However, if you intend to propose labeling claims for specific age subgroups, you would need to design and power your studies to demonstrate efficacy in these subgroups.

**Question 10:**

Does the Agency agree that patients who roll over from the efficacy study to the LTSS, and hence receive linaclotide for 12 weeks in the Phase 3 efficacy trials and 40 weeks of treatment in the LTSSs will be considered to have 52 weeks of exposure for the purpose of meeting the ICH safety requirements, even if they receive placebo during the 4-week Randomized Withdrawal Period at the end of the efficacy trials?

**FDA Response to Question 10:**

The patients you describe will have 12 weeks of treatment, followed by no treatment for 4 weeks during the randomized withdrawal period, followed by 40 weeks of treatment in the

LTSS. Since the combined 12 weeks plus 40 weeks in the LTSS equals 52 weeks, consistent with ICH guidelines, we have no objection to this plan.

**Question 11:**

As recommended in your written response to Question 8 from the CC EOP-2 meeting on May 15, 2008, we have reviewed the FDA's electronic source documentation concerns that are delineated in the "Study Section" of the draft "FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims." To address these concerns, we plan to provide trial investigators with direct access to the data that patients report in the IVRS, so that the data can be reviewed on a regular and ongoing basis. By providing this access, we avoid having exclusive control of source documents (i.e., by the sponsor) and allow investigators to confirm the accuracy of the patient-reported data. In addition, upon completion of the study, we plan to provide each investigator with a CD-ROM containing all patient-reported data entered into the IVRS. This copy will be maintained at that trial center and will be available for review during sponsor audits and FDA inspections. Does the Agency agree that this plan meets the FDA's electronic source documentation concerns that are delineated in the draft guidance?

**FDA Response to Question 11:**

We agree with your proposal.

**2.4 Pediatric**

**Question 12:**

Under the provisions of Section 505B(a)(3) of the Federal Food, Drug and Cosmetic Act, Ironwood and Forest plan to request a partial waiver from conducting a CC study with linaclotide in children who are younger than age 2 years and from conducting an IBS-C study in children who are younger than age 5 years. Does the Agency agree that the rationales (provided in Section 9.4 of the briefing book) for requesting a partial waiver in these age groups for both CC and IBS-C pediatric population would support a partial waiver request?

**FDA Response to Question 12:**

Although final decisions about waivers and deferrals are made at the time of approval, our preliminary recommendations are as follows:

**Waivers:**

**For Irritable Bowel Syndrome with constipation:**

**Yes.** A partial waiver request from conducting studies of linaclotide in children with IBS-C who are younger than 5 years of age is supported by section 505B(a)(4)(B)(i) of PREA as necessary studies are impossible or highly impracticable. IBS-C is not well defined in this age group and the number of patients is too small. Studies are required for pediatric patients 6 – 17 years of age.

**For chronic constipation:**

**No.** A partial waiver request from conducting studies of linaclotide in children younger than 2 years of age for the treatment of chronic constipation is not supported by section 505B(a)(4)(B)(iii) of PREA. Medications to treat constipation in younger children represent a meaningful therapeutic benefit over existing therapies as prescription and over the counter products for treating constipation have not been adequately studied in this age group. In addition, a substantial number of pediatric patients 6 months - 2 years of age suffer from chronic constipation. A partial waiver request from conducting studies in children younger than 6 months of age is appropriate, but studies are required in patients  $\geq$  6 months of age.

Of note, juvenile animal toxicology studies should be performed prior to initiation of the studies in pediatric patients to assess potential developmental age-specific toxicities and differences in sensitivity between adult and immature animals. (Please refer to the Guidance for Industry, Nonclinical Safety Evaluation of Pediatric Drug Products on the Agency's web page: <http://www.fda.gov/cder/guidance/index.htm>).

You need to conduct repeat-dose juvenile animal toxicity studies in a rodent (1-month duration) and a non-rodent (3-months duration) species.

#### **Deferrals:**

The Agency agrees with deferring pediatric studies for both indications until safety and efficacy have been established in adults. You should begin work on the juvenile animal studies, development of an age appropriate formulation, inclusion and exclusionary criteria for pediatric patients with CC and IBS-C, and age appropriate PRO measures for the study of IBS.

We remind you that per the Pediatric Research Equity Act (PREA) of 2007, you must submit a pediatric plan that includes:

- 1) certification of the grounds for deferring the pediatric studies;
- 2) a description of the planned or ongoing pediatric studies;
- 3) evidence that the pediatric studies are being conducted or will be conducted with due diligence and at the earliest possible time; and
- 4) a timeline for completion of such pediatric studies.

