

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208854Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208854

SUPPL # N.A

HFD # 180

Trade Name Symproic

Generic Name naldemedine

Applicant Name Shionogi Inc.

Approval Date, If known: March 23, 2017

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)

b) 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

c) Did the applicant request exclusivity?

YES NO

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

None

d) 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:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

IND #

YES

! NO

!

! Explain:

Investigation #2

!

IND # YES

! NO

!

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

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

YES NO

If yes, explain:

Name of person completing form: CDR Cheronda Cherry-France
Title: Regulatory Project Manager
Date: 3.23.2017

Name of Division Director signing form: Donna Griebel, M.D.
Title: Division Director

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

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

/s/

CHERONDA L CHERRY-FRANCE
03/23/2017

DONNA J GRIEBEL
03/23/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208854 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: N.A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Symproic Established/Proper Name: naldemedine Dosage Form: tablets		Applicant: Shionogi Inc. Agent for Applicant (if applicable): Ting Chen Senior Director Regulatory Affairs
RPM: CDR Cheronda Cherry-France		Division: DGIEP (Division of Gastroenterology and Inborn Errors)
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: 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.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>3.23.2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Not A Part 3 Combination Product
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
- Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? - If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) March 23, 2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ 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>)	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name	Reviewed received OSE 6.22.2016
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ None 5.23.2016 DMEPA: ☒ 1.13.2017 DRISK: 2.7.2017 DMPP: ☒ 1.27.2017 OPDP/DDMAC: ☒ 1.25.2017 SEALD: ☒ None CSS: ☒ See Clinical Consults Section for CSS Review 1.18.2017 Product Quality ☒ See Product Quality Section: CMC /Quality Review 3.9.2017 Other: ☒ DPMH (Maternal) 1.13.2017; DAAAP 11.9.2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	5.23.2016
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC If PeRC review not necessary, explain:	N.A
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	(1) 3.21.2017 (2) 3.21.2017 (3) 3.20.2017 (4) 3.20.2017 (5) 3.20.2017 (6) 3.16.2017 (7) 3.10.2017 (8) 2.27.2017 (9) 2.21.2017 (10) 2.17.2017 (11) 2.17.2017 (12) 1.20.2017 (13) 1.13.2017 (14) 12.15.2016 (15) 12.14.2016 (16) 12.1.2016 (17) 11.15.2016 (18) 10.20.2016 (19) 10.18.2016 (20) 10.6.2016 (21) 9.29.2016 (22) 9.22.2016 (23) 9.16.2016 (24) 9.7.2016 (25) 9.2.2016 (26) 8.31.2016 (27) 8.29.2016 (28) 8.23.2016 (29) 8.19.2016 (30) 8.12.2016 (31) 8.11.2016 (32) 8.3.2016 (33) 7.26.2016

	(34) 7.26.2016 (35) 7.13.2016 (36) 6.23.2016 (37) 6.17.2016 (38) 6.7.2016 (39) 6.6.2016 (40) 6.3.2016 (41) 5.6.2016 (42) 5.5.2016 (43) 4.29.2016 (44) 4.19.2016 (45) 4.15.2016 (46) 4.7.2016 (47) 3.31.2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ October 5, 2013
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ March 15, 2013
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ August 31, 2016
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ December 13, 2016; teleconference; loaded DARRTs on December 14, 2016
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	Filing/Planning Meeting: May 5, 2016 and mailed No filing issues 6.3.2016 (Sent Via IR located in the outgoing email communications)
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ 3.23.2017
Division Director Summary Review (<i>indicate date for each review</i>)	☒ 3.23.2017
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 3.22.2017
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ 1 PMR dated: 3.20.2017
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ 3.23.2017
• Clinical review(s) (<i>indicate date for each review</i>)	3.23.2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	page 256 of the Clinical Reviewers Review in section 13.2.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ 1.18.2017
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - 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>)	☐
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ 11.8.2016 & 10.13.2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☒ 12.10.2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☒ 11.23.2016 & Appendices 12.4.2016
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☒ 11.21.2016 & Tertiary Review concurred on 11.22.2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☒ 7.21.2016
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Product Quality		☐ None
❖ Product Quality Discipline Reviews ⁶		
• Tertiary review (<i>indicate date for each review</i>)		☐ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)		☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)		☒ 11.22.2016 & Addendum on 3.9.2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)		☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)		
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		See page 64 of 134 of the OPQ combined review and the section is titled environmental analysis
☐ Review & FONSI (<i>indicate date of review</i>)		
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)		
❖ Facilities Review/Inspection		
☐ Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)		☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ N.A
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ N.A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

CHERONDA L CHERRY-FRANCE
03/28/2017

Cherry-France, Cheronda

From: Cherry-France, Cheronda
Sent: Friday, March 10, 2017 9:38 AM
To: 'tchen@shionogi.com'
Subject: NDA 208854/Symproic(naldemedine) Observational PMR Update: no later than March 13, 2017 at 8AM (EST)
Attachments: NDA 208854 Observational PMR.docx
Importance: High

Hello Ting:

The safety team has reviewed the observational PMR. Please review attachment and let me know if you have any questions.

If you are okay with the changes please submit to the application **no later than March 13, 2017 at 8AM (EST)**.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

*White Oak Building 22 Room: 5237
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-7295 (office)
(301) 796-9904 (fax)
Cheronda.Cherry-France@fda.hhs.gov

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PMR/PMC Description: 3174-1

A post-marketing, observational epidemiologic study comparing Symproic (naldemedine) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Ensure an adequate number of patients with at least 12 months of Symproic (naldemedine) exposure at the end of the study.

Additional Study Information

Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to Symproic (naldemedine)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among Symproic (naldemedine) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the Symproic (naldemedine)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria.

Comment [A1]: Suggest these instructions not be part of the PMR description

PMR/PMC Schedule
Milestones:

Final Protocol Submission:	11/ 2017
Study Completion:	11/ 2023
Final Report Submission:	11/ 2025
Other: <u>interim reporting</u>	11/ 2020

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CHERONDA L CHERRY-FRANCE
04/07/2017

From: [Cherry-France, Cheronda](#)
To: "Chen, Ting"
Subject: NDA 208854 Symproic(naldemedine) Clinical Information Request by 12 PM EST on 3.22.2017
Date: Tuesday, March 21, 2017 5:52:08 PM
Importance: High

Ting: **Clinical Information Request by 12 PM EST on 3.22.2017**

Study V9235, please present a breakdown of numbers of subjects within the "White" subgroup of the trial who entered the trial and continued a baseline laxative regimen through the trial vs. not. Present the numbers by treatment arm.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

*White Oak Building 22 Room: 5237
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CHERONDA L CHERRY-FRANCE
03/21/2017

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854 Symproic(naldemedine) Clinical Information Request by COB 3.21.2017
Date: Tuesday, March 21, 2017 11:34:37 AM
Importance: High

Ting: **Clinical Information Request by COB 3.21.2017**

Study V9235, please present a breakdown of numbers of subjects within the "Black" subgroup of the trial who entered the trial and continued a baseline laxative regimen through the trial vs. not. Present the numbers by treatment arm.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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CHERONDA L CHERRY-FRANCE
03/21/2017

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854/Symproic(naldemedine): In reference to DEA Scheduling
Date: Monday, March 20, 2017 4:05:29 PM

Ting:

Please use this verbiage and place on your company's official letter head.

Shionogi is in agreement with the FDA that they will not market Symproic (naldemedine) until the Drug Enforcement Administration has made a final scheduling decision.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
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CHERONDA L CHERRY-FRANCE
03/21/2017

From: [Chen, Ting](#)
To: [Cherry-France, Cheronda](#)
Subject: RE: any labeling update? NDA 208854 Symproic(naldemedine) Label & MG Due Back by Noon 3.20.2017
Date: Monday, March 20, 2017 1:55:07 PM
Attachments: [NDA 208854 Label Sent to Sponsor on 3 17 2017 revised copy 3 20 2017-Shionogi final clean.docx](#)
[NDA 208854 MG Sent to Sponsor on 3 17 2017-Shionogi final clean.docx](#)
Importance: High

Dear Roni,

Per discussion, Attached is the final clean version of the proposed USPI and Medication Guide. The PI has incorporated our agreement below. We also performed the final QC/Edits to fix all the spacing/formatting where it applicable.

If there is no additional comment, we will submit via gateway shortly.

Best regards,
Ting

From: Cherry-France, Cheronda [mailto:Cheronda.Cherry-France@fda.hhs.gov]
Sent: Monday, March 20, 2017 12:40 PM
To: Chen, Ting
Subject: RE: any labeling update? NDA 208854 Symproic(naldemedine) Label & MG Due Back by Noon 3.20.2017
Importance: High

Ting:

Here is our response to: **We agree with the edits proposed to remove** (b) (4)

- Update the hypersensitivity in Contraindication and ADR section – **Will accept the addition of bronchospasm and rash**; propose to delete the second sentence in Section 6.1: Less common ADR: Two patients developed symptoms of hypersensitivity following a single dose of SYMPROIC. One patient reported bronchospasm and another rash. (b) (4).

Regarding the last bullet, the sponsor had proposed a modified sentence:

(b) (4)

We cannot agree to describe (b) (4) **due to the design issues that were previously communicated.**

Thanks,
-Roni

From: Chen, Ting [mailto:tchen@shionogi.com]

Sent: Monday, March 20, 2017 10:36 AM
To: Cherry-France, Cheronda
Subject: RE: any labeling update? NDA 208854 Symproic(naldemedine) Label & MG Due Back by Noon 3.20.2017

Dear Roni,

We understood the Agency's position. However, even though the [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Would the Agency consider this modified sentence?

Ting

[REDACTED] (b) (4)

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]
Sent: Monday, March 20, 2017 9:54 AM
To: Chen, Ting
Subject: RE: any labeling update? NDA 208854 Symproic(naldemedine) Label & MG Due Back by Noon 3.20.2017

Ting please see response from the team below :

Recently, in the course of writing final reviews, the review team re-evaluated [REDACTED] (b) (4)
[REDACTED]
The Clinical Studies section is generally limited those studies that are considered adequate and well-controlled. [REDACTED] (b) (4)
[REDACTED] (b) (4)

Thanks,
-Roni

From: Chen, Ting [<mailto:tchen@shionogi.com>]
Sent: Friday, March 17, 2017 12:30 PM
To: Cherry-France, Cheronda
Subject: RE: any labeling update? NDA 208854 Symproic(naldemedine) Label & MG Due Back by Noon 3.20.2017
Importance: High

Dear Roni,

Per our conversation, we are surprised that this sentence (in Section 14 of the proposed USPI) has been removed from the proposed USPI based on the comment in A4. This sentence has been in the proposed PI since December 2016 and we thought it has been reviewed and agreed upon by the Division. Since we are down to the wire, I am wondering if FDA can have a second look. Thank you very much in advance for your help!

Ting

(b) (4)

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]
Sent: Friday, March 17, 2017 12:15 PM
To: Chen, Ting
Subject: RE: any labeling update? NDA 208854 Symproic(naldemedine) Label & MG Due Back by Noon 3.20.2017
Importance: High

Ting: **Label & MG Due Back by Noon 3.20.2017**

Attached in this email is label and MG for NDA 208854. If you have any questions please email or call.

Thanks,
-Roni

From: Chen, Ting [<mailto:tchen@shionogi.com>]
Sent: Friday, March 17, 2017 11:20 AM
To: Cherry-France, Cheronda
Subject: any labeling update?

Dear Roni,

Just wanted to a quick follow up, any news on the labeling update?

Best regards,
Ting

Comment to Sponsor: We have deleted this sentence regarding the

(b) (4)

(b) (4)

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CHERONDA L CHERRY-FRANCE
03/21/2017

From: [Chen, Ting](#)
To: [Cherry-France, Cheronda](#)
Subject: RE: NDA 208854 Symproic(naldemedine) Label & MG : Due back by 8 AM (EST) 3.14.2017
Date: Thursday, March 16, 2017 2:20:18 PM

Perfect! Thanks

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]
Sent: Thursday, March 16, 2017 2:11 PM
To: Chen, Ting
Subject: RE: NDA 208854 Symproic(naldemedine) Label & MG : Due back by 8 AM (EST) 3.14.2017

Please submit a CBE-0.....

Thanks,

-Roni

From: Chen, Ting [<mailto:tchen@shionogi.com>]
Sent: Friday, March 10, 2017 8:28 AM
To: Cherry-France, Cheronda
Subject: RE: NDA 208854 Symproic(naldemedine) Label & MG : Due back by 8 AM (EST) 3.14.2017

Dear Roni,

(b) (4) I am wondering if the revised
label (b) (4)

Best regards,

Ting

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]
Sent: Thursday, March 09, 2017 6:40 PM
To: Chen, Ting
Subject: NDA 208854 Symproic(naldemedine) Label & MG : Due back by 8 AM (EST) 3.14.2017

Ting: **Due back by 8 AM (EST) 3.14.2017**

I hope all is well. Attached in this email is the label and medication guide. If you have any questions please do not hesitate to call or email.

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
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CHERONDA L CHERRY-FRANCE
03/21/2017

From: [Cherry-France, Cheronda](#)
To: "[Chen, Ting](#)"
Subject: NDA 208854 Symproic(naldemedine) IR from Clinical Regarding Study Subjects: Please respond by COB 3.20.2017
Date: Monday, March 20, 2017 10:11:02 AM
Importance: High

Ting: **Please respond by COB 3.20.2017**

Please provide the efficacy analyses from Study V9235 by sex, age and race – in particular change from baseline at week 12? We are particularly interested in the sex subgroup analysis.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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CHERONDA L CHERRY-FRANCE
03/20/2017

From: [Cherry-France, Cheronda](mailto:Cherry-France.Cheronda)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854/Symproic(naldemedine) post marketing requirement (PMR) : Please Confirm
Date: Monday, February 27, 2017 10:57:25 AM
Importance: High

Hello Ting:

Please confirm that below dates are correct along with the verbiage for this **post marketing requirement (PMR)**. Here is the link <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/>

A post-marketing, observational epidemiologic study comparing SYMPROIC (naldemedine) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to SYMPROIC (naldemedine)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among SYMPROIC (naldemedine) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the SYMPROIC (naldemedine)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of SYMPROIC (naldemedine) exposure at the end of the study.

The timetable you submitted on February 23, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2017
Interim Report Submission:	November 2020
Study Completion:	November 2023
Final Report Submission:	November 2025

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
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CHERONDA L CHERRY-FRANCE
02/27/2017

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854 Symproic (naldemedine): Information Request Regarding Container : Due Back COB 2.24.2017 at 8AM (EST)
Date: Tuesday, February 21, 2017 10:55:26 AM
Importance: High

Hello Ting: **Due Back COB 2.24.2017 at 8 AM EST**

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. Insert the statement, "Dispense the enclosed Medication Guide to each patient" on the principal display panel as required by 21 CFR 208.24(d).

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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CHERONDA L CHERRY-FRANCE
02/21/2017

From: [Cherry-France, Cheronda](mailto:tchen@shionogi.com)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854 SYMPROIC® (naldemedine) tablets: PMR/PMC DISCUSSION COMMENTS; Due By 2.24.2017 at 8AM EST
Date: Friday, February 17, 2017 1:01:14 PM
Importance: High

Hello Ting: **Due By 2.24.2017 at 8AM EST**

Please refer to your New Drug Application (NDA) dated March 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symproic (naldemedine), 0.2 mg tablets. The agency has proposed this template language below and you may edit as needed. Please submit a proposal to address this requirement and timetables for, final protocol submission, study completion, and submission of final report for the postmarketing requirement described above within 7 days from the date of this communication.

A post-marketing, observational epidemiologic study comparing SYMPROIC (naldemedine) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to SYMPROIC (naldemedine)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among SYMPROIC (naldemedine) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the SYMPROIC (naldemedine)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of SYMPROIC (naldemedine) exposure at the end of the study.