We will present your pediatric plan to the FDA Pediatric Review Committee which is legislatively mandated to provide consultation on all pediatric assessments and plans and on all deferral and waiver requests prior to approval of an application or supplement which triggers PREA.

If your product is approved, the pediatric studies required under PREA will be noted as a required postmarketing commitment in your approval letter.

## **2.5 PRO**

Volume 2 of this briefing book describes the basis for the proposed primary and secondary patient reported outcome (PRO) endpoints that will be used in the Phase 3 efficacy trials for linaclotide.

#### **Question 13:**

In the Clinical Trial section of the Target Product Profile (TPP), Ironwood and Forest plan to include the results of several secondary endpoints that will be assessed during the Phase 3 program. These endpoints include; SBM Frequency, CSBM Frequency, Stool Consistency,

Severity of Straining, Abdominal Pain, Abdominal Discomfort, Bloating, Constipation Severity, and IBS Symptoms Severity. (b) (4)

**FDA Response to Question 13:**

Although many of the secondary endpoint measure concepts that may be clinically relevant to IBS-c patients, (b) (4)

(b) (4). A listing of each individual sign/symptom associated with IBS-c as a secondary endpoint does not establish that the overall composite concept of IBS-c is improved with treatment. Therefore, it is recommended that you establish the relationships between each item and the overall concept of IBS-c by combining all of the subconcepts into a single comprehensive instrument. Item representation or weighting should be based upon clinical importance. For example, if pain and discomfort are most important then these items should have more weight in making a conclusion of treatment benefit.

In addition, the “constipation severity” and “IBS severity” items are patient ratings of change. As such, they can be useful for interpreting other study results, e.g., in defining a clinically meaningful change (responder definition) based on criteria which are defined a priori. However, as single items they cannot adequately assess all of the subconcepts associated with their intended complex measure, (b) (4)

Linked Applications

Sponsor Name

Drug Name

-----  
IND 63290

-----  
IRONWOOD  
PHARMACEUTICALS  
INC

-----  
MD-1100

-----  
**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/

-----  
THOMAS N MORENO  
08/25/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 63,290

Microbia  
Attention: Christine Pierce, Regulatory Affairs  
320 Bent St.  
Cambridge, MA 02141

Dear Ms. Pierce:

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

We also refer to the meeting between representatives of your firm and the FDA on May 15, 2008. The purpose of the meeting was to discuss the development program for linaclotide and the chronic constipation indication.

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

If you have any questions, call me at (301) 796-2247.

Sincerely,

*{See appended electronic signature page}*

Thomas Moreno, M.S.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

Enclosure - Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2  
**Meeting Date and Time:** May 15, 2008, 2:00 PM  
**Meeting Location:** FDA, White Oak Campus  
**Application Number:** IND 63,290  
**Product Name:** Linaclotide  
**Received Briefing Package** April 10, 2008  
**Sponsor Name:** Ironwood Pharmaceuticals  
**Meeting Requestor:** Christine Pierce  
**Meeting Chair:** Dr. Hugo Gallo-Torres  
**Meeting Recorder:** Thomas Moreno

**Meeting Attendees:**

**FDA Attendees**

Donna Griebel, M.D., Director, Division of Gastroenterology Products (DGP)  
Hugo Gallo-Torres, M.D., Ph.D., P.N.S., Medical Team Leader, DGP  
Nancy Snow, D.O., Medical Officer, DGP  
Thomas Moreno, M.S., Regulatory Project Manager, DGP  
Sushanta Chakder, Ph.D., Acting Supervisory Pharmacologist, DGP  
David Joseph, Ph.D., Pharmacology Reviewer  
Michael Welch, Ph.D., Deputy Director, Division of Biometrics III  
Sue-Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology III (DCP3)  
David Gortler, Ph.D., Clinical Pharmacology Reviewer, DCP3  
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment III  
Felicia Collins, M.D., Medical Reviewer, PMHS  
Erik Henrikson, Regulatory Health Project Manager, Pediatric and Maternal Health Staff (PMHS)  
Ann-Marie Trentacosti, M.D., Reviewer, Study Endpoints and Label Development (SEALD) Team

**Sponsor Attendees**

**Microbia:**

Toni Chancellor

Rob Busby, Ph.D., Sr. Director, Analytical Pharmacology/DMPK

Mark Currie, Ph.D., Sr. V.P., Research and Development and Chief Scientific Officer

Jeff Johnston, M.D., V.P., Clinical, Biometrics and Regulatory Affairs, Chief Medical Officer

BJ Lavins, M.D., Sr. Director, Clinical Research  
Jim MacDougall, Ph.D., Sr. Director, Biostatistics & Data Management  
Ashley Milton, Ph.D., Director, Clinical Pharmacology  
Christine Pierce, M.S., Manager Regulatory Affairs  
Gwyn Reis, Sr. Director, Regulatory Affairs

Forest Laboratories, Inc.:

John Castellana, Ph.D., Sr. VP Clinical Operations & Biometrics  
Haim Erder, Executive Director, Health Outcomes  
Andreas Grill, Sr. Director, Developmental Pharmaceuticals and PR&D Project Management  
Harvey Schneier, M.D., Executive Director, Clinical Development GI & Emerging Therapies  
Marco Taglietti, M.D., Executive VP Forest Research Institute, Chief Medical Officer  
Lucy Wynohradnyk, Director, Project Management

## **1 Background**

Ironwood Pharmaceuticals (formerly Microbia) and Forest Laboratories are co-developing linaclotide for the treatment of Chronic Constipation (CC) and Irritable Bowel Syndrome with constipation (IBS-C). The development program has reached the end of phase 2 and the sponsor seeks feedback and agreement concerning the phase 3 plans, the impact of renal clearance rate data, and a pediatric deferral. A separate meeting request has been submitted to discuss IBS-C and this meeting is primarily focused on the CC indication.

## **2 Sponsor Questions, FDA Responses, and Meeting Discussion**

The FDA responded with preliminary responses on May 12, 2008, to the questions submitted by Ironwood Pharmaceuticals. The following meeting minutes contain each sponsor question, the FDA preliminary response, and key points from the meeting discussion.

### **2.1 Nonclinical**

#### **Question 1:**

Based upon the data provided to the GI Division to date and the summary of studies provided in the briefing book, does the GI Division agree that the nonclinical safety data are adequate to support initiation of Phase 3 clinical trials and that the nonclinical program is adequate to support an NDA submission for linaclotide?

#### **FDA Response to Question 1:**

The adequacy of the nonclinical safety data to support initiation of Phase 3 trials will be determined from our review of the chronic toxicology studies. We agree that the nonclinical program is adequate to support an NDA submission.

### **2.2 Clinical Pharmacology**

**Question 2:**

We do not believe that it would be informative to conduct a battery of drug-drug interaction studies because linaclotide is not quantifiable in human plasma at anticipated therapeutic doses, because as a peptide, linaclotide does not interact with the cytochrome P-450 (CYP-450) enzyme system, and because the potential of linaclotide to affect the GI absorption of drugs such as digoxin, which are routinely monitored, can be adequately addressed through labeling. Does the GI Division agree with the plan for not conducting drug interaction studies?

**FDA Response to Question 2:**

This appears reasonable at this time.

**Question 3:**

We believe that conducting a thorough QTc study with linaclotide is not indicated because linaclotide has a highly-localized distribution and qualifies as a drug for which the recommendations in the ICH E14 guidance might not apply. Does the GI Division agree that it is not necessary to perform a thorough QTc study with linaclotide?

**FDA Response to Question 3:**

No we do not agree. You should conduct a thorough QT study for the following reasons:

1. Linaclotide is a new molecular entity, with limited experience in humans. A thorough QT study would help to characterize its effect on cardiac conduction and, if normal, would provide reassurance as to the drug's safety.
2. Although admittedly at high doses, preclinical studies in animals have shown systemic effects. It is important that we extrapolate those potential systemic effects to humans.
3. The details of the potential systemic bioavailability of Linaclotide and/or its resulting metabolites are still under investigation.

The thorough QT study may be carried out in parallel with the clinical studies now underway.

**Discussion**

FDA to consult QT-Interdisciplinary Review Team concerning the study design. FDA to contact sponsor within four weeks to provide an update.

**2.3 Biopharmaceutics**

**Question 4:**

Based on the rapid dissolution of the Phase 2 formulation, the proposed Phase 3 and the to-be-marketed formulations as well as the immediate availability of linaclotide at its site of action upon dissolution, we believe that the bioequivalence of immediate release (IR) linaclotide capsules to other linaclotide IR formulations, including new formulations developed during Phase 3, can be demonstrated based solely on *in vitro* dissolution.

Therefore, we would request a waiver of the requirement to provide *in vivo* bioequivalence results for any new IR formulations.

Does the GI Division concur with this approach?