Submit your proposal to your NDA and prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission: **POSTMARKETING CORRESPONDENCE** .

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

CHERONDA L CHERRY-FRANCE
02/17/2017

From: [Cherry-France, Cheronda](#)
To: "[Chen, Ting](#)"
Subject: RE: NDA 208854/Symproic(naldemedine) LABEL & Medication Guide Due back 2.24.2017 at 8AM (EST)
Date: Friday, February 17, 2017 8:57:08 AM

Hello Ting: **LABEL & Medication Guide Due back 2.24.2017 at 8AM (EST)**

Here is our response to highlighted area : To the Sponsor: (b) (4)

(b) (4) Likewise, the intended message is not about (b) (4). The anticipated response rate in that patient population is described in the Clinical Studies section. Instead, we wish to describe the population more recently initiated on opioids and inform healthcare providers if that type of "naïve" patient is begun on SYMPROIC, their initial response may be less than described in the clinical studies.

&

IR for naldemedine: AR rate calculations for labeling

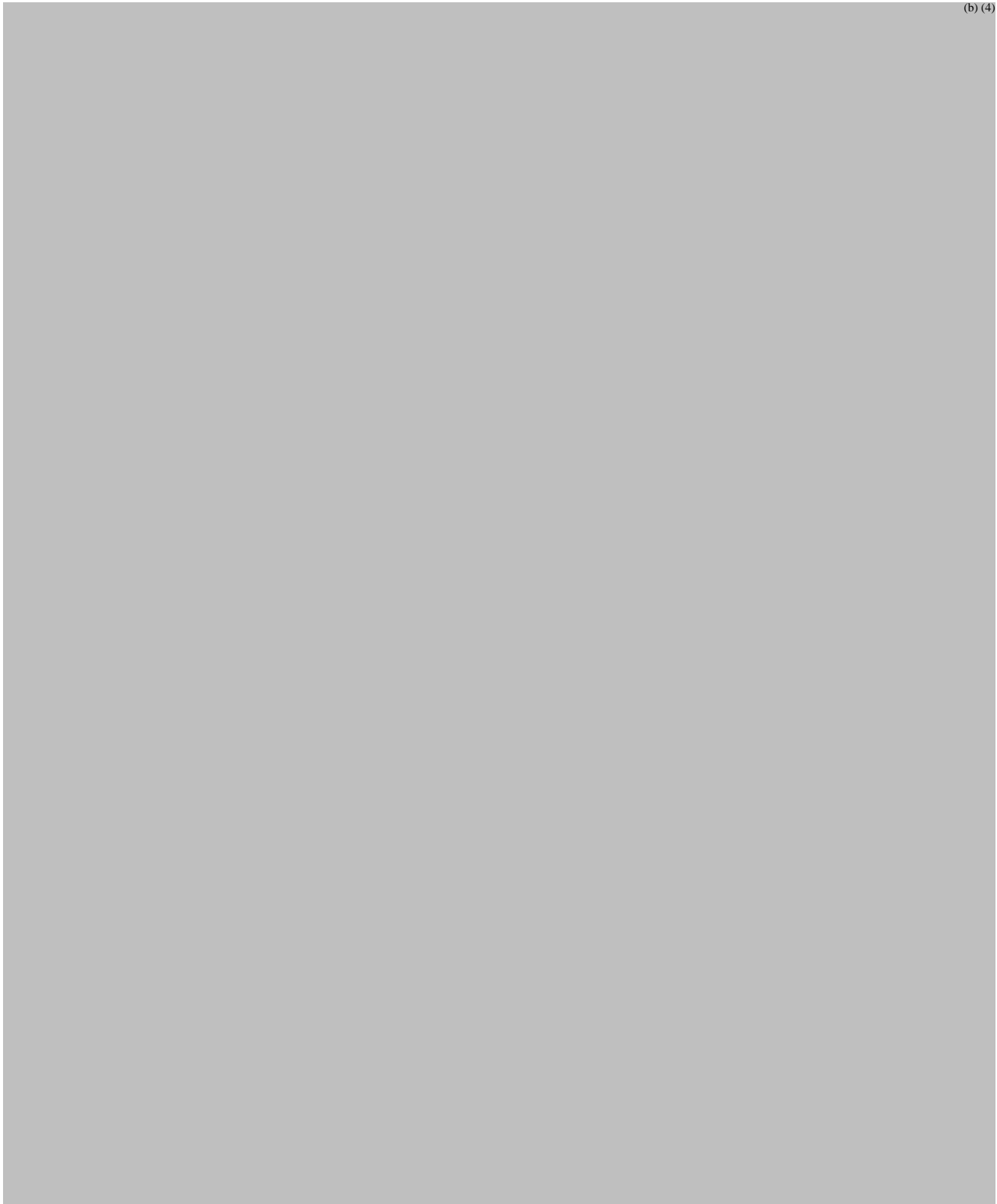
For the tables of common adverse reactions (Tables 1 and 2) in Section 6.1 of the prescribing information (PI), calculations of AR rates should include all subjects with (b) (4)

(b) (4). The results of our calculations for these tables are inconsistent with the data you had provided. In the version of the label sent on February 9, 2017, the data in Tables 1 and 2 were edited to reflect our calculations. For clarification, we are providing a description of our methods and tables with our (b) (4) rate calculations (%).

(b) (4)

(b) (4)

(b) (4), the label should report data rounded to the nearest whole number.
Datasets can be provided upon request if additional clarification is needed.



Please confirm these results using the (b) (4)

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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From: Chen, Ting [mailto:tchen@shionogi.com]
Sent: Tuesday, February 14, 2017 9:01 PM
To: Cherry-France, Cheronda
Subject: RE: NDA 208854/Symproic(naldemedine) LABEL & Medication Guide Due back 2.21.2017 at 8AM (EST)
Importance: High

Dear Roni,

Per discussion, we would like to know when we will be receiving the Clinical IR per comment A4 in Section 6.1: To the Sponsor. There is a discrepancy between the calculation provided by the sponsor and the adverse event data sets. An IR is being sent to address this issue and final numbers are pending.

In Section 2.1 for comment A1/A2: To the Sponsor: See the supportive rationale for this statement from the

transcripts of a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee on June 11-12, 2014. The speaker was Gavril Pasternack, MD, PhD.

You may also propose alternative wording of this statement for consideration.....

Shionogi Response: The sponsor understood FDA's position. We would like to refer to the wording proposed by the Agency at the Late-Cycle meeting/Dec 15 version of the label ' (b) (4)

Does the Agency agree?

-

Let me know if this makes sense.

Best regards,

Ting

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]

Sent: Thursday, February 09, 2017 2:20 PM

To: Chen, Ting

Subject: RE: NDA 208854/Symproic(naldemedine) LABEL & Medication Guide Due back 2.21.2017 at 8AM (EST)

Importance: High

Hello Ting:

Attached in this email is the label and medication guide for NDA 208854.

Both the label and medication are due back to the agency by 8AM (EST) on 2.21.2017.

- Please keep label and medication guide *separate*.
- Submit to me via email on 8AM the true and exact copy via WORD and to the application (I will need a tracked and WORD clean.)
- We are shooting for PMR clearance hopefully by 2.16.2017. (It has its own internal team to circulate.)

If you have any question do not hesitate to email or call.

Thank you so much for your patience.

R,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

CHERONDA L CHERRY-FRANCE
02/17/2017

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854 Symproic(naldemedine) DAAAP IR: Due back by 11AM on 1.24.2017
Date: Friday, January 20, 2017 11:38:59 AM
Importance: High

Ting: **Due back by 11AM EST on 1.24.2017**

We acknowledge receipt of your 1/17/17 response to the Agency's IR to provide (b) (4)

Provide clarification for the following discrepancies:

(b) (4)

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

CHERONDA L CHERRY-FRANCE
01/20/2017

From: [Cherry-France, Cheronda](#)
To: "tchen@shionogi.com"
Subject: NDA 208854 naldemedine (Symproic) - DAAAP Clinical IR; Due by COB 1.18.2017
Date: Friday, January 13, 2017 11:05:20 AM
Importance: High

Hello Ting: **(Division of Anesthesia, Analgesia, and Addiction Products/ DAAAP)Clinical IR; Due by COB 1.18.2017**

In your revised label, Section 6.1 Clinical Trials Experience, under Opioid Withdrawal, the following clarification and additional information is needed:

1. Your proposed label states the following: (b) (4)

[Redacted]

However, the Statistical Analysis Plan for the protocols for Studies 1, 2 and 3 actually states the following:

[Redacted] (b) (4)

[Redacted]. Clarify the discrepancy and propose the language that should be included in the label.

2. [Redacted] (b) (4)

[Redacted]

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
CDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

CHERONDA L CHERRY-FRANCE
01/13/2017



NDA 208854

LABELING PMR/PMC DISCUSSION COMMENTS

Shionogi Inc.
Attention: Ting Chen
Senior Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated March 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **Symproic (naldemedine), 0.2 mg tablets**.

We also refer to our June 3, 2016, letter in which we notified you of our target date of December 15, 2016, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On March 23, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by **January 5, 2017**. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Postmarketing Requirements/ Commitments:

- A postmarketing requirement (PMR) for major adverse cardiovascular events (MACE) is being considered. Note that the PMR would reflect class-based thinking for the peripherally acting mu opioid receptor antagonists (PAMORAs).

If you have any questions, call me, at (301) 796-7295.

Sincerely,

{See appended electronic signature page}

Cheronda Cherry-France, R.N., B.S.N., M.H.A.
LCDR/USPHS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

ENCLOSURE: Label

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CHERONDA L CHERRY-FRANCE
12/15/2016

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854/Symproic(naldemedine): Clinical Pharmacology labeling IR regarding drug-drug interactions due by COB 11.18.2016
Date: Tuesday, November 15, 2016 9:12:51 PM
Importance: High

Hello Ting: Due by COB 11.18.2016

Clinical Pharmacology labeling IR regarding drug-drug interactions:

1. **Strong CYP3A4 inhibitors:** Our assessment of the data submitted suggests that it may not be necessary [REDACTED] (b) (4). Instead, the general dose of 0.2 mg *qd* may be acceptable for use with strong or moderate CYP3A inhibitors as well as p-gp inhibitors, along with adequate monitoring of these patients for adverse events.

-
Rationale: *The observed fold-increase in AUC with strong CYP3A4 inhibitors (~2.9-fold) was not vastly different from the fold increase noted with moderate CYP3A4 inhibitors or p-gp inhibitors (~1.9-fold), for which the label proposes the general dosing of 0.2 mg qd. In addition, exposure-response data suggests only a weak correlation between naldemedine systemic exposure and adverse events.*

2. **Efavirenz:** We recommend the following revisions to Section 12.3 - Efavirenz (moderate CYP3A inducer): Simulation using physiologically-based pharmacokinetic modeling suggested that concomitant use of efavirenz, decreases exposure to naldemedine by 43%. [REDACTED] (b) (4). [REDACTED] The clinical consequence of this decreased exposure is unknown.

Rationale: *The rationale provided to [REDACTED] (b) (4)*
[REDACTED] (b) (4)

Please respond within one to two business days informing us whether you are in agreement with this assessment. If you do not agree, respond with clear justification for our consideration.

Thanks,

Roxi

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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CHERONDA L CHERRY-FRANCE
11/15/2016

**PeRC Meeting Minutes
October 19, 2016**

PeRC Members Attending:

John Alexander (acting PeRC chair)

Jacqueline Yancy

Meshaun Payne

Hari Sachs

Karen Davis Bruno

Raquel Tapia

Tom Smith

Wiley Chambers NON-RESPONSIVE

Kevin Krudys

Lily Mulugeta

Dionna Green

Freda Cooner

Victor Baum

Gerri Baer

Donna Snyder

Shrikant Pagay

Barbara Buch

Adrienne Hornatko-Munoz

Agenda

NON-RESPONSIVE

9:00	NON-RESPONSIVE			
9:50				
10:10				
10:25				
10:45				
10:55				
11:10				
11:25				

NDA
208854

Symproic (naldemedine) Full
Waiver with Agreed iPSP

DGIEP

Cheronda
Cherry-
France

Treatment of opioid-induced
constipation in adult patients with
chronic non-cancer pain

NON-RESPONSIVE

NON-RESPONSIVE

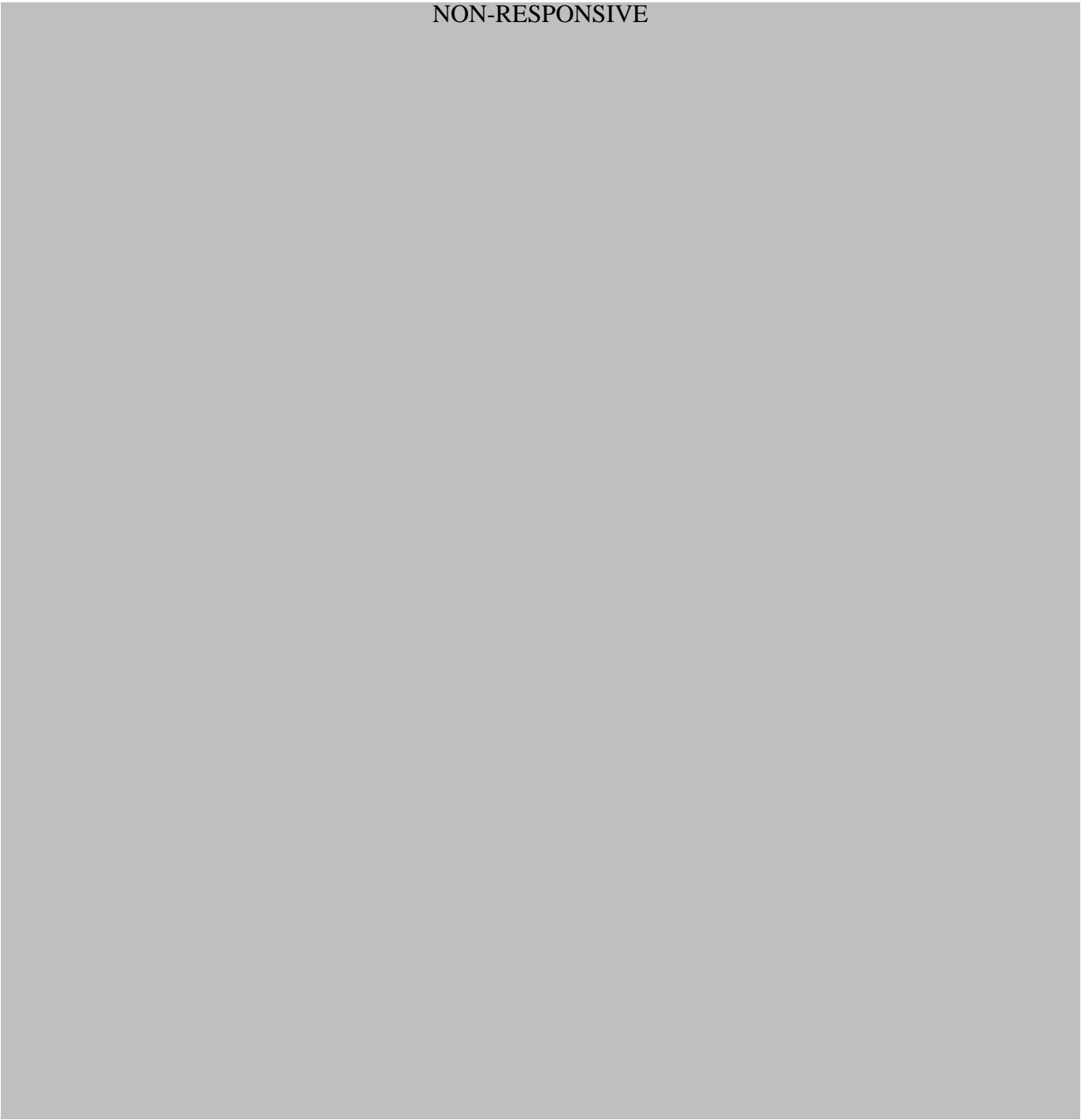
Symproic (naldemedine) Full Waiver with Agreed iPSP

- Proposed Indication: Treatment of opioid-induced constipation in adult patients with chronic non-cancer pain

PeRC Recommendations:

- The PeRC concurred with the full waiver.

NON-RESPONSIVE



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/s/

JACQUILINE A YANCY
11/03/2016

From: [Cherry-France Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854/Symproic(naldemedine): DAAAP Clinical IR: Please respond by COB 10.24.2016
Date: Thursday, October 20, 2016 10:30:37 AM
Attachments: [image001.png](#)
Importance: High

Hello Ting: **Please respond by COB 10.24.2016**

1. Opioid Analgesics: The clinical reports state that, "summary statistics of average total daily and weekly dose of opioids and change from baseline by week were calculated by treatment group. The following 3 types of opioid data were used for analysis: electronic data capture (EDC) data, eDiary data, and eDiary data without discrepant subjects (i.e., eDiary data excluding subjects who had discrepant data between EDC and eDiary data). The discrepant data were defined as total daily dose (TDD) in eDiary data >200% of EDC data for ≥ 5 days during the treatment period. The opioid data for subjects who met the criteria were reviewed by the medical team and the eDiary data without discrepant subjects were decided prior to unblinding." The analysis conducted using eDiary data without discrepant subjects was considered as the main analysis for average total daily and weekly dose of opioids and change from baseline by week. Provide the following clarifications:

- Describe the difference between the EDC and eDiary data. Specifically, describe the source of the electronic data, how it was collected, and why it would differ from the data collected in the eDiary. Although the statistical analysis plan describes how the TDD for opioids was calculated, it does not clearly define how the data were derived.
- Explain the reasons why the data in the eDiary would be discrepant with the EDC and provide the rationale for primarily using the eDiary data without discrepant subjects in your analyses.
- Provide a tabulation of the number of subjects in each category of data (EDC, ed diary, and eDiary without discrepant subjects) and include the following information:
 - The number of subjects that were discrepant;
 - How much opioid they were discrepant by;
 - Possible explanations for those discrepancies

2. Outliers of numeric rating score (NRS): Provide a summary table of the total number of outliers for NRS (defined as subjects with a change from baseline of ≥ 2 at least once during the Treatment Period) for Studies V9231 and V9232 similar to the one shown below for Study V9235.

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COPY**

Shionogi Inc.
Naldemedine (S-297995)
Protocol:1326V9235
Page 1 of 1
Table 14.3-6.2 Outliers of NRS
Safety Population

NRS	Naldemedine 0.2 mg	Placebo
	N=621 n (%)	N=619 n (%)
Outliers	208 (34.3)	205 (33.9)
Non-outliers	398 (65.7)	399 (66.1)
Total	606 (100.0)	604 (100.0)

3. Outliers of TDD (Total Daily Dose) of opioids: Provide a summary table of the total number of outliers (defined as a change from baseline in TDD of opioid for at least one day during the Treatment Period of $\geq 10\%$ or $\geq 30\%$ increase) for Studies V9231 and V9232.

You state that for Study V9235, since opioid dose data were not collected daily in an eDiary as was done in Studies V9231 and V9232, but through the Concomitant Medication CRF, minor fluctuations of daily dosing were not captured and therefore, for subjects in Study V9235, TDD outliers could not be identified. However, for subjects in Study V9235 who experienced opioid withdrawal or possible opioid withdrawal, identify (by subject ID) those subjects who experienced a $\geq 30\%$ increase in baseline opioid dose based on concomitant medication data.

4. In the proposed label, you state the following: (b) (4)

(b) (4)

(b) (4) Provide the subject ID numbers for the subjects identified to support this labeling information.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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CHERONDA L CHERRY-FRANCE
10/20/2016

From: [Cherry-France, Cheronda](#)
To: "tchen@shionogi.com"
Subject: NDA 208854- labeling related IR: Please respond no later than COB 10.21.2016
Date: Tuesday, October 18, 2016 6:33:18 AM
Importance: High

Hello Ting: **Please respond no later than COB 10.21.2016**

Section 12.3 of the proposed label states the following regarding efavirenz (moderate CYP3A inducer): "Simulation using physiologically-based pharmacokinetic modeling suggested that concomitant use of efavirenz, decreases exposure to naldemedine by (b) (4)% (b) (4).

In this regard, justify using phase 3 clinical trial or other data as to why you consider the (b) (4). For example, your justification may include efficacy data from (b) (4).

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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CHERONDA L CHERRY-FRANCE
10/18/2016

From: [Cherry-France, Cheronda](#)
To: "tchen@shionogi.com"
Subject: NDA 208854 Symproic(naldemedine) Labeling deficiencies : Please Correct ASAP
Date: Thursday, October 06, 2016 1:33:39 PM
Importance: High

Hello Ting: Labeling deficiencies : Please Correct ASAP

1. Regarding PI

- "SYMPROIC (naldemedine)" in the label should be revised to "SYMPROIC (naldemedine) tablets"
- Strength should include the equivalence statement, "(equivalent to 0.26mg of naldemedine tosylate)"

2. Regarding container and carton labels:

- The Proprietary name, established name and strength should be expressed as follows:

Symproic
(Naldemedine) tablets
0.2mg

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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(301) 796-9906 (fax)
Cheronda.Cherry-France@fda.hhs.gov

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/s/

CHERONDA L CHERRY-FRANCE
10/06/2016

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854/Symproic(naldemedine) OPQ Carton/Container labeling comments from OPQ - naldemedine: Please correct ASAP
Date: Thursday, September 29, 2016 8:07:24 AM

Hello Ting: **Please correct ASAP**

The current Prescribing Information was revised on 7/3/2016 as requested per filling communication letter dated 6/3/2016.

Please update the submitted Draft Carton and container labeling with the following equivalency statement on the side panel: Each tablet contains 0.2mg of naldemedine (equivalent to 0.26 mg of naldemedine tosylate).

Thanks,

Roxi

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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CHERONDA L CHERRY-FRANCE
09/29/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208854

INFORMATION REQUEST

Shionogi Inc.
Attention: Ting Chen, M.S.
Senior Director Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Mr. Chen:

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

We also refer to your September 19, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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.

We have the following information request from Process:

In your response dated 09/19/2016, we noticed that you included Table 2 with non-critical process parameters in Section P.3.4. Please provide basis or justification for Critical and Non-critical process parameters and controls; and respective approaches in the events when out-of-specification occurs. Please note all the acceptance criteria in the table must be met during commercial manufacturing production. Note the controls in Table 2 are critical to assure compression and coating process steps. Revise the table as necessary.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov. Please respond by **September 30, 2016**.

Sincerely,

Truong
Quach
-S

Digitally signed by
Truong Quach -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=FDOP, cn=Truong Quach -S,
0.9.2342.19200300.10
0.1.1=2001511949
Date: 2016.09.22
15:37:37 -04'00'

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Cherry-France_Cheronda
To: ["lchen@shionogi.com"](mailto:lchen@shionogi.com)
Subject: NDA 208854 Symproic (naldemedine) DAAAP Clinical IR Due: COB 9.26.2016
Date: Friday, September 16, 2016 1:57:32 PM
Importance: High

Hello Ting:

Please see request below from Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and it is **due: COB 9.26.2016**.

1. Provide a copy of the Elevated COWS (Clinical Opioid Withdrawal Scale) assessment tool used in the Phase 3 studies V9231, V9232, and V9235 or explain where, in the protocols, a copy can be found. Describe the scoring method used. Identify how many subjects in Phase 3 studies V9231, V9232, and V9235 had the Elevated COWS performed and total scores of the Elevated COWS.

2. Narratives for subjects with opioid withdrawal (Investigator/SMQ identified and possible opioid withdrawal) vary in detail and content both among and within Phase 3 studies V9231, V9232, and V9235. Resubmit narratives for these subjects that include, at a minimum, the following information:

- The preferred terms associated with the opioid withdrawal event (separate from the terms in the COWS and/or SOWS) and if this information is not available it should be so stated.
- Name and dose of the maintenance opioid the subject was receiving at the time of the opioid withdrawal event and whether there was a change in dosing of opioid that may have contributed to the opioid withdrawal event.
- Identify whether the subject required concomitant (rescue) analgesics (opioid or non-opioid) during the study and describe the timing of rescue analgesic use related to the opioid withdrawal event.
- The number and percentage of outliers for the Numeric Rating Scale (NRS) results were summarized by treatment group. The outliers were defined as subjects who had a change from baseline of ≥ 2 at least once during the Treatment Period. The number and percentage of outliers of Total Daily Dose of Opioid ($\geq 10\%$ increase from baseline and $\geq 30\%$ increase from baseline) was also summarized by treatment group. Identify the Outliers of Total Daily Dose of Opioid and/or Numeric Rating Scale for subjects who experienced opioid withdrawal.
- State whether the subject required treatment of the opioid withdrawal event (and if so, what the treatment was) and the outcome of the event.
- Include Investigator/Sponsor determination of causality of the opioid withdrawal event.

Populate the following table by study for events of opioid withdrawal (SMQ identified and possible):

Subject ID	Onset of OW (Treatment Day)	Preferred Terms of OW	Maintenance Opioid(s)/Dose at time of OW	Change in opioid dose related to OW	Outlier of TDD of Opioid (Y/N)	Use of Opioid or Non-opioid Rescue Analgesic (Y/N)	NRS Outlier (Y/N)	Treatment of OW/Outcome	Investigator/Sponsor Determination of Causality of OW Event

Y=yes; N=no; TDD=Total Daily Dose; OW=opioid withdrawal

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
 LCDR, U.S. Public Health Service Commissioned Corps
 Regulatory Health Project Manager
 Division of Gastroenterology and Inborn Errors Products
 Office of Drug Evaluation III
 CDER/FDA

White Oak Building 22 Room: 5237
 10903 New Hampshire Avenue
 Silver Spring, Maryland
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Cheronda.Cherry-France@fda.hhs.gov

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/s/

CHERONDA L CHERRY-FRANCE
09/16/2016



NDA 208854

INFORMATION REQUEST

Shionogi Inc.
Attention: Ting Chen, M.S.
Senior Director Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Mr. Chen:

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

We also refer to your August 19, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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.

We have the following information request from Process:

- 1. In your response to Process Request 1 submitted on 08/19/2016, it is stated that there is no reprocessing performed. Please update section P.3.3 to clearly indicate that you will follow 21CFR 211.115 for any re-processing during the production of commercial batches.*
- 2. In your response to Process Request 3 submitted on 08/19/2016, you agree to specify [REDACTED] (b) (4). However, these changes are not reflected in 3.2.P.3.4. Please update it to include these changes.*
- 3. In reference to the response to Process Request 4 submitted on 08/19/2016, please address the following and update 3.2.P.3.4 accordingly:*

a.

b.

c.

(b) (4)

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.
Please respond by **September 19, 2016**.

Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Truong
Quach

Digitally signed by Truong Quach
Date: 9/07/2016 09:27:41 AM
GUID: 5407887a000a1c163198a394481b0ee6

From: [Cherry-France, Cheronda](#)
To: "Chen, Ting"
Subject: NDA 208854/Symproic (naldemedine) PBPK Information Request Due September 9th
Date: Friday, September 02, 2016 10:04:20 AM
Importance: High

Hello Ting: (Submit the updated report and pertinent model files by EOB Sep 9, 2016.)

When developing naldemedine PBPK model, you assumed that fluconazole and cyclosporine co-administration can completely inhibit first pass metabolism(#S-297995-CB-341-N). The assumptions are questionable because cyclosporine and fluconazole are not strong CYP3A inhibitors. The observed PK profiles of several DDI studies suggest that cyclosporine may only affect oral absorption of naldemedine by inhibiting intestinal P-gp. As such, alternative model cannot be ruled out.

You should construct an alternative naldemedine PBPK model with F_a equal to $1/1.78$, assuming coadministration of cyclosporine completely inhibits intestinal P-gp without affecting gut and liver CYP3A. With the new F_a , repeat retrograde and other analyses to determine possible combination of $CL_{int,CYP3A}$, $CL_{int,additional}$, and F_g . Use metabolite identification data from your mass balance studies to facilitate model building.

Use the final alternative model to repeat DDI simulations included in your study report ((#S-297995-CB-341-N) and your responses to FDA's information requests dated on June 16 (itraconazole DDI) and August 30 (naldemedine DDI at steady state), respectively.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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/s/

CHERONDA L CHERRY-FRANCE
09/02/2016



NDA 208854

MID-CYCLE COMMUNICATION

Shionogi Inc.
Attention: Ting Chen
Sr. Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Chen:

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

We also refer to the face to face between representatives of your firm and the FDA on August 30, 2016. The purpose of the meeting is to provide you an update on the status of the review of your application.

A record of the meeting is enclosed for your information.

If you have any questions, call me at (301) 796-7295.

Sincerely,

{See appended electronic signature page}

Cheronda Cherry-France, R.N., B.S.N., M.H.A.
LCDR/USPHS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 30, 2016 @ 10:00 AM -11:30 AM EST
Application Number: 208854
Product Name: Symproic (naldemedine)
Indication: treatment of opioid-induced constipation in adult patients with chronic non-cancer pain
Applicant Name: Shionogi
Meeting Chair: Dr. Lauren Weintraub
Meeting Recorder: LCDR Cheronda Cherry-France

FDA ATTENDEES

Julie Beitz, M.D., Director, Office of Drug Evaluation III
Amy Egan, M.D., Assistant Director, Office of Drug Evaluation III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joette Meyer, Pharm. D., Associate Director for Labeling, DGIEP
Joyce Korvick, M.D., M.P.H., Deputy Director of Safety, DGIEP
Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP
Lauren Weintraub, M.D., Medical Officer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Tracy Behrsing, PhD, Pharmacology Reviewer, DGIEP
Sue-Chih Lee, PhD, Team Leader, Division of Clinical Pharmacology III (DCPIII)
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, DCPIII, OCP
Yuching Yang, Ph.D., Physiologically-Based Pharmacokinetic (PBPK) Reviewer
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)
George Kordzakhia, Ph.D., Statistical Reviewer, Division of Biometrics III (DB III)
Ling Lan, Ph.D., Statistical Reviewer, Division of Biometrics (DB III)
Danuta Gromek-Woods, Ph.D., Chemistry Team Leader, Office of Product Quality
Sarah Ibrahim, Ph.D., Chemistry Reviewer
Nitin Mehrotra, Ph.D., Pharmacometrics Team Leader, Division of Pharmacometrics, Office of Clinical Pharmacology (OCP)
Ginneh Stowe, MS, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology
Lisa Harinstein, Pharm D, Safety Evaluator, Division of Pharmacovigilance I
Joel Weissfeld, MD, MPH, Medical Officer, Division of Epidemiology I (DEPI I)
Kira Leishear White, PhD, MS, Epidemiologist, Division of Epidemiology I (DEPI I)
[REDACTED], Eastern Research Group, Inc.

APPLICANT ATTENDEES

Ting Chen, MS	Senior Director, Regulatory Affairs, Shionogi Inc.
Ravi Chivukula	Director, Regulatory CMC, Shionogi Inc.
Juan Camilo Arjona Ferreira, MD	Senior VP Clinical, Clinical Development, Shionogi Inc.
Marc Lesnick, PhD	SVP Regulatory Affairs, Shionogi Inc.
Kevin Halloran, PhD	SVP Regulatory Affairs CMC/QA, Shionogi Inc.
Yamada, Tadaaki, MS	Associate Director, Biometrics, Shionogi Inc.
Toshihiro Wajima, PhD	Senior Director, Head of Clinical pharmacology & Pharmacokinetics, Shionogi & Co., Ltd.