**FDA Response to Question 4:**

No. In view of the significant formulation changes that you propose for the drug product that will be used in Phase 3 clinical trials and subsequently in the marketed product, it is not sufficient to demonstrate bioequivalence solely on the basis of *in vitro* dissolution testing. However, since you report that neither linaclotide nor its principal metabolite is detectable in plasma at the proposed dose, a bioequivalence study is not possible. Therefore, you will need to conduct your Phase 3 studies with the formulation that you plan to market. Some limited formulation changes can be made based on the comparability dissolution profiles, without the need for bioequivalence studies. You may use the following document (which may be found on the FDA website) as a guide to the types of formulation changes that would not require bioequivalence studies: “Guidance for Industry/ Immediate Release Solid Oral Dosage Forms/ Scale-up and Post Approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation”

**Discussion**

In accordance with FDA's *Guidance For Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*, a waiver of bioequivalence studies can only be granted for Class 1 compounds, i.e. those with both high solubility and high permeability. Although the solubility of linaclotide is high, its permeability is very low. Consequently, bioequivalence studies of product reformulations cannot be waived. However, if the applicant can provide an alternate plan to linking the different formulations, it should be submitted for our consideration. Both safety and efficacy should be considered in this plan. Although possible approaches were discussed at the meeting, including PK studies using formulations with the extreme levels of the various proposed excipients, no decision could be made at the meeting. It was concluded that the sponsor's plan could be discussed at a forthcoming CMC meeting that the firm plans to have with FDA.

The sponsor was also requested to provide evidence that the permeability of the drug substance is low, and that the low levels of linaclotide and its principal metabolite in plasma are indeed due to low permeability of the drug substance and not due to complete (or nearly complete) digestion of the peptide in the stomach.

## 2.4 Clinical

**Question 5:**

The Phase 2 studies of linaclotide in CC used Rome II diagnostic criteria with minor modifications as the basis for patient enrollment. As the data from these studies were used to design the Phase 3 CC trials, we plan to base enrollment into the Phase 3 clinical trials on the modified Rome II diagnostic criteria, rather than on the recently published Rome III diagnostic criteria. Does the GI Division agree that using the modified Rome II criteria for patient enrollment is acceptable?

**FDA Response to Question 5:**

Your approach of using Rome II rather than Rome III criteria is acceptable.

**Discussion**

The sponsor definition using modified Rome II is acceptable.

**Question 6:**

Does the GI Division agree that the inclusion and exclusion criteria for the Phase 3 trials adequately define a population of patients with CC, in whom the safety and efficacy of linaclotide can reasonably be assessed?

**FDA Response to Question 6:**

Yes, we agree that the inclusion and exclusion criteria for the Phase 3 trials adequately define a population of patients with CC.

**Question 7:**

We plan to conduct two adequate and well-controlled 12-week efficacy trials in patients with CC to support the following indication: "Linaclotide is indicated for the treatment of CC in adults." The primary efficacy endpoint in both trials will be complete spontaneous bowel movement (CSBM) overall responder. (A CSBM overall responder is a patient who meets the criteria of being a CSBM weekly responder for 9 out of the 12 treatment weeks. A CSBM weekly responder is a patient who has a CSBM frequency during the treatment week that is at least 3 CSBMs/week and increases by at least 1 CSBM/week from pretreatment.) Does the GI Division agree with the selection of the overall CSBM responder as the primary endpoint and that positive results using this primary endpoint in the pivotal clinical trials will support the proposed indication in the labeling?

**FDA Response to Question 7:**

We find your endpoints acceptable. Your primary endpoint of CSBM overall responder (i.e. weekly responder 9 of 12 treatment weeks) incorporates a weekly responder rate of  $\geq 3$  CSBM/week and an increase by at least one or more CSBM.

However, the definition of a responder should include a clinically meaningful change for the patient. We recommend that you include a patient rating of change question which quantifies the patient's assessment of improvement.

**Discussion**

The sponsor will relate a CSBM responder to a patient rating of change in order to define a chronic constipation responder. The definition of clinically meaningful change, based upon patient input, will be decided a priori.

**Question 8:**

In the Clinical Trial section of the Target Product Profile (TPP), we have included seven secondary endpoints that will be assessed during the Phase 3 program and are candidates for

(b) (4). It is understood that the appropriate statistical adjustment for multiplicity will be made and that the results will only be included for the endpoints where a clinically and statistically significant difference between linaclotide and placebo is demonstrated. Does the GI Division agree that, provided the results are favorable, data regarding these secondary endpoints (b) (4)

**FDA Response to Question 8:**

(b) (4)

We also have the following comments:

Although the collection of daily symptoms of constipation is encouraged, you have not justified that the proposed secondary endpoints represent a comprehensive list of all of the clinically important symptoms of constipation, based upon patient input. For example, the symptom, abdominal discomfort, appears to be more representative of irritable bowel syndrome, as opposed to chronic constipation. In addition, although patient ratings of change (i.e. constipation severity item) can be useful to ensure that a new instrument is comprehensive and to calibrate a clinically significant change on that new instrument for study data interpretation, they are not recommended for use as study endpoints (b) (4)

We recommend that you consider developing/utilizing an instrument which, based upon patient input represents a meaningful, complete, comprehensive, and appropriate measurement of the symptoms of constipation.