1.0 INTRODUCTION

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 or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 ONGOING REVIEW ISSUES

Clinical Pharmacology:

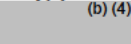
- Drug-drug Interactions: Naldemedine AUC increased approximately 2-fold in presence of moderate CYP3A4 inhibitors as well as with P-gp inhibitors. No dose adjustments are proposed in your draft labeling despite an exposure-response noted for adverse events. In this regard, we are reviewing safety data from phase 3 trials in patients who were on concomitant medications classified as inhibitors of CYP3A4 and/or P-gp. We also sent you an information request asking for Physiologically-based pharmacokinetic (PBPK) simulations, primarily to evaluate the feasibility of an alternate dosing regimen in presence of such inhibitor drugs.
- We are currently reviewing the adequacy of the submitted PBPK model for predicting drug interaction between efavirenz and naldemedine.

**Meeting Discussion Points: (See power point slide presentation from Shionogi)
Shionogi will provide information on study discontinuations in phase 3 clinical trial patients who were documented to be on both naldemedine and drug(s) classified as inhibitors of CYP3A4 and/or P-glycoprotein.**

Shionogi will also evaluate the late onset adverse events for evidence of newly started concomitant medications classified as inhibitors of CYP3A4 and/or P-glycoprotein.

Chemistry, Manufacturing, and Controls:

-  (b) (4)

Meeting Discussion Points: (See power point slide presentation from Shionogi) FDA requested a summary of available stability data of the batch used for the  (b) (4) study. The applicant will provide batch manufacturing dates, batch numbers and packaging dates. Shionogi will clarify in the NDA that the expiration dating period starts with the introduction of API in the manufacturing process.

Shionogi will submit an amendment to the NDA with additional  (b) (4) month stability data in September 2016.

Biopharmaceutics:

- An Information Request was communicated to you asking for you  (b) (4) acceptance criterion of disintegration time from the proposed  (b) (4) minutes to  (b) (4) minutes. If you agree, the disintegration method and acceptance criterion will be used in the release and stability testing for quality control of your proposed drug product upon approval.

Meeting Discussion Points: Shionogi has agreed with the proposed acceptance criterion for the disintegration test.

3.0 INFORMATION REQUESTS: Already sent out on 8.29.2016 & Due by 9.9.2016

1. For the following 6 subject deaths, please provide any available coroner reports, autopsy reports, and diagnostic study results (e.g., blood toxicology/drug levels, serum chemistries, radiographic studies, electrocardiograms, echocardiograms, etc.) used to determine the patient's cause of death. If none are available, please specify whether the reported cause of death was a presumptive diagnosis.

- 1) 22359-018
- 2) 52352-002
- 3) 52375-007

- 4) 52437-005
- 5) 52442-017
- 6) 52449-005

2. For each of the 7 subjects/events in the following table, please specify whether the adverse event was adjudicated by the Cardiovascular Advisory Committee (CAC). Please provide narratives for those adjudicated by the CAC.

Subject ID	Adverse Event
22359-018	Death/Overdose
50403-001	Angina unstable
52342-020	Myocardial infarction
52352-002	Death/Overdose
52398-006	Acute coronary syndrome
52415-004	Myocardial infarction
52432-015	Myocardial infarction

3. Please provide a list of the cases of opioid withdrawal that were investigator-identified vs. those identified by retrospective audit of safety data.
4. Please provide narratives for the adverse events in the following table. In addition to listings of medical history and concomitant medications, narratives should list patients' other adverse events and describe the diagnostic evaluation performed for the event of interest, treatment(s) administered, and event progression. In addition, please include CAC assessments for all adjudicated events.

Subject ID	Adverse Event
11102-005	HYPERTENSIVE URGENCY
12205-006	DIASTOLIC HYPERTENSION
12305-015	SYNCOPE
12316-003	TACHYCARDIA
12328-007	HYPERTENSION
12333-005	CARDIAC FAILURE CONGESTIVE
12333-009	ANGINA
12344-008	HYPERTENSION
12347-003	ANGINA PECTORIS
12347-004	HYPERTENSION
12354-001	HYPERTENSION
22003-003	HYPERTENSION
22310-011	PALPITATIONS
22314-007	HYPERTENSION
22316-021	HYPERTENSION
22321-018	TACHYCARDIA
22324-008	LEFT VENTRICULAR HYPERTROPHY
	HYPOTENSION
22326-012	SYNCOPE
22327-019	HYPERTENSION

22330-004	HYPERTENSION
22336-004	HYPERTENSION
22349-004	HYPERTENSION
22358-007	AMNESIA (2 episodes, separate AEs)
22359-001	HYPOTENSION
22359-019	TACHYCARDIA
22359-025	HYPERTENSION
50402-004	ANGINA PECTORIS
50702-008	CHEST PAIN
50712-004	HYPERTENSION
50801-001	EXTRASYSTOLES
51201-001	HYPERTENSION
51202-003	ATRIAL FIBRILLATION
51203-002	ATRIAL FIBRILLATION
51209-001	BUNDLE BRANCH BLOCK LEFT
51701-001	SUPRAVENTRICULAR EXTRASYSTOLES
51701-006	MEMORY IMPAIRMENT
52002-003	HYPERTENSION
52203-004	HYPERTENSION
52204-004	PALPITATIONS
	SINUS TACHYCARDIA
	HYPERTENSION
52204-006	PALPITATIONS
52220-001	RAYNAUD'S PHENOMENON
52220-003	ATRIAL FIBRILLATION
52223-001	BUNDLE BRANCH BLOCK LEFT
52225-006	SYNCOPE
52231-002	DIASTOLIC DYSFUNCTION
	PALPITATIONS
52233-006	ATRIAL FIBRILLATION
52304-011	HYPERTENSION
52305-013	HYPOTENSION
52313-012	BLOOD PRESSURE FLUCTUATION
52314-015	CHEST PAIN
52316-014	AMNESIA
52319-001	HYPERTENSION
52319-004	THROMBOPHLEBITIS, LEGS
52319-008	HYPERTENSION
52320-013	SYNCOPE
52322-009	HYPOTENSION
52328-007	CARDIAC DISCOMFORT
52328-016	SYNCOPE
52334-014	EDEMA
52334-023	TACHYCARDIA
52335-001	HYPERTENSION

	LEFT VENTRICULAR HYPERTROPHY
52335-004	CONVULSION
52335-011	BRADYCARDIA
52340-005	CONVULSION
52342-003	SYNCOPE
52342-020	MYOCARDIAL INFARCTION
52348-037	HYPERTENSION
52348-043	PERIPHERAL COLDNESS
52349-008	INFRARENAL ABDOMINAL AORTIC ANEURYSM
	HYPERTENSION
52352-008	HYPERTENSION
52354-025	HYPOTENSION
52356-005	RIGHT BUNDLE BRANCH BLOCK
52357-002	VENTRICULAR EXTRASYSTOLES
52361-008	HYPERTENSION (2 episodes, separate AEs)
52361-016	AMNESIA
52363-009	HYPERTENSION
52363-011	HYPERTENSION
52363-013	HYPERTENSION
52363-014	HYPERTENSION
52364-038	TACHYCARDIA
52364-039	HYPERTENSION
52368-020	ANGINA UNSTABLE
52368-026	SYNCOPE
52368-028	CARDIAC FAILURE CONGESTIVE
52385-022	ANGINA PECTORIS
52389-001	PALPITATIONS
52389-015	HYPERTENSION
52398-004	HEPATIC ARTERY STENOSIS
52398-005	ANGINA PECTORIS
	ENCEPHALOPATHY
52398-006	ACUTE CORONARY SYNDROME
52401-006	SYNCOPE
52410-005	ATRIAL FIBRILLATION
52410-006	EDEMA
52415-004	CARDIOMEGALY
52417-006	LEFT POPLITEAL ANEURYSM
	RIGHT POPLITEAL ANEURYSM
	HYPOTENSION
52418-005	HYPERTENSION
52424-001	VENTRICULAR EXTRASYSTOLES
52429-001	ATRIAL FIBRILLATION
52429-009	HYPERTENSION
52432-004	HYPERTENSION
52432-015	MYOCARDIAL INFARCTION

52433-030	LOSS OF CONSCIOUSNESS
52439-004	ARRHYTHMIA, SUPRAVENTRICULAR
52442-011	HYPERTENSION
52450-002	SWELLING
52450-007	CHEST DISCOMFORT
52460-001	HYPERTENSION
52467-001	BRADYCARDIA
52470-004	ARRHYTHMIA, SUPRAVENTRICULAR
52470-007	HYPERTENSION

4.0 RISK MANAGEMENT

Based on the information currently available, we do not believe that a REMS will be necessary, at this time. We will make a final determination for the need for a REMS at the completion of the review cycle.

5.0 ADVISORY COMMITTEE MEETING

THERE ARE NO PLANS AT THIS TIME FOR AN ADVISORY COMMITTEE MEETING

6.0 LATE-CYCLE MEETING

SCHEDULED FOR DECEMBER 13, 2016 @ 9:00AM (EST) ON WHITE OAK CAMPUS

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/s/

CHERONDA L CHERRY-FRANCE
08/31/2016

From: [Cherry-France, Cheronda](#)
To: "Chen, Ting"
Subject: NDA 208854 Symproic (naldemedine): Clinical Information Request Due COB September 9th
Date: Monday, August 29, 2016 5:01:07 AM
Importance: High

Good Morning Ting: Clinical Information Request **Due COB September 9th**

As discussed on Friday, August 26th that I was resend this information request separately. The team continues to review your NDA submission and request the following:

1. For the following 6 subject deaths, please provide any available coroner reports, autopsy reports, and diagnostic study results (e.g., blood toxicology/drug levels, serum chemistries, radiographic studies, electrocardiograms, echocardiograms, etc.) used to determine the patient's cause of death. If none are available, please specify whether the reported cause of death was a presumptive diagnosis.

- 1) 22359-018
- 2) 52352-002
- 3) 52375-007
- 4) 52437-005
- 5) 52442-017
- 6) 52449-005

2. For each of the 7 subjects/events in the following table, please specify whether the adverse event was adjudicated by the Cardiovascular Advisory Committee (CAC). Please provide narratives for those adjudicated by the CAC.

Subject ID	Adverse Event
22359-018	Death/Overdose
50403-001	Angina unstable
52342-020	Myocardial infarction
52352-002	Death/Overdose
52398-006	Acute coronary syndrome
52415-004	Myocardial infarction
52432-015	Myocardial infarction

3. Please provide a list of the cases of opioid withdrawal that were investigator-identified vs. those identified by retrospective audit of safety data.
4. Please provide narratives for the adverse events in the following table. In addition to listings of medical history and concomitant medications, narratives should list patients' adverse events and describe the diagnostic evaluation performed for the event of interest, treatment(s) administered, and event progression. In addition, please include CAC assessments for all adjudicated events.

Subject ID	Adverse Event
11102-005	HYPERTENSIVE URGENCY
12205-006	DIASTOLIC HYPERTENSION
12305-015	SYNCOPE
12316-003	TACHYCARDIA
12328-007	HYPERTENSION
12333-005	CARDIAC FAILURE CONGESTIVE
12333-009	ANGINA
12344-008	HYPERTENSION
12347-003	ANGINA PECTORIS
12347-004	HYPERTENSION
12354-001	HYPERTENSION
22003-003	HYPERTENSION
22310-011	PALPITATIONS
22314-007	HYPERTENSION
22316-021	HYPERTENSION
22321-018	TACHYCARDIA
22324-008	LEFT VENTRICULAR HYPERTROPHY ----- HYPOTENSION
22326-012	SYNCOPE
22327-019	HYPERTENSION
22330-004	HYPERTENSION
22336-004	HYPERTENSION
22349-004	HYPERTENSION
22358-007	AMNESIA (2 episodes, separate AEs)
22359-001	HYPOTENSION
22359-019	TACHYCARDIA
22359-025	HYPERTENSION
50402-004	ANGINA PECTORIS
50702-008	CHEST PAIN
50712-004	HYPERTENSION
50801-001	EXTRASYSTOLES
51201-001	HYPERTENSION
51202-003	ATRIAL FIBRILLATION
51203-002	ATRIAL FIBRILLATION
51209-001	BUNDLE BRANCH BLOCK LEFT
51701-001	SUPRAVENTRICULAR EXTRASYSTOLES
51701-006	MEMORY IMPAIRMENT
52002-003	HYPERTENSION
52203-004	HYPERTENSION
52204-004	PALPITATIONS ----- SINUS TACHYCARDIA -----

	HYPERTENSION
52204-006	PALPITATIONS
52220-001	RAYNAUD'S PHENOMENON
52220-003	ATRIAL FIBRILLATION
52223-001	BUNDLE BRANCH BLOCK LEFT
52225-006	SYNCOPE
52231-002	DIASTOLIC DYSFUNCTION
	PALPITATIONS
52233-006	ATRIAL FIBRILLATION
52304-011	HYPERTENSION
52305-013	HYPOTENSION
52313-012	BLOOD PRESSURE FLUCTUATION
52314-015	CHEST PAIN
52316-014	AMNESIA
52319-001	HYPERTENSION
52319-004	THROMBOPHLEBITIS, LEGS
52319-008	HYPERTENSION
52320-013	SYNCOPE
52322-009	HYPOTENSION
52328-007	CARDIAC DISCOMFORT
52328-016	SYNCOPE
52334-014	EDEMA
52334-023	TACHYCARDIA
52335-001	HYPERTENSION
	LEFT VENTRICULAR HYPERTROPHY
52335-004	CONVULSION
52335-011	BRADYCARDIA
52340-005	CONVULSION
52342-003	SYNCOPE
52342-020	MYOCARDIAL INFARCTION
52348-037	HYPERTENSION
52348-043	PERIPHERAL COLDNESS
52349-008	INFRARENAL ABDOMINAL AORTIC ANEURYSM
	HYPERTENSION
52352-008	HYPERTENSION
52354-025	HYPOTENSION
52356-005	RIGHT BUNDLE BRANCH BLOCK
52357-002	VENTRICULAR EXTRASYSTOLES
52361-008	HYPERTENSION (2 episodes, separate AEs)
52361-016	AMNESIA
52363-009	HYPERTENSION
52363-011	HYPERTENSION
52363-013	HYPERTENSION

52363-014	HYPERTENSION
52364-038	TACHYCARDIA
52364-039	HYPERTENSION
52368-020	ANGINA UNSTABLE
52368-026	SYNCOPE
52368-028	CARDIAC FAILURE CONGESTIVE
52385-022	ANGINA PECTORIS
52389-001	PALPITATIONS
52389-015	HYPERTENSION
52398-004	HEPATIC ARTERY STENOSIS
52398-005	ANGINA PECTORIS
	ENCEPHALOPATHY
52398-006	ACUTE CORONARY SYNDROME
52401-006	SYNCOPE
52410-005	ATRIAL FIBRILLATION
52410-006	EDEMA
52415-004	CARDIOMEGALY
52417-006	LEFT POPLITEAL ANEURYSM
	RIGHT POPLITEAL ANEURYSM
	HYPOTENSION
52418-005	HYPERTENSION
52424-001	VENTRICULAR EXTRASYSTOLES
52429-001	ATRIAL FIBRILLATION
52429-009	HYPERTENSION
52432-004	HYPERTENSION
52432-015	MYOCARDIAL INFARCTION
52433-030	LOSS OF CONSCIOUSNESS
52439-004	ARRHYTHMIA, SUPRAVENTRICULAR
52442-011	HYPERTENSION
52450-002	SWELLING
52450-007	CHEST DISCOMFORT
52460-001	HYPERTENSION
52467-001	BRADYCARDIA
52470-004	ARRHYTHMIA, SUPRAVENTRICULAR
52470-007	HYPERTENSION

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

CDER/FDA

*White Oak Building 22 Room: 5237
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Silver Spring, Maryland*

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(301) 796-7295 (office)

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Cheronda.Cherry-France@fda.hhs.gov

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/s/

CHERONDA L CHERRY-FRANCE
08/29/2016

From: [Cherry-France, Cheronda](mailto:Cherry-France.Cheronda)
To: "tchen@shionogi.com"
Subject: NDA 208854 Symproic(naldemedine): BioPharm Information: COB August 29, 2016
Date: Tuesday, August 23, 2016 3:14:41 PM

Hello Ting: Please respond no later than COB August 29, 2016

Biopharm Information Request in response to CMC IR Response from Applicant on Q4 dated August 19, 2016:

Based on your disintegration data generated during stability test with a mean of around (b) (4) seconds (initial at release), your proposed acceptance criterion of (b) (4). Therefore, we recommend an acceptance criterion of NMT (b) (4) min for disintegration test in drug product specifications. This will be applied to release and stability testing as a quality control of your drug product.