In addition, although the choice of an IVRS system is an acceptable method of data collection, we recommend that you review the FDA's source documentation concerns that are delineated in the "Study Design" section of the draft "FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."

**Discussion**

The sponsor proposes to review the literature in order to ascertain if an instrument which measures the signs and symptoms of chronic constipation and has evidence of content validity, based upon input from the target population of patients, is currently available. If not, then the sponsor will consider performing qualitative studies with the target population of patients and develop a new instrument that represents a composite of the important signs and symptoms of chronic constipation and has evidence of content validity.

The sponsor was encouraged to keep FDA abreast of their instrument development as it unfolds, so that FDA can provide recommendations.

The concepts measured by an instrument that measures the signs and symptoms of constipation and has evidence of content validity (b) (4)

**Question 9:**

We estimate that approximately 70 patients enrolled into the two Phase 3 pivotal efficacy trials for CC will be older than age 65 years and that about 70 patients will be male. (The Phase 3 efficacy trials in IBS-C will provide a similar number of patients in these subpopulations.) Does the GI Division agree that the efficacy results in these subpopulations, if they are similar to those of the overall population, would support the proposed indication in the labeling?

**FDA Response to Question 9:**

If the results for the subpopulation of patients >65 years of age are similar to those obtained in the general population, and have been replicated, they might support an indication that would not exclude the >65 years of age group. However, these comparative analyses would be considered exploratory if you do not design your study to demonstrate efficacy in these specific sub-groups.

**Discussion**

No specific number of patients for elderly or other sub-populations is required in NDA submission to preclude labeling limitations.

**Question 10:**

[REDACTED] (b) (4)

**FDA Response to Question 10:**

[REDACTED] (b) (4)

**Question 11:**

We plan to include a 4-week Randomized Withdrawal Period in one of the two Phase 3 efficacy trials to meet the Division's request to assess whether the cessation of linaclotide dosing is associated with a rebound in the symptoms of CC (FDA-Microbia Type-C meeting, June 5, 2006). Does the GI Division agree that including a randomized withdrawal phase in one trial is sufficient for this purpose?

**FDA Response to Question 11:**

No, we recommend including a randomized withdrawal phase in both trials in order to have replication of the findings. We also recommend that you re-randomize your patients at the end of the treatment period.

**Question 12:**

In order to assess the long-term safety of linaclotide, we plan to allow patients from the pivotal efficacy trials to rollover into open-label, extension studies and to allow patients who were pretreatment failures in the pivotal efficacy trials to enter the same safety studies. It is estimated that approximately 20 to 35% of the patients in the long-term safety database will be pretreatment failure patients. Does the GI Division agree that this approach would support the long-term safety of linaclotide?

**FDA Response to Question 12:**

Please define a pretreatment failure. It is not clear to us whether allowing patients who were pretreatment failures in the pivotal efficacy trials to enter the safety studies would be acceptable.

(In your protocol you designate a 2 week pretreatment phase to assess baseline disease activity. In the pretreatment periods the patients will provide daily information via the interactive voice response system (IVRS) regarding:

- daily bowel habits and daily patients symptom severity assessments
- weekly patient global assessment of relief of constipation symptoms
- per protocol rescue medication usage

**Discussion**

Sponsor will change “pre-treatment failure” to “randomization ineligible.”

**Question 13:**

As previously agreed to by the Division (FDA-Microbia Type-C meeting, September 25, 2006), we plan to provide evidence regarding the long-term safety of linaclotide from a combined safety database of patients with CC and patients with IBS-C. It is estimated that the combined safety population will exceed the ICH minimum requirements for the total number of patients treated with linaclotide (1500 patients), the number treated for 6 months (300 patients), and the number treated for 12 months (100 patients). It is also estimated that approximately half of the patients with at least 6 and 12 months of exposure to linaclotide will come from patients with CC. Does the GI Division agree that, if these minimum estimates are attained, the long-term safety database will be sufficient to support the approval of linaclotide for the treatment of CC?

**FDA Response to Question 13:**

From the proposed approach, it appears that the long-term safety database would be large enough. However whether these long-term safety data are sufficient to support approval will be assessed during our review of the NDA submission.