Revise accordingly in Sections 3.2.P.5.1 Specifications; 3.2.P.5.2 Analytical Procedures Summary; 3.2.P.5.2.10 Analytical Procedures - Disintegration; 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment and 2.3.QOS – Drug Product.

Thanks,

Roxi

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

CHERONDA L CHERRY-FRANCE
08/23/2016

From: [Cherry-France, Cheronda](#)
To: "tchen@shionogi.com"
Subject: NDA 208854: naldemedine: PBPK Information Request Due by COB 8.26.2016
Date: Friday, August 19, 2016 10:12:24 AM
Importance: High

Good Morning Ting: **Submit this information by COB 8.26.2016**

PBPK Information Request:

Use the naldemedine and CYP3A inhibitor models to simulate the following scenarios:

1. Naldemedine 0.2 mg once daily (q.d.) to steady state with/without coadministration of itraconazole
2. Naldemedine 0.2 mg once every other day (q.o.d.) to steady state with/without coadministration of itraconazole
3. Naldemedine 0.2 mg once daily (q.d.) to steady state with/without coadministration of fluconazole
4. Naldemedine 0.2 mg once every other day (q.o.d.) to steady state with/without coadministration of fluconazole

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

CHERONDA L CHERRY-FRANCE
08/19/2016



NDA 208854

INFORMATION REQUEST

Shionogi Inc.
Attention: Ting Chen, M.S.
Senior Director Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Mr. Chen:

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

We also refer to your August 10, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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.

We have the following information request for Biopharmaceutics:

Based on our analysis of dissolution and disintegration results for all three batches under stability testing at 25°C/60% RH (Table 3, 5, 7, 9, 11, 13 in Section 3.2.P.8.3), the disintegration test demonstrates a better discriminatory power compared to the dissolution test. The drug release at 10 min didn't show significant difference in dissolution from (b) (4) M under stability testing while there is a clear trend (b) (4) (b) (4) in disintegration time from (b) (4) seconds) to (b) (4) seconds) under stability testing. Therefore, for quality control purpose, we recommend that in addition to the dissolution test, the disintegration test be implemented on release and stability, in accordance to ICH Guideline Q6A: Decision tree (b) (4)

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov. Please respond by **August 19, 2016**.

Sincerely,

Truong
Quach -S

Digitally signed by Truong
Quach -S
DN: cn=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
c=US, email=Truong.Quach -S,
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Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208854

INFORMATION REQUEST

Shionogi Inc.
Attention: Ting Chen, M.S.
Senior Director Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Mr. Chen:

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

We also refer to your March 23, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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.

We have the following information request for Process:

1. *Reprocessing statement is not found in your submission. Please provide it or specify the location if provided. Update Section P.3.3 accordingly.*
2. *In 3.2.P.2.1, you evaluated drug substance particle size impact on drug product quality with D90 ranged from (b) (4) μm . You proposed drug substance particle size control limit as D90 not more than (b) (4) μm in drug substance specification. However, lower limit of drug substance D90 was not defined which may adversely affect processability and stability. Please define drug substance D90 lower limit.*
3. *Please address the following concerns in section P.3.3 and P.3.4. Revise these sections accordingly.*

a.



In your application, you propose a (b) (4) month (b) (4). Please be reminded that the date of manufacture is defined as the date when the drug substance is mixed with any excipients, therefore, any excessive (b) (4) the manufacturing processes will reduced significantly the available shelf life of the finished drug product. Based on the ICH guideline Q1A, the shelf life determination should start for the product that is already packaged.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov. Please respond by **August 19, 2016**.

Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Truong
Quach

Digitally signed by Truong Quach
Date: 8/11/2016 12:35:51PM
GUID: 5407887a000a1c163198a394481b0ee6

From: [Cherry-France, Cheronda](mailto:Cherry-France.Cheronda)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854/Symproic (naldemedine): Clinical IR & COA IR due COB August 8, 2016
Date: Wednesday, August 03, 2016 7:04:16 AM
Importance: High

Good Morning Ms. Ting: **Clinical IR & COA (Clinical Outcome Assessment) IR due Monday, COB August 8, 2016**

Just to let you know we are coming up on the following dates: Mid-cycle Meeting to discuss how the review is coming and this is our (FDA's internal meeting): August 16, 2016.

We will be meeting with you and your team Tuesday, August 30, 2016 via teleconference **or** face-2-face your preference at 10:00 AM to 11:30 AM (Eastern Standard Time).

1. Submit SDTM and ADaM Datasets with the following clinical trial data from Study 1107V9221:
 - a. Efficacy data, including:
 - 1) Baseline constipation data, bowel movement frequency
 - 2) Spontaneous bowel movements events per week
 - 3) Bristol Stool Scale grades
 - 4) Assessments of other constipation-related symptoms (abdominal bloating, discomfort, etc.)
 - 5) Laxative use data
 - b. Pharmacokinetic concentrations
 - c. Questionnaires-safety assessments (Clinical Opiate Withdrawal Scale Score, 11-point Numerical Intensity Rating Scale of pain)
2. Submit Adverse Event data in SDTM and ADaM datasets for the following studies:
 - a. 0824V9211
 - b. 0917V9213
 - c. 1007V9214
 - d. 1101V9216
3. Provide a copy of the full patient-reported eDiary exactly as it was administered to patients (i.e., electronic screen shots), including the Bowel Movement and Constipation Assessment (BMCA) diary.
4. Provide a copy of the Subject Global Satisfaction (SGS) questionnaire as it was administered to patients. Include any patient instructions and the item stem of the question (all response options) provided to patients.
5. For Study V9231 and V9232, provide cumulative distribution function (CDF) as specified below (see sub-bullets a and b below) for each of the following 3 key secondary endpoints: (total of 12 CDF plots, 6 plots for each clinical trial)
 - First key secondary endpoint: change in frequency of SBMs per week from baseline to the last 2 weeks of treatment
 - Third key secondary endpoint: change in frequency of CSBMs per week from baseline

to the last 2 weeks of treatment

- Fourth key secondary endpoint: change in frequency of SBMs without straining per week from baseline to the last 2 weeks of treatment
 - a) For each of the 3 secondary endpoints listed above, provide separate CDF plots (total of 6 plots, 3 per clinical trial) using Week 12 SGS scores with pooled data for the naldemedine and placebo treatment groups, with the following:
 - Change in secondary endpoint score on the x-axis
 - Curves for the SGS scores of 7, 6, 5, 4, and 3.
 - Graph legends that report the total number of subjects included in each CDF curve
 - b) For each of the three secondary endpoints listed above, provide CDF plots with separate curves for the treatment and placebo groups with secondary endpoint change score on x-axis. Note the SGS will not be included in these six plots.
6. For both Study V9231 and V9232, submit recalculations of the four key secondary endpoints based on the actual number of observed bowel movements in a week (without pro-rating based on the number of completed diary entries), using the following formula to determine “weekly frequency” for the first, third, and fourth secondary endpoints[†] (see item 5):
- (Total number of SBMs[†] in the last two weeks)* 7/14**
- [†] *SBMs, CSBMs, or SBMs without straining, as specified for the particular secondary endpoint*
- Submit these recalculations using the following datasets of patients:
- a) All patients with available data
 - b) Only patients with ≥4 completed diary entries per week (i.e., excluding patients from the analyses if <4 completed diaries per week); for the 3 secondary endpoints with 2-week periods for analysis, patients must have completed ≥8 diary entries for the 2-week period and ≥4 diary entries for each individual week to be included in the analysis.
7. Using the recalculated results from item 6a (non-pro-rated data for all patients with evaluable data), provide 12 additional cumulative distribution function (CDF) plots using the SGS questionnaire, using the procedures described in item 5—i.e., 12 CDF plots with separate plots for each of the 3 specified key secondary endpoints (for both Study V9231 and V9232), with 6 CDF plots using Week 12 SGS scores and pooled patient data and 6 CDF plots with separate curves for the naldemedine and placebo treatment groups (without SGS data).
8. Provide separate Spearman correlations and scatterplots for each of the 3 secondary endpoint change scores (specified in Item 5) vs. the Week 12 SGS scores, using the following data:
- a. Current calculations of BM frequency (corrected for number of completed diary entries) for Study V9231 and V9232, as submitted in the NDA
 - b. Recalculated results from item 6a (non-pro-rated data for all patients with evaluable

data) for Study V9231 and V9232

Thanks,

Roni

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LCDR, U.S. Public Health Service Commissioned Corps
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/s/

CHERONDA L CHERRY-FRANCE
08/03/2016

From: [Cherry-France, Cheronda](#)
To: "[Chen, Ting](#)"
Subject: NDA 208854 (naldemedine) : Clin Pharm Information Request Due: COB 07/28/2016
Date: Tuesday, July 26, 2016 7:03:05 AM
Importance: High

Ting: **(Clin Pharm Information Request Due: COB 07/28/2016)**

With regard to your NDA 208854, we have the following information request. Please submit your response with supporting data by COB 07/28/2016:

- For the Mass Balance Study 1016V9215, clarify the percentage of radioactivity in feces that corresponds to unchanged drug.
- Based on the overall data, discuss the significance of biliary secretion in the elimination of naldemedine in humans (i.e., biliary clearance as % of total body clearance).

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
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CHERONDA L CHERRY-FRANCE
07/26/2016



NDA 208854

INFORMATION REQUEST

Shionogi Inc.
Attention: Ting Chen, M.S.
Senior Director Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Mr. Chen:

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

We also refer to your March 23, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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.

We have the following information request for Bio Pharmaceutical:

1. *Submit complete dissolution data (include individual, mean +/- SD, mean dissolution profile) for stability data of three primary stability batches (1211081, 1302009, and 1303011) tested at 25°C/60% RH.*
2. *We recommend (b)(4) the proposed dissolution acceptance criterion to NLT (b)(4)% in 10 min.*

We request that you acknowledge your acceptance of the recommended dissolution acceptance criterion. Implement the recommended dissolution acceptance criterion for future SUPAC manufacturing changes of your proposed drug product, and provide the revised specifications table in M3.5.1 with the updated acceptance criterion for the dissolution and stability test.

3. *In the meantime, your proposed drug product releases very rapidly using the proposed dissolution method (e.g. more than (b)(4)% of labelled amount of drug) is released within 10*

min). There is limited discriminatory ability for your proposed dissolution method. Although the current dissolution method is needed, we recommend you to develop disintegration test (as described in guidance ICHQ6A: Decision tree (b) (4) for quality control purpose (release and stability testing). Alternatively, you can consider applying modeling approaches such as physiologically based pharmacokinetic (PBPK) modeling to show that the proposed dissolution method can reject drug product batches with unsatisfied in vivo performance.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov. Please respond by **August 10, 2016**.

Sincerely,

Truong
Quach -S

Digitally signed by Truong
Quach -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Truong Quach -S,
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Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Executive CAC

Date of Meeting: July 19, 2016

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Mukesh Summan, Ph.D., DBRUP, Alternate Member
Sushanta Chakder, Ph.D., DGIEP, Pharm Tox Supervisor
Tracy Behrsing, Ph.D., DGIEP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 208854

Drug Name: Naldemedine tosylate; S-297995 monotosylate

Sponsor: Shionogi, Inc.

Background:

S-297995 monotosylate is an opioid antagonist under development for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain.

Rat Carcinogenicity Study

In a 104-week carcinogenicity study in Crl:CD(SD) rats, animals were administered S-297995 monotosylate by oral gavage at doses of 10, 30, or 100 mg/kg/day in 0.5% w/v methylcellulose aqueous solution. The control animals received 0.5% w/v methylcellulose aqueous solution by oral gavage. Dose selection was based on the high dose having an AUC value > 25 times that in humans, and these doses received prior concurrence from the ECAC. In this study, all surviving females from all dose groups were terminated early (from Week 103) when the number of surviving females in the control group reached 15 animals. This differs from the usual execCAC recommendation of terminating a sex when control reaches 20. There were no drug-related neoplastic findings in male or female rats.

Mouse Carcinogenicity Study

In a 104-week carcinogenicity study in Crl:CD1(ICR) mice, S-297995 monotosylate was administered by oral gavage. Animals were treated with doses of 10, 30, or 100 mg/kg/day in 0.5 % w/v methylcellulose aqueous solution. The control animals received 0.5% w/v methylcellulose aqueous solution by oral gavage. Dose selection was based on the high dose having an AUC value >25 times that in humans, and the doses received prior concurrence from the ECAC. There were no drug-related neoplastic findings in male or female mice.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was adequate, noting prior agreement with the protocol.
- The Committee concluded that there were no drug related neoplasms for both males and females.

Mouse:

- The Committee concurred that the study was adequate, noting prior agreement with the protocol.
- The Committee concluded that there were no drug related neoplasms for both males and females.

Karen Davis Bruno, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DGIEP
/SChakder, DGIEP
/TBehrsing, DGIEP
/CCherry-France, DGIEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
07/21/2016

KAREN L DAVIS BRUNO
07/21/2016

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854 Naldemedine Clin Pharm IR for Datasets due COB 7.15.2016
Date: Wednesday, July 13, 2016 5:02:36 PM
Importance: High

Hi Ting: **Please submit requested information by COB 07/15/2016**

As a follow up to our information request for datasets and your response received on April 15, 2016, we have the following additional information request:

Submit plasma naldemedine and metabolite concentration-time data and PK parameter datasets, containing all relevant information for analysis such as treatment groups and dosing information, in SAS transport file format for each of the phase 1 Clinical Pharmacology studies. With the provided combined dataset under the population PK tab of the electronic submission, we are unable to clearly distinguish subgroups of interest (for e.g. healthy vs. mild vs. moderate Hepatic Impairment cohorts in study # V921C). Also the dataset provided doesn't include sponsor-generated PK parameters for our verification.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

*White Oak Building 22 Room: 5237
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-7295 (office)
(301) 796-9906 (fax)
Cheronda.Cherry-France@fda.hhs.gov

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/s/

CHERONDA L CHERRY-FRANCE
07/13/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208854

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Shionogi Inc.
300 Campus Drive
Florham Park, NJ 07932

ATTENTION: Ting Chen, MS
Senior Director, Regulatory Affairs

Dear Mr. Chen:

Please refer to your New Drug Application (NDA) dated and received March 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naldemedine, Tablets, 0.2 mg.

We also refer to your correspondence, dated and received April 19, 2016, requesting review of your proposed proprietary name, Symproic.

We have completed our review of the proposed proprietary name, Symproic and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 19, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ginneh Stowe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4049. For any other information regarding this application, contact Cheronda Cherry-France, Regulatory Project Manager in the Office of New Drugs, at (301) 796-7295.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

TODD D BRIDGES
06/23/2016

From: [Chen, Ting](#)
To: [Cherry-France, Cheronda](#)
Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission
Date: Friday, June 17, 2016 4:01:42 PM

Ok, make sense 😊

From: Cherry-France, Cheronda [mailto:Cheronda.Cherry-France@fda.hhs.gov]
Sent: Friday, June 17, 2016 3:57 PM
To: Chen, Ting
Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission

It is a clarification and I am unable to an addendum to the Filing Communication letter. It will just be an update in which I will file in our communication package.