**2.5 Pediatric**

**Question 14:**

We believe that linaclotide should not be studied in children until the safety and efficacy have been established in adults. Therefore, under the provisions of Section 505B(a)(3) of the Federal Food, Drug and Cosmetic Act, we plan to request a deferral of pediatric studies until after approval. Does the GI Division agree with this plan?

**FDA Response to Question 14:**

Yes, we are in agreement with your plan to defer pediatric studies (also known as the pediatric assessment) until after approval. However, we remind you that per the Pediatric Research Equity Act (PREA) of 2007, you must submit a pediatric plan that includes:

- 1) certification of the grounds for deferring the pediatric assessment;
- 2) a description of the planned or ongoing pediatric studies;
- 3) evidence that the pediatric studies are being conducted or will be conducted with due diligence and at the earliest possible time; and
- 4) a timeline for completion of such pediatric studies.

We will present your pediatric plan to the FDA Pediatric Review Committee which is legislatively mandated to provide consultation on all pediatric assessments and plans and on all deferral and waiver requests prior to approval of an application or supplement which triggers PREA.

If your product is approved, the pediatric studies required under PREA will be noted as a required postmarketing commitment in your approval letter.

**Discussion**

The Sponsor noted its intention to submit information about its pediatric development plan in its EOP2 meeting background package for IBS-constipation. This EOP2 meeting is anticipated to occur in Summer 2008.

Linked Applications

Sponsor Name

Drug Name

IND 63290

IRONWOOD  
PHARMACEUTICALS  
INC

MD-1100

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

/s/

THOMAS N MORENO  
07/14/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,290

Microbia, Inc.  
Attention: Christine Pierce  
Manager of Regulatory Affairs  
320 Bent Street  
Cambridge, MA 02141

Dear Ms. Pierce:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Linaclotide Acetate/MD-1100 Acetate.

We also refer to the meeting between representatives of your firm and the FDA on April 19, 2007. The purpose of the meeting was to discuss the primary endpoint, duration of treatment, End of Phase 2 meetings, and data packages.

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 Cristi Stark, Regulatory Project Manager, at (301) 796-1007.

Sincerely,

*{See appended electronic signature page}*

Cristi L. Stark, M.S.  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** April 19, 2007  
**TIME:** 1:00pm  
**LOCATION:** CDER WO 1315  
**APPLICATION:** IND 63,290  
**DRUG NAME:** Linaclotide Acetate  
**TYPE OF MEETING:** B

**MEETING CHAIR:** Hugo Gallo-Torres, M.D., Ph.D.

**MEETING RECORDER:** Cristi Stark, M.S.

### **FDA ATTENDEES:** (Title and Office/Division)

Sushanta Chakder, Ph.D., Pharm/Tox Reviewer, DGP/ODEIII  
Hugo Gallo-Torres, M.D., Ph.D., Clinical Team Leader, DGP/ODEIII  
David Joseph, Ph.D., Pharm/Tox Reviewer, DGP/ODEIII  
Joyce Korvick, M.D., M.P.H., Deputy Director, DGP/ODEIII  
Nancy Snow, M.D., Medical Officer, DGP/ODEIII  
Cristi Stark, M.S., Project Manager, DGP/ODEIII  
Mike Welch, Ph.D., Statistical Team Leader, DBIII/OB

### **EXTERNAL CONSTITUENT ATTENDEES:**

Alexander Bryant, Ph.D., Senior Director, Pharmacology  
Mark Currie, Ph.D., Senior Vice President, Research and Development & CSO  
Jeffrey Johnston, M.D., Vice President, Clinical Development and CMO  
Caroline Kurtz, Ph.D., Senior Director of Program Management  
Bernard Joseph Lavins, Jr., M.D., Senior Director & Head of Clinical Research  
James MacDougall, Ph.D., Senior Director, Data Management and Biostatistics  
Christine Pierce, Manager of Regulatory Affairs  
Gwyn Reis, Senior Director of Regulatory Affairs  
Winifred Begley, Regulatory Affairs

(b) (4)

### **BACKGROUND:**

For Phase 2 clinical studies, MCP-103-201 (Chronic Constipation study) and MCP-103-202 (IBS-C study), linaclotide acetate is being administered as a solid oral dosage form in the form of hard-shell gelatin capsules at dose strengths of (b) (4). The components of the solid oral formulation are linaclotide acetate (Lot# PPL-MD11000601A), microcrystalline cellulose, NF (b) (4), and Gelatin capsules (b) (4).

For the chronic constipation development program, the dose regimen employed in the Phase 2b study (MCP-103-201) is once daily for 4 weeks, while the planned Phase 3 trials will be once daily for 12 weeks.