Does that make sense?

Roni

From: Chen, Ting [mailto:tchen@shionogi.com]
Sent: Friday, June 17, 2016 3:50 PM
To: Cherry-France, Cheronda
Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission
Importance: High

Dear Roni,

Sorry, one more question, Does the clarification question replace the original Question 5 from the Filing Communication Letter?

Best regards,
Ting

Question 5

Please provide the information requested below for Protocols 1314V9231, 1315V9232, and 1326V9235, the three phase 3 clinical trials conducted in subjects with OIC and chronic, non-cancer pain.

- a. To facilitate our understanding of how subject symptom data were used to determine response, recurrence, and eligibility, and were transmitted from eDiaries during the clinical trial and prepared for submission to the Agency, please provide a flow diagram and narrative that tracks the course of data generated by the subject using the eDiaries. **Please describe how the data were collected, transmitted and reviewed.** This should include a description concerning data reviewed by the clinical investigator during the trial, data that were used to populate the case report form (CRF) and data that were used for analysis. The diagram should identify who was responsible for each step in the process; including description of what entity (e.g., clinical investigator, automatic population from eDiaries, calculation from sponsor program, etc.) was responsible for calculation of eligibility and determination of response. Please note specific points in dataflow where an audit trail exists.

- b. **Please provide a flow diagram and narrative that tracks the course of the eDiary data to the clinical investigator (CI) for archiving at the end of the trial** so that the CI will be able to fulfill the responsibilities under 21CFR312.62.
- c. **Provide the name of the CRO, if any, responsible for the eDiary system for the diary data.**
- d. **Provide the location or locations of the documents related to the information request above** (e.g., in clinical trial file at sponsor site, at CRO, etc.) **and the location of the diary data** (e.g., at investigator site, sponsor site, at CRO, etc.)
- e. **Submit the Patient eDiary guide, the site guide, and any other guides provided to clinical site staff and patients.**

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]

Sent: Friday, June 17, 2016 3:19 PM

To: Chen, Ting

Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission

Ting: see the [blue](#) highlights below and let me know if you still have questions....

As discussed in during the June 16 naldemedine (NDA 208854) team meeting and the communication with Shionogi, the following is the clarification regarding the information request for CRF procedures used for naldemedine phase 3 clinical trials (communicated in the 74-day Filing Letter).

Clinical Information Request- Clarification of Information Request communicated in the Naldemedine Filing Communication dated June 3, 2014

We have the following requests for information to facilitate our understanding of how subject symptom data were obtained and used to determine subject eligibility and response to treatment during the phase 3 clinical trials, Studies 1314V9231,1315V9232, and 1326V923. Please note that we are not requesting submission of any copies of eDiary entries or other CRF documents with individual patient data.

1. Submit samples of the eDiary and any other forms used for patient-reported assessments [e.g., electron data capture (EDC) methods, paper forms, sections of the electronic case report form (eCRF), not already submitted in the NDA].
2. Submit all guides provided to patients and site investigator staff that provides instructions for collection and transmission of data (e.g., Patient eDiary guide, site guide, etc.)
3. Provide the name of the clinical research organization (CRO), if any, responsible for the eDiary system and handling of eDiary data
4. Describe the procedures used to capture, transmit, and review data from eDiary entries and other patient-reported assessments. This information needs to cover all steps in the flow of

data, including archiving at the end of the trial, as required by the clinical investigator under 21 CFR 312.62. For your submission, we have the following requests:

- a. Provide a flow diagram that tracks data from generation through initiation of data analyses.
- b. Identify the parties responsible for each step in the dataflow process, including all parties (i.e., subject and any intermediaries) permitted to record patient-reported data and the parties responsible for populating the eCRF case report form (CRF)
- c. Describe the flow of data from patient eDiary entries to preparation for data analysis
- d. Describe all methods (e.g., paper forms, computer entry, etc.) used to elicit, record, and transmit patient-reported data from sources other than the eDiary, including all questionnaires and standardized assessments . Please clarify the procedures used for those assessments performed at clinic visits vs. those performed by patients between visits.
- e. For all questionnaires, please explain how these were administered, and how results were recorded.
- f. Description of the methods (e.g., report by clinical investigator, automatic population from eDiaries, calculation from sponsor program, etc.) involved in each step in the dataflow
- g. Describe the specific points in the dataflow where an audit trail exists

Thanks,

Roni

From: Chen, Ting [<mailto:tchen@shionogi.com>]
Sent: Friday, June 17, 2016 2:45 PM
To: Cherry-France, Cheronda
Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission

Don't worry; I am sure you will have a lots to clear and catching up before you leave 😊

Regarding the data flow for the questionnaires, is the Reviewer looking for COWS, SOWS, NRS or she wants ALL questionnaires?

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]
Sent: Friday, June 17, 2016 2:42 PM
To: Chen, Ting
Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission

Thanks and sorry so late sending it...

Roni

From: Chen, Ting [<mailto:tchen@shionogi.com>]
Sent: Friday, June 17, 2016 2:41 PM
To: Cherry-France, Cheronda
Subject: RE: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission

Dear Roni,

Got it. Thank you very much!

Wishing you a very happy vacation ☺

ting

From: Cherry-France, Cheronda [<mailto:Cheronda.Cherry-France@fda.hhs.gov>]
Sent: Friday, June 17, 2016 2:38 PM
To: Chen, Ting
Subject: Naldemedine (NDA 208854) 120-Day Safety Update- Request for Early Submission

Hi Ting:

We agree to Shionogi's request for early submission of an integrated safety update (prior to Day 120 of the naldemedine NDA review cycle, already completed), per the discussion via tele-conference call between the Medical Officer (Lauren Weintraub) and Regulatory Project Manager (LCDR Roni Cherry-France) and applicant (Shionogi/Ting Chen) on June 16 for NDA 208854. The following is a summary of our discussion with the Applicant with respect to the Applicant's request, the agreements made by the Applicant if the Division agrees to the request, and the information provided by the Applicant that was used in support of our decision. This email is intended as documentation for our records .

Shionogi has completed all trials in both the cancer and non-cancer pain patient populations, including extension studies and does not plan to initiate any new clinical trials

- There are no patients receiving, or expected to receive, treatment with naldemedine under a compassionate use/expanded access protocol anywhere worldwide.
- Marketing applications for naldemedine have been submitted in the U.S. and Japan (submitted concurrently), and naldemedine is not currently marketed in any foreign market.
- The integrated safety update covers the entire period between data cutoff for NDA submission and study completion (including follow-up) for all subjects enrolled in naldemedine clinical trials.

Consequently, the information submitted in a 120-day safety update would be identical to this safety update covering the period between NDA data cutoff and completion of the clinical trial program, provided no additional exposure to naldemedine occurs in the next month.

To be compliant with NDA requirements, the Applicant agrees to submit a letter to the NDA on Day 120, in lieu of the 120-Day Safety Update. The letter will include a reference the submission with the integrated safety update that covers the period between NDA data cutoff and the completion of naldemedine clinical trials, and will confirm that no naldemedine exposure has occurred under any condition (i.e., clinical trials, expanded access/compassionate use, or post-marketing) since the completion of naldemedine clinical trials. However, if any treatment with naldemedine occurs during this time period, the Applicant agreed that a formal 120-Day Safety Update will be submitted.

Finally the Applicant informed us that the submission of the supplemental data for the 52-week safety trial (Study V9235), including the Supplemental Period Data Set report and the updated

datasets with combined data from the Core Period and Supplemental Period of Study V9235 (as agreed up during the pre-NDA meeting) and the analyses of combined Core Period and Supplemental Period data (requested by the Division on June 6, 2016), will also be submitted earlier than Day 120 with the completed integrated safety update.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

*White Oak Building 22 Room: 5237
10903 New Hampshire Avenue
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Cheronda.Cherry-France@fda.hhs.gov

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CHERONDA L CHERRY-FRANCE
06/17/2016

From: [Cherry-France, Cheronda](mailto:tchen@shionogi.com)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854: Site Specific Data IR
Date: Tuesday, June 07, 2016 11:36:42 AM
Importance: High

Hi Tien:

For each of the following 12 clinical trial sites (6 sites for Study 1314V9231 and 6 sites for Study 1315V9232), please provide the individual subject data listings (hereafter referred to as "line listings") for all enrolled subjects. We request that the data be provided in folders by site.

For Study 1314V9231:

1. Site 12336, CI: Teresa Sligh, M.D.
2. Site 12326, CI: Richard Krause, M.D.
3. Site 12343, CI: Gilbert Weiner, D.O.
4. Site 12344, CI: James Wild, M.D.
5. Site 12305, CI: Samir Arora, M.D.
6. Site 12334, CI: Larry Reed, Ph.D., M.D.

For Study 1314V9232:

1. Site 22301, CI: Othon Wiltz, M.D.
2. Site 22363, CI: Colin Campbell, D.O.
3. Site 22347, CI: M.A Mahmud, M.D.
4. Site 22359, CI: Regina Thurman, M.D.
5. Site 22330, CI: Barry McLean, M.D.
6. Site 22348, CI: Atoya Adams, M.D.

For each site, provide line listings for the following data (Note that numbered listings in parentheses below are the locations within the NDA submission corresponding to the requested data item):

1. Subject listing for treatment assignment
2. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated (Listing 16.2.2-1.1)
3. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued (Listing 16.2.2-1.2)
4. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol (Listing 16.2.1-2.2)
5. Listing of study medication accountability (compliance) and elapsed times and plasma concentration PK population (Listings 16.2.2-6.1 and 16.2.4)
6. By subject listing, of adverse events (AEs), serious adverse events (SAEs), deaths and dates (Listings 16.2.3-1.1 through 16.2.3-1.6)
7. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation (Listings 16.2.1-2 and 16.2.1-5.1)
8. By subject listing of the endpoint efficacy parameters. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

- a. Specifically, we are requesting the rescue laxative eDiary (Listing 16.2.2-2.1.)
 - b. We are also requesting the daily diary results for the bowel movement and constipation assessment diary. The data listing submitted in the NDA contain only the derived data of “SBM responder.”
9. By subject listing of concomitant medications (Listings 16.2.1-7.1 through 16.2.1-7.5)
10. By subject listing of:
- a. Numeric Rating Scale for pain (NRS), (Listing 16.2.3-6.1)
 - b. Clinical Opiate Withdrawal Scale (COWS) Scores with and without Abdominal Pain Score (Listing 16.2.3-7.1.1)
 - c. COWS Scores for Subjects with COWS score ≥ 5 post-dose and Change from Baseline ≥ 1 (Listing 16.2.3-7.1.2)
 - d. Elevated COWS Corresponding to COWS score ≥ 5 post-dose and Change from Baseline ≥ 1 (Listing 16.2.3-7.1.3)

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

CHERONDA L CHERRY-FRANCE
06/07/2016

From: [Cherry-France, Cheronda](#)
To: "Chen, Ting"
Subject: RE: Question related to D-120 safety update - clarification for the updated dataset
Date: Monday, June 06, 2016 5:39:37 PM

Hi Ting: (Here is our response to your query about 120-day safety update)

We agree with your general plan for the 120-day safety update to submit a (1) Supplemental Report for Study V9235 and (2) updated, integrated datasets for Study V9235 that includes both the Core Period and Supplement Period (STDM; ADaM; Define file; Reviewer Guide). However, we request that you also submit integrated analyses using data from both the Core Period and Supplement Period for the following information:

- Subject dropouts and discontinuations
- Study drug exposure (see 3 shell tables below for information requested)
- Cardiovascular adverse events
- MACE subgroup of cardiovascular adverse events

Shell Table 1 for Integrated Study Drug Exposure Results

	Naldemedine 0.2 mg (N=)	Placebo (N=)
Duration Category: n (%)		
≥1 day to <4 weeks		
≥4 weeks to <8 weeks		
≥8 weeks to <12 weeks		
≥12 weeks to <16 weeks		
≥16 weeks to <20 weeks		
≥20 weeks to <24 weeks		
≥24 weeks to <28 weeks		
≥28 weeks to <32 weeks		
≥32 weeks to <36 weeks		
≥36 weeks to <40 weeks		
≥40 weeks to <44 weeks		
≥44 weeks to <48 weeks		
≥48 weeks to <52 weeks		
≥52 weeks		

Shell Table 2 for Integrated Study Drug Exposure Results

	Naldemedine 0.2 mg (N=)	Placebo (N=)
Duration Category: n (%)		
≥1 day		
≥4 weeks		
≥8 weeks		

≥12 weeks		
≥16 weeks		
≥20 weeks		
≥24 weeks		
≥28 weeks		
≥32 weeks		
≥36 weeks		
≥40 weeks		
≥44 weeks		
≥48 weeks		
≥52 weeks		

Shell Table 3 for Integrated Study Drug Exposure Results

	Naldemedine 0.2 mg (N=)	Placebo (N=)
Duration (days)		
Mean (SD)		
Median		
Range (min, max)		
Total patient-years ^a		

^a Total patient-years is calculated as the sum of the duration of treatment exposure in years for all patients in the safety analysis set (i.e., received ≥1 dose of study medication).

Thanks,

Roni

From: Cherry-France, Cheronda
Sent: Monday, June 06, 2016 12:39 PM
To: 'Chen, Ting'
Subject: RE: Question related to D-120 safety update - clarification for the updated dataset

This is to acknowledge receipt. I will reach out to the team and get back with you shortly.
 Thanks,
 Roni

From: Chen, Ting [<mailto:tchen@shionogi.com>]
Sent: Monday, June 06, 2016 12:26 PM
To: Cherry-France, Cheronda
Subject: Question related to D-120 safety update - clarification for the updated dataset

Dear Roni,

Per my voice message, we would like to seek a clarification related to the dataset submission for the

D-120 safety update. At the Pre-NDA meet we had reached agreement with the agency regarding the submission of D-120 safety update (see Discussion 1): we will submit the Supplemental Report and updated dataset for Study V9235: the updated dataset includes the Core Period and Supplement Period (Integrated dataset for V9235 which include: STDM; ADaM; Define file; Reviewer Guide). Is our interpretation correct?

Best regards,
Ting

Discussion 1:

The FDA and the sponsor agreed that the initial dataset is acceptable for the NDA submission, given that the goal of the safety study evolved from a CVOT to a general safety study, and there will be sufficient safety data at the time of NDA submission to support initiation of review. The sponsor will submit a summary report including only the supplemental data and an integrated dataset for Study 1326V9235 at or before the day 120 safety update. The FDA considers these data important to support the NDA but cautioned that the submission could result in a review clock extension depending on the amount of data submitted, as well as if any safety signals are identified during the initial review of safety data.