For the irritable bowel syndrome with constipation development program, the dose regiment used in the Phase 2b (MCP-103-202) and the Phase 3 studies is once daily for 12 weeks.

#### **MEETING OBJECTIVES:**

- To affirm that the primary endpoint used in our IBS-C Phase 2b and 3 clinical trials should be based on the severity of a specific symptom.
- To affirm that the primary endpoint used in our IBS-C Phase 2b and 3 clinical trials would support the indication statement proposed in Section 3.4 of the briefing book.
- To affirm that the duration of treatment proposed in our Phase 3 clinical trials would support the indication statement proposed in Section 3.4 of the briefing book.
- To obtain agreement that the Division would hold two End of Phase 2 meetings to cover the indications of CC and IBS-C separately and that the information proposed to be included in the data packages to support these meetings would be adequate.

#### **DISCUSSION POINTS:**

##### **Clinical Questions**

1. Based on the outcome of the Type C meeting held between Microbia and the Division on September 25, 2006, the primary endpoint for the Phase 2b trial in patients with IBS-C is improvement in a single pre-defined symptom i.e., changes from Pre-treatment in CSBM weekly frequency during the 12-week treatment period. A responder endpoint based on that same symptom, CSBM complete responder, has been included as a secondary endpoint and will be used as the primary endpoint for the Phase 3 clinical trials. Does the Division agree that these efficacy endpoints are consistent with the Division's comments regarding the choice of primary endpoint (i.e., that the primary endpoint should focus on severity of a specific symptom) and that they will support the design of the Phase 3 studies in IBS-C?

**FDA Response:** As outlined in the FDA Draft Guidance [add link], the following should be considered. When evaluating an appropriate primary endpoint for any clinical trial, an endpoint model should be developed. Review of the endpoint model is based upon the target population, specific disease, and treatment. In creating this endpoint model, all of the patient reported (PRO) and non-PRO endpoints should be identified and the hierarchy and hypothesized relationships between all treatment benefit endpoints intended to support claims, delineated.

As noted by the Rome III Committee<sup>1</sup>, IBS is a functional bowel disorder in which abdominal pain or discomfort is associated with change in bowel habit, and with features of disordered defecation. Criteria for diagnosis for IBS are as follows:

**Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following:**

- 1 Improvement with defecation**
- 2 Onset associated with a change in frequency of stool**
- 3 Onset associated with a change in form (appearance) of stool**

**Based upon the Rome III criteria for IBS, it is recommended you develop an endpoint model and consider alternative primary endpoints in your clinical trials, based upon the input from specialists and patients.**

**In addition, we have the following comments:**

- **IBS-C is a complex disease associated with several domains (e.g., change in stool frequency, severity of pain, bloating, frequency of episodes). Therefore, it is recommended that you establish a clear description of the relationship of the items to the domains and the domains to the concepts of interest (conceptual framework).**
- **The patient-reported outcome measurement that you choose for your clinical trials should be appropriate, comprehensive, and interpretable (adequate content validity). Based upon patient interviews, the content validity should confirm that target concepts represent what the target population considers important regarding their condition and treatment.**

***Discussion at Meeting:*** Microbia stated that they are working on an endpoint model and have additional questions regarding the conceptual framework for individual items. FDA replied to have the questions sent directly through the review division for a SEALD response (SEALD was unable to attend the meeting).

2. Microbia proposes that the CSBM primary efficacy endpoint in the Phase 3 studies for IBS-C should be CSBM complete responder (a CSBM complete responder is a patient who meets the criteria of being a CSBM weekly responder for 9 out of the 12 treatment weeks. A CSBM weekly responder is a patient who has CSBM frequency that is at least 3 and increases by at least 1 from pre-treatment during the treatment week). It is anticipated that the use of CSBM as the primary endpoint will support the statement “Linaclotide is indicated for the treatment of IBS-C in the adult population” and will not limit the indication to the treatment of constipation in patients with IBS-C. Does the Agency agree that, if the Phase 3 studies are successful, the proposed primary efficacy endpoint will support the anticipated indication?

**FDA Response: We agree with the primary endpoints of:**

- **9 out of 12 weeks response**
- **3 CSBM per week and an increase by 1 from baseline**

***Discussion at Meeting:*** Microbia requested clarification if the primary endpoint for both Phase 3 studies is a single symptom of CSBM responder. Where a CSBM responder satisfies two conditions: a weekly score of 3 CSBM and an increase in 1 from baseline, and a complete CSBM weekly responder fro 9 out of the 12 treatment weeks. FDA agreed.