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/s/

CHERONDA L CHERRY-FRANCE
06/06/2016



NDA 208854

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Shionogi Inc.
Attention: Ting Chen
Senior Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms.Chen:

Please refer to your New Drug Application (NDA) dated and received March 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Symproic (naldemedine) oral tablets 0.2 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **March 23, 2017**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

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, mid-cycle, 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 **December 15, 2016**. In addition, the planned date for our internal mid-cycle review meeting is **August 16, 2016**. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. We have identified a discrepancy between the ITT population of Study 1315V9232 reported in the Analysis Data Reviewer’s Guide versus the Clinical Study Report. The Analysis Data Reviewer’s Guide for Study 1315V9232 (Section 3.4) states that two subjects were randomized in Study 1315V9232 and subsequently also randomized in Study 1326V9235, and therefore, these subjects were excluded from the ITT population as well as the Safety, PP, and mITT populations of Study 1315V9232. However, the Clinical Study Report for Study 1315V9232 (Figure 10-2, pg. 67) states that three randomized patients were excluded from the Study 1315V9232 ITT population due to double enrollment in Studies 1315V9232 and Study 1326V9235. Please provide a listing of randomized patients in Study 1315V9232 who were excluded from the ITT population and the reasons for exclusion.
2. You have not provided a complete listing of protocol deviations and violations for Study 1326V9235 (as of the data cutoff date of 24 June 2015). The submitted SDTM dataset (DV) only lists 6 protocol deviations [“Double enrollment at different sites per subject” (n=5) and “No study drug administration during treatment period” (n=1)], and only two are listed in the Protocol Deviation section (Section 16.2.2, Listing 16.2.1-2) of the Study 1326V9235 Clinical Study Report (2 misrandomized subjects). Provide .xpt datasets [STDM (DV) and ADaM (ADDV)] which include all protocol deviations and violations for Study 1326V9235, as of the data cutoff date of 24 June 2015.
3. For each of the three phase 3 studies conducted in subjects with opioid-induced constipation (OIC) and chronic non-cancer pain (Studies 1314V9231, 1315V9232, and 1326V9235), please submit calculations of total study drug exposure expressed in total patient-years (i.e., the sum of the duration of treatment exposure in years for all patients in the trial’s safety analysis dataset) using the format of the following table.

Clinical Trial	Study Treatment Arm			
	Naldemedine 0.2 mg		Placebo	
	Safety Analysis Population (n)	Study Drug Exposure (patient-years)	Safety Analysis Population (n)	Study Drug Exposure (patient-years)
1314V9231				
1315V9232				
1326V9235				

4. Please provide a list of all data collected via the eDiary [e.g., daily opioid medication use (maintenance and breakthrough), study medication compliance, rescue medication use (bisacodyl or other laxatives), SOWS scores, 11-point NRS scores, etc.].

5. Please provide the information requested below for Protocols 1314V9231, 1315V9232, and 1326V9235, the three phase 3 clinical trials conducted in subjects with OIC and chronic, non-cancer pain.
 - a. To facilitate our understanding of how subject symptom data were used to determine response, recurrence, and eligibility, and were transmitted from eDiaries during the clinical trial and prepared for submission to the Agency, please provide a flow diagram and narrative that tracks the course of data generated by the subject using the eDiaries. Please describe how the data were collected, transmitted and reviewed. This should include a description concerning data reviewed by the clinical investigator during the trial, data that were used to populate the case report form (CRF) and data that were used for analysis. The diagram should identify who was responsible for each step in the process; including description of what entity (e.g., clinical investigator, automatic population from eDiaries, calculation from sponsor program, etc.) was responsible for calculation of eligibility and determination of response. Please note specific points in dataflow where an audit trail exists.
 - b. Please provide a flow diagram and narrative that tracks the course of the eDiary data to the clinical investigator (CI) for archiving at the end of the trial so that the CI will be able to fulfill the responsibilities under 21CFR312.62.
 - c. Provide the name of the CRO, if any, responsible for the eDiary system for the diary data.
 - d. Provide the location or locations of the documents related to the information request above (e.g., in clinical trial file at sponsor site, at CRO, etc.) and the location of the diary data (e.g., at investigator site, sponsor site, at CRO, etc.)
 - e. Submit the Patient eDiary guide, the site guide, and any other guides provided to clinical site staff and patients.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified format items from the SRPI checklist and have additional high-level content and format comments and requests for additional information for you to consider (see attached PI). We request you (b) (4) Medication Guide, to be consistent with other drugs in the class.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **July 1, 2016**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

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

PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

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 reference the waiver granted on May 11, 2016 and referenced IND 107475, for the pediatric study requirement for this application.

If you have any questions, call LCDR Cheronda Cherry-France, Regulatory Project Manager, at (301) 796-7295.

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

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

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/s/

DONNA J GRIEBEL
06/03/2016

From: [Cherry-France, Cheronda](#)
To: [Chen, Ting](#)
Cc: [Lesnick, Marc](#)
Subject: IND 107475 (naldemedine) Agreed iPSP needed ASAP
Date: Friday, May 06, 2016 7:24:59 AM
Attachments: [IND 107475 Sponsor's Copy.pdf](#)
Importance: High

Hi Ting:

We have an *ongoing* review of application NDA 208854 and realized that that for IND 107475 there is no agreed iPSP on file. Therefore, submit an "**Agreed Initial Pediatric Study Plan**" in WORD and PDF formats ASAP. I have also attached a copy of the correspondence that was sent on January 21, 2014 electronically.

We have the following comments and requests:

- We have completed our review of the initial Pediatric Study Plan and request for a waiver from PREA. We acknowledge that you do not intend to conduct studies in pediatric subjects and will submit a request for waiver from all requirements from PREA in a marketing application for S-297995 (naldemedine) Tablets.
- Please submit a letter within 90 days of receipt of this communication, stating your agreement or disagreement with our understanding of the initial Pediatric Study Plan.

There is no indication that the highlighted correspondence was received. It would have been due to the agency around April 21, 2014.

If you have any questions, please email or call.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

*White Oak Building 22 Room: 5237
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-7295 (office)
(301) 796-9906 (fax)
Cheronda.Cherry-France@fda.hhs.gov

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notify us immediately by telephone at (301) 796-6295. Thank you.

*****Secure Email*****

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). It is the only way FDA can communicate confidential information to you via email. If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/s/

CHERONDA L CHERRY-FRANCE
05/10/2016

From: [Cherry-France, Cheronda](#)
To: [Chen, Ting](#)
Cc: ["Lesnick, Marc"](#)
Subject: NDA 208854 Symproic (naldemedine) Clinical Information Request: Due COB Friday, May 6th
Date: Thursday, May 05, 2016 8:03:44 AM

Hi Ting: **Clinical Information Request: Due COB Friday, May 6, 2016**

In the "EX" SDTM datasets submitted for the phase 3 clinical trials, we have identified discrepancies between the exposure end dates in the "EDC" and "EDIARY" Exposure Categories (EXCAT) for some subjects. Please provide the following information:

- Clarification of how the exposure end date was defined and reported for each of the exposure categories (EDC and EDIARY) in the "EX" SDTM datasets;
- Reason(s) for these observed discrepancies between exposure end dates for the EDC and EDIARY exposure categories (data under the variable term "EXENDTC");
- Instructions for which variables and datasets should be used to determine the actual end date of exposure for all subjects; i.e., actual date of a subjects' last administered dose prior to discontinuation or the cutoff date used for your submitted data analyses.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/s/

CHERONDA L CHERRY-FRANCE
05/05/2016



NDA 208854

INFORMATION REQUEST

Shionogi Inc.
Attention: Ting Chen, M.S.
Senior Director Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Mr. Chen:

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

We also refer to your March 23, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections 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.

We have the following information request for Drug Substance:

1.

(b) (4)

2. *Provide Certificates of Analysis of all reagents, solvents and auxiliary materials used in the synthesis of naldemedine tosylate drug substance.*

3. *Identify (b) (4) b) naldemedine tosylate used in the syntheses of all naldemedine tosylate drug substance batches.*

4.

(b) (4)

5. Provide detailed rationale for the changes implemented to the manufacturing processes of naldemedine tosylate during development (b) (4)

6. (b) (4)

7. An enantioselective determination of your chiral drug substance should be part of the specification. Justify the use of a (b) (4) for assay in the drug substance specifications.

8. You state in 3.2.S.4.5 Justification of Specification, p. 13:

(b) (4)

Provide experimental evidence to validate these statements.

9. (b) (4) is included as a test conducted during stability evaluation of your drug substance. Include a test for (b) (4) as part of the release specifications for the naldemedine tosylate drug substance.

10. Provide justification for manufacturing the three commercial drug substance batches at approximately (b) (4) the size of the pilot-scale size. Also, provide the intended batch size of proposed future commercial batches of naldemedine tosylate drug substance.

11. The reference standard for naldemedine tosylate should be updated with material obtained from a drug substance batch representative of the current manufacturing process. Although the Certificate of Analysis provided for the current naldemedine tosylate reference standard (RS88001) is adequate, this batch was manufactured in 2008 using the previous (b) (4) manufacturing process. A retest period beyond (b) (4) months has not been established for the drug substance.

In addition we have the following information request for Process:

1. On page 7 of 3.2.P.2.1 (Pharmaceutical Development Report section Components of the Drug Product) (b) (4) (b) (4) (b) (4). If detection method is used, provide method validation information, including method sensitivity and selectivity.

2.

(b) (4)

3.

If you have any questions, please contact me, at (240) 4025826 or at truong.quach@fda.hhs.gov.
Please respond by **5/15/2016**.

Sincerely,

Truong
Quach -S

Digitally signed by Truong
Quach -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.100.1.1=2001
511949
Date: 2016.04.29 10:00:37 -0400

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: [Cherry-France, Cheronda](#)
To: ["Chen, Ting"](#)
Cc: [Lesnick, Marc](#)
Subject: NDA 208854 Symproic (naldemedine) IR from PBPK Reviewer due COB May 15th
Date: Tuesday, April 19, 2016 12:40:22 PM
Importance: High

Hi Ting:

Provide this information below by the end of business day on **May 15, 2016**.

We have conducted initial review of your PBPK report that predicts drug-drug interaction (DDI) between efavirenz and naldemedine. Provide the following information for review:

1. Simulations of the effect of a strong CYP3A inhibitor (itraconazole) on the exposure of naldemedine using your final naldemedine PBPK model. Simulation conditions should be the same as those described in your Clinical Study 1502V921E. Simulated naldemedine exposure changes should be compared with observed values.
2. Provide the model files used to generate the final PBPK simulations described in your PBPK report (including simulations related to the PK and DDI for naloxegol and efavirenz) and those requested in item 1. These files include, but are not limited to drug model files, population files, and workspace files (.cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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Cheronda.Cherry-France@fda.hhs.gov

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/s/

CHERONDA L CHERRY-FRANCE
04/19/2016

From: [Cherry-France, Cheronda](#)
To: "tchen@shionogi.com"
Subject: NDA 208854 (naldemedine) IR Clinical Pharmacology and biopharmaceutics studies: (Due no later than 12:00PM (EST), April 25, 2016)
Date: Friday, April 15, 2016 9:16:20 AM

Hi Ting: (Due no later than 12:00PM (EST), April 25, 2016)

Electronic datasets could not be located for the phase 1 Clinical Pharmacology and biopharmaceutics studies (with the exception of the thorough QT study). Please submit the datasets, including demographic information, in SAS transport file format. If the information has already been included in the NDA submission, provide the exact location for our review. If you have any questions, please email or call.

Thanks,

Roxi

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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CHERONDA L CHERRY-FRANCE
04/15/2016

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Subject: NDA 208854 Clin Pharm and Cardiac Safety IR request Due by 12:00PM April 11th
Date: Thursday, April 07, 2016 5:16:16 PM
Attachments: [NDA 208854 Highlights ClinPharm and Cardiac Safety. Information Request due noon April 11.doc](#)
Importance: High

Hi Ting:

Attached in this email is the table below. Please complete the attached ClinPharm and Cardiac Safety Table and send it back to us by **12:00PM (Eastern Standard Time) April 11, 2016**. I will let you know if any additional information is needed once the team has had the chance to look into the submission in detail.

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC

	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

Thanks,

Roxi

Cheronda Cherry-France, RN BSN MHA
 LCDR, U.S. Public Health Service Commissioned Corps
 Regulatory Health Project Manager
 Division of Gastroenterology and Inborn Errors Products
 Office of Drug Evaluation III
 CDER/FDA

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/s/

CHERONDA L CHERRY-FRANCE
04/07/2016

From: [Cherry-France, Cheronda](#)
To: ["tchen@shionogi.com"](mailto:tchen@shionogi.com)
Cc: [Carr, James](#)
Subject: NDA 208854 Symproic (naldemedine)
Date: Thursday, March 31, 2016 7:20:49 AM

Good Morning, Mr./Ms. Chen:

I am happy to inform you that I (LCDR Roni Cherry-France) will be Regulatory Project Manager managing NDA 208854 Symproic (naldemedine) for CDR James Carr.

Shionogi requested the following via email:

Could you please let me know when I will be receiving the acknowledgment letter? **Within 14 Days of initial submission dated on March 23** (I will also plan to go give you a call around Tuesday or Wednesday of next week to introduce myself. ☺)

Also, when will I expected to receive the Day-60 and Day-74 letters, do I need to add 60-days to the review timeline, i.e.: Day-60 is around July 23 and D-74 letter will be around Aug 8?

For NDAs, a separate 60-day filing letter does not need to be issued, if fileable (pending upon review; I will keep you posted)

We are in the process of reviewing your application and I wanted to confirm a couple of forms. This may be an oversight and if you could just let me know that will be great.

- 1) Financial Disclosure : (I see the reference, and not a signature page. It states attached, but I do not see it.)

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].

- 2) Clinical Trials Database: (I do not see this form)

Is form FDA 3674 included with authorized signature?

If yes, ensure that the application is also coded with the supporting document category, "Form 3674."

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

CHERONDA L CHERRY-FRANCE
03/31/2016



IND107475

MEETING MINUTES

Shionogi Inc.
Attention: Ting Chen, MS
Senior Director, US Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Naldemedine (S-297995) tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 30, 2015. The purpose of the meeting was to obtain concurrence on the details of the submission of the information in a New Drug Application to be filed in first half of 2016. This follows the phase 3 studies of naldemedine in the treatment of opioid-induced constipation (OIC) in subjects with chronic non-cancer pain receiving opioid therapy.

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

If you have any questions, call me, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

LCDR James Carr, MPAS, PA-C
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research Center for
Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 30, 2015, 9:30AM-10:30AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: 107475
Product Name: Naldemedine (S-297995) tablets
Indication: **Opioid induced constipation**
Sponsor/Applicant Name: Shionogi Inc.

Meeting Chair: Laurie Muldowney
Meeting Recorder: James Carr

FDA ATTENDEES

Amy Egan, M.D., M.P.H., Deputy Director (acting), Office of Drug Evaluation III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs, Office of Drug Evaluation III
Laurie Muldowney, M.D., Acting Clinical Team Leader, Division of Gastroenterology and Inborn Errors Products
Dina Zand, M.D., Medical Officer Reviewer, Division of Gastroenterology and Inborn Errors Products
Sushanta Chakder, Ph.D. Supervisory Pharmacologist, Division of Gastroenterology and Inborn Errors
Tracy Bersing, Ph.D., Non Clinical Reviewer, Division of Gastroenterology and Inborn Errors Products
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III
Lisa Lin, M.B.A., Senior Regulatory Analyst, OBI/eData
Susan Leibenhaut, M.D., Acting Team Leader, Division of Good Clinical Practice Compliance
Shahla Farr, Ph.D., Statistical Reviewer, Division of Biometrics III
James Carr, MPAS, PA-C, Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products

SPONSOR ATTENDEES

Tohko Arai, Manager, Drug Safety Evaluation, Research Laboratory for Development, Shionogi & Co., Ltd.
Tsutae Den Nagata, M.D., Ph.D., FFPM, Chief Medical Officer, Shionogi & Co., Ltd.
Yoichi Sato, Head Global Regulatory Affairs, Shionogi & Co., Ltd.
Toshihiro Wajima, Ph.D., Senior Director, Head of Clinical Pharmacology & Pharmacokinetics, Shionogi & Co., Ltd.
Tomoyuki Yukizawa, M.P.H., Global Project Leader, Global Project Management, Shionogi & Co., Ltd.
Juan Camilo Arjona Ferreira, M.D., Senior VP Clinical, Clinical Development & Medical Affairs, Shionogi Inc.
Ting Chen, M.S., Senior Director, Regulatory Affairs, Global Development Projects, Shionogi Inc.
Marc Lesnick, Ph.D., Senior VP Regulatory Affairs, Shionogi Inc.
Glenn O'Brien, B.S., Associate Director, Statistical Programming, Shionogi Inc.
Jysotsu Reddy, M.D., Medical Director, Clinical Development, Shionogi Inc.
Amrik Shah, Ph.D., Senior Director, Biostatistics, Shionogi Inc.
Tadaaki Yamada, M.S., Senior Manager, Biometrics, Shionogi Inc.