Microbia asked if they replicate the Phase 3 trials to meet the primary and secondary endpoints, would the Agency agree this meets the proposed indication? FDA stated that an answer cannot be committed until data are reviewed; however, this is a reasonable approach. In general it is ok to move from global to singular endpoints. But there may be some concern if some claims are tied into secondary endpoints with no statistical considerations. Microbia replied that they would account for multiplicity and reflect it in the protocol.

3. Like the Phase 2b trial, the Phase 3 studies will have a 2-week pre-treatment period, a 12-week treatment period, and a 2-week post-treatment period. We believe, if efficacy is demonstrated over 12 weeks of treatment, this trial will support the long-term use of linaclotide in patients with IBS-C. We also believe that a 2-week post-treatment period will allow for the assessment of the drug's potential to cause rebound constipation. Does the Agency agree?

**FDA Response: The trial should include a 4-week post-treatment period in order to assess for rebound constipation.**

**If effects are shown in the presently designed trial (12 weeks) the data will support the short-term (up to 12 weeks) use of Linaclotide only. To obtain a claim for long-term use of the drug, the trial duration needs to be 6 to 12 months.**

*Discussion at Meeting:* Microbia asked for clarification on what data are needed for an indication without short-term use. They plan for two 12-week, double blind, placebo controlled trials which will roll into a 9 month open-label treatment. FDA replied that 12 week trials are considered short-term use. Open-label information is important for safety but will not yield efficacy data. IBS is a chronic disease, for an indication for continuous use it must have a trial that is at least 6 months in length with randomized, double-blind, clinical data. This will allow for the determination of durability of effect. If the indication will only be treating the symptoms intermittently, 12-week trials are sufficient. Microbia clarified that they intend to have an indication for chronic use.

### **Regulatory Questions**

4. The Guidance for Industry: "Formal meetings with sponsors and applicants for PDUFA products," dated February 2000 section B Type B meeting states:

"---FDA expects generally to grant only one of each of the Type B meetings for each potential application. The Agency may grant more than one each of the Type B meetings when it would be beneficial to hold separate meetings to discuss unrelated issues."

Microbia believes that the two indications being sought (chronic constipation and IBS-C) warrant discussion in two separate End of Phase 2 (EOP2) meetings. Does the Agency agree?

**FDA Response: We will grant separate meetings if appropriate based on the status of the individual development programs.**

*Discussion at Meeting:* No further discussion needed.

5. We have outlined below (see section 7.2) the clinical and nonclinical information that we intend to provide in advance of End of Phase 2 meeting discussions. While final reports for all nonclinical studies supporting the Phase 3 clinical program will be submitted at least one month in advance of Phase 3 initiation, the EOP2 pre-meeting package(s) will contain summary information, including data tables and text, for these studies. Will summary information be adequate to support End of Phase 2 meeting discussions?

**FDA Response:** The preclinical package, including full reports of chronic toxicology and reproductive toxicology studies, must be submitted with ample time for thorough review and evaluation prior to the initiation of Phase 3 trials. These full reports should be submitted separate from your End of Phase 2 meeting package.

**Clinical summaries included in your End of Phase 2 briefing package should be adequate to answer questions for your Phase 3 program.**

*Discussion at Meeting:* Microbia stated that the nonclinical study reports may not be available in advance of the End of Phase 2 meeting. However, they will be ready one month prior to the initiation of Phase 3 trials. Is that acceptable? FDA replied that at a minimum the study report must be submitted one month prior to initiation of Phase 3 trials; the sooner, the better.

**Additional Comment:**

**Your background package indicates that dogs will be used in your 9-month chronic toxicology study. Given that monkeys have been used as the non-rodent species in previous toxicology studies, please clarify the rationale for your current choice of species.**

*Discussion at Meeting:* Microbia confirmed that the 9-month chronic toxicology study will have monkeys as the non-rodent species, not dogs.

**DECISIONS (AGREEMENTS) REACHED:**

- CSBM responder is adequate
- Final indication appears adequate if successful; however, the final data determine the indication
- Six month efficacy trial is required for a chronic indication (plans will be discussed at the End of Phase 2 meeting)

**ACTION ITEMS:**

- Microbia will submit the PRO questions under the IND and via email to the project manager.
- Microbia will provide summaries of nonclinical and clinical information in the briefing package for the End of Phase 2 meeting. The full nonclinical study reports that are needed to support the Phase 3 studies will be submitted no later than one month prior to the initiation of Phase 3. These study reports will be submitted in an amendment(s) to the IND, but not in the End of Phase 2 meeting package.

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/s/

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Cristi Stark  
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