1.0 BACKGROUND

The initial Investigational New Drug (IND) Application (IND 107475) was submitted to the FDA on March 26, 2010. IND 107475 is being developed for the indication and treatment of opioid induced constipation (OIC). Shionogi would like to obtain concurrence on the details for submission of the New Drug Application (NDA) to be filed in the first half of 2016.

2. DISCUSSION

2.1. Regulatory

Question 1: *As agreed at the Type C meeting on September 18, 2014, Shionogi will submit the additional safety information from Study 1326V9235 in the Day-120 Safety Update. In addition, Shionogi plans to submit as part of the Day-120 Safety Update the safety information from the two on-going Japanese studies 1336V9238 (N=40) and 1339V9239 (N=10). Does the Agency agree with this approach?*

FDA Response to Question 1:

No we do not agree. It is acceptable to update the safety information from the two ongoing Japanese studies in the Day-120 Safety Update, however, Study 1326V9235 should be complete at the time of NDA submission.

Discussion 1:

The FDA and the sponsor agreed that the initial dataset is acceptable for the NDA submission, given that the goal of the safety study evolved from a CVOT to a general safety study, and there will be sufficient safety data at the time of NDA submission to support initiation of review. The sponsor will submit a summary report including only the supplemental data and an integrated dataset for Study 1326V9235 at or before the day 120 safety update. The FDA considers these data important to support the NDA but cautioned that the submission could result in a review clock extension depending on the amount of data submitted, as well as if any safety signals are identified during the initial review of safety data.

Question 2: *Shionogi plans to request*

(b) (4)

(b) (4)

(b) (4) *Does the Agency agree to*

(b) (4)

- *Shionogi plans to submit a request for*

(b) (4)

FDA Response to Question 2:

(b) (4)

2.2. Clinical

Question 3: *With regard to the proposed format for integration of efficacy, does the Agency agree with the Summary of Clinical Efficacy (SCE) outline including the statistical analysis plan and draft shell report?*

FDA Response to Question 3:

The proposed format for your SCE appears to be acceptable.

Question 4: *With regard to the proposed format for integration of safety:*

a. Does the Agency agree with the Summary of Clinical Safety (SCS) outline including the statistical analysis plan and draft shell report?

b. Does the agency agree with the selection of adverse events of particular interest?

FDA Response to Question 4:

- a. The SCS seems generally acceptable. See response to Question 6.
- b. The proposed adverse events of particular interest appear acceptable, however, based on a recent safety report received of a single case of potential liver injury, hepatocellular injury should be included as an adverse event of particular interest (See response to Question 6). In addition, please refer to the Meeting Minutes from the Type C Meeting on 18 September 2014 for detailed comments regarding opioid withdrawal and pain assessment.

Question 5: *Shionogi does not plan to present separate ISS and ISE documents. Instead, in addition to the SCE and SCS presented in Module 2, 2.7.3 and 2.7.4, respectively, Shionogi plans to present all additional tables, listings and figures corresponding to ISS/ISE in Module 5, M5.3.5.3, where the ISS and ISE would be located. Does the Agency agree?*

FDA Response to Question 5:

We do not agree. The ISE and ISS are required in applications submitted to the FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively). While there may be exceptions to this requirement, as you have conducted multiple efficacy trials in the same population for this indication, a separate ISE and ISS are required. Although one of the goals of the ISE and ISS is to summarize the available effectiveness and safety data, these documents are intended to provide an integrated analysis, going beyond a simple summary. The Module 2 Summaries of Clinical Safety and Efficacy are intended to provide data summaries; however, these documents are not intended to provide the needed level of detail appropriate for an ISS/ISE. Rather Section 2.73 and 2.74 should contain summarized information derived from the full ISS and ISE, respectively. FDA has a number of relevant Guidance documents which provide additional recommendations on how to construct these summaries, including: Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document and Guidance for Industry M4E: The CDT – Efficacy.

<http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

Question 6: *Shionogi only plans to submit in the NDA case report forms (CRFs) and serious adverse event (SAE) narratives for all SAEs reported for patients with OIC in chronic non-cancer pain studies. Does the Agency agree?*

FDA Response to Question 6:

No, we do not agree. Based on a recent safety report received 4 September 2015 of a single case meeting Hy's law criteria, you should also submit narratives/clinical summaries for all reported cases of liver injury and/or hepatitis which occurred in clinical trials under this IND including the following information, as available:

- a clinical summary including laboratory test results and concomitant medications, from the time of enrollment in the relevant study to the most recent follow-up
- time course of AE from initiation of therapy, as well as any information on dechallenge and rechallenge, if available
- assessment of relatedness to naldemedine (S-297995)

In addition, you should summarize any cases meeting the Hy's law laboratory criteria for drug-induced liver injury ($ALT \geq 3 \times ULN$ and bilirubin $\geq 2 \times ULN$ at the same visit). Finally, you should provide summary tables describing abnormal liver related clinical lab values from each of your completed and ongoing studies. This should include:

- ALT
 - ULN to $\leq 3.0 \times ULN$
 - $>3.0 \times ULN$ to <5 to $\leq 10 \times ULN$
 - $>10 \times ULN$
- AST
 - ULN to $\leq 3.0 \times ULN$
 - $>3.0 \times ULN$ to <5 to $\leq 10 \times ULN$
 - $>10 \times ULN$
- Bilirubin
 - ULN to $\leq 2 \times ULN$
 - $>2 \times ULN$

Discussion 6:

The sponsor will provide the data requested in FDA's response to question #6 for all studies of naldemedine in which a control arm was used. This includes studies conducted in Japan and not under the IND.

Question 7: Individual datasets for all Phase 3 studies in OIC patients with chronic non-cancer pain and TQT study will be submitted to the Agency. Pooled SCS/SCE derived datasets (format and details of datasets provided below) will also be submitted.

Does the Agency agree?

a. The naldemedine eCTD submission will contain 2 types (SDTM and ADaM) of datasets, both to be submitted in SAS Version 5 transport file format with corresponding documentation:

i. SDTM datasets (version 3.1.2) with *define.xml* documentation and the annotated CRF (*acrf.pdf*) for studies 1204V9219, 1314V9231, 1315V9232 and 1326V9235

ii. ADaM datasets with *define.xml* documentation will be provided for studies 1314V9231, 1315V9232 and 1326V9235

b. In addition, harmonized analysis datasets used for the SCE (1314V9231, 1315V9232) and SCS (1107V9221, 1314V9231, 1315V9232 and 1326V9235) will be provided

FDA Response to Question 7:

A1. Your approach is acceptable. Please also submit the study data review's guide

A2. Your approach is acceptable. Please also submit the analysis data review's guide. Regarding the analysis data for the TQT study (i.e., 1204V9219), although it is not a requirement, we request that you include them in the NDA submission to assist our review.
B. Your approach is acceptable.

Please also see our responses to Question 5 regarding the ISS and ISE. Please be sure to submit the data for the two pivotal Phase 3 studies, individually, for our review and analyses.

Discussion 7:

The FDA finds the sponsor's proposed approach acceptable.

Question 8: Programs (SAS code) for the analysis of the primary and key secondary efficacy endpoints for the two pivotal Phase 3 studies (1314V9231 and 1315V9232) will be submitted in ASCII (*.TXT) and PDF format. Does the Agency agree?

FDA Response to Question 8:

This is acceptable; however, in addition to the programs for analyzing the primary and secondary endpoints, please also submit your analysis programs that were used to derive the analysis data from the raw data to assist our review.

Discussion 8:

The FDA finds the sponsor's proposed approach acceptable.

Question 9: Does the Agency agree with the clinical pharmacology package including population PK and PK/PD analyses and consider it to be sufficient for the filling of an NDA?

FDA Response to Question 9:

In general, the proposed Clinical Pharmacology package appears adequate for the NDA submission. Your Pop PK and PK/PD plan appears reasonable. If the patient population, trial design and end point are same, we recommend you to pool the data from various trials to perform PK/PD analysis for efficacy and safety. For general expectations of submitting pharmacometric data and models, please refer to the following website, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDE/R/ucm180482.htm>.

The following additional Clinical Pharmacology aspects need to be addressed at the time of NDA submission:

1. Potential for drug interaction of naldemedine with gastric acid reducing agents (e.g., PPIs, H2-blockers, and antacids); please refer to agency meeting minutes dated March 15, 2013 in this regard.
2. Drug-drug interaction potential of major metabolite(s) of naldemedine as pertaining to major drug metabolizing enzymes and transporters (DDI should be initially assessed *in vitro*; *in vivo* studies may be needed depending on the results of these studies).
3. Bioanalytical method validation reports and study sample assay reports for review.

Discussion 9:

Regarding the absence of DDI studies with gastric acid reducing agents, the FDA finds the sponsor's proposed solubility based rationale to be reasonable. The sponsor will submit the justification in the NDA submission for FDA review.

The FDA agrees that the potential for drug-drug interactions with metabolites needs to be addressed if the metabolite(s) represent $\geq 25\%$ of parent drug AUC. The sponsor needs to adequately justify the observed differences in the percentage of metabolites (ranging from $\sim 7\%$ to 28% for nor-naldemedine based on information in the Investigator's Brochure) relative to parent exposure in the various phase 1 and phase 2 clinical trials and provide a thorough explanation in the NDA if DDI studies for metabolite(s) are not conducted. The sponsor should refer to the agency's drug-drug interaction guidance in this regard, specifically section IV.A.3: "Considerations of the metabolites of investigational drugs", as they address this issue.

Question 10: *With regard to PK data, all datasets used for the population PK analyses including dosing and covariate information (NONMEM datasets) will be provided as SAS transport files from all Phase 1, 2 and 3 studies in which PK samples were collected. Does the Agency agree?*

FDA Response to Question 10:

Yes, we agree.

2.3. Non-Clinical

Question 11: *Does the Agency agree with the described nonclinical pharmacology, DMPK and toxicology package and consider it to be sufficient for a filing of an NDA?*

FDA Response to Question 11:

Yes, your nonclinical program appears to be adequate to support the filing of an NDA.

Question 12: *Does the Agency agree that the described abuse potential studies have fully characterized the abuse potential of naldemedine? Does the Agency need any other information to ensure naldemedine (b) (4) product upon approval?*

FDA Response to Question 12:

No, we do not agree. It is not possible to determine whether a thorough abuse potential assessment has been conducted until you have completed your three ongoing animal abuse liability studies (a drug discrimination study in rats, a self-administration study in monkeys, and a physical dependence study in rats). These data will inform our decision regarding whether there are abuse-related signals that demonstrate the need for a human abuse potential study.

Your abuse potential evaluation should be based on the studies described in the 2010 Guidance for Industry: Assessment of Abuse Potential of Drugs. A complete abuse potential assessment for naldemedine will be comprised of data from all abuse-related preclinical and clinical studies submitted in the NDA. Clinical data typically include a summary of abuse-related adverse events from clinical studies, as well as the results from a human abuse potential (HAP) study, if required. In general, a HAP study is necessary unless data from the animal and human studies show there are no abuse signals. If a HAP study is required, CSS is available to review the design of the study prior to its initiation. The final report for a completed HAP study, if it is necessary, must be included at the time of NDA submission.

Once your abuse potential assessment is complete and included in your submitted NDA, we will evaluate naldemedine to determine whether it has abuse potential and whether a scheduling action under the CSA is supported. If a review of all abuse-related data by CSS shows that naldemedine does not have abuse potential that warrants scheduling, we will recommend decontrol.

However, the final decision regarding whether a drug will be decontrolled is made by the Drug Enforcement Administration.

Question 13: *With regard to raw data sets from nonclinical studies Shionogi will provide the tumor datasets for the mouse and rat carcinogenicity studies. Does the Agency find this acceptable?*

FDA Response to Question 13:

Yes, your proposal is acceptable.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our DATE communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an

original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any

previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission

[21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

7.0 MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

8.0 Office of Scientific Investigations (OSI) Requests

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 those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to 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 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

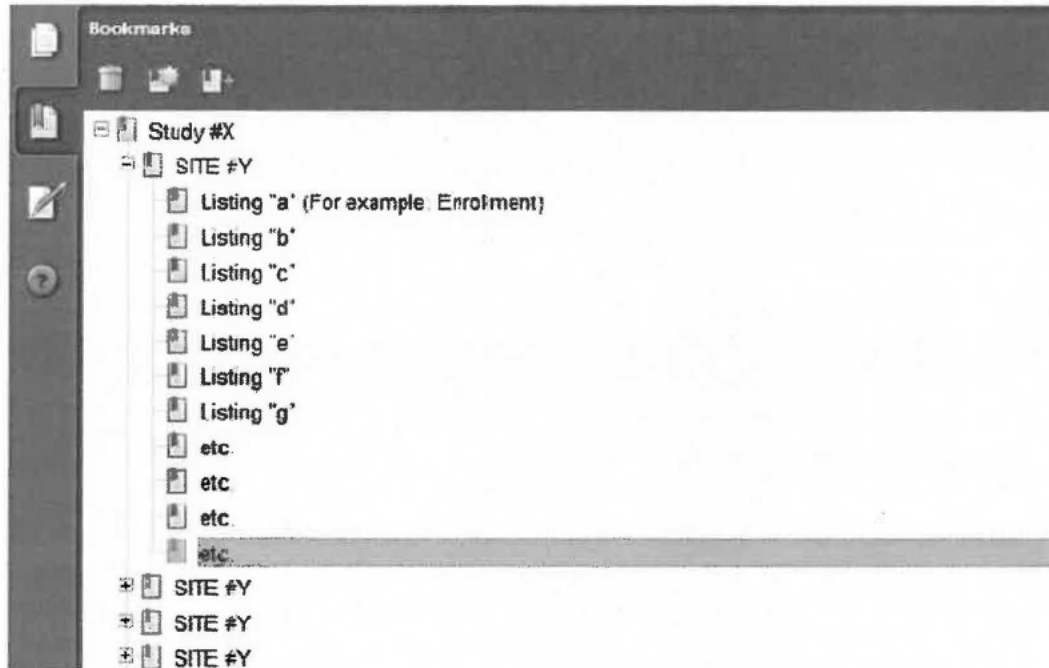
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

- 1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal 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. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.**
- 2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:**
 - a. Number of subjects screened at each site**
 - b. Number of subjects randomized at each 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 pivotal clinical trials:**
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection**

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - 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, including a 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 testing (e.g., laboratory, ECG) 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. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft **Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning**” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1**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 Item¹	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:**

```

[ ] [m5]
  [ ] datasets
    [ ] bimo
      [ ] site-level

```

- 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.**

¹ Please see the OSI Pre-NDA/BLA 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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

NONE

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor responses for further discussion (attached)

Shionogi would like to seek further clarifications during our meeting for Questions 1, 6, 7, 8, 9 in response to the Agency's pre-meeting comments.

Question 1: *As agreed at the Type C meeting on September 18, 2014, Shionogi will submit the additional safety information from Study 1326V9235 in the Day-120 Safety Update. In addition, Shionogi plans to submit as part of the Day-120 Safety Update the safety information from the two on-going Japanese studies 1336V9238 (N=40) and 1339V9239 (N=10). Does the Agency agree with this approach?*

FDA Response to Question 1:

No we do not agree. It is acceptable to update the safety information from the two ongoing Japanese studies in the Day-120 Safety Update, however, Study 1326V9235 should be complete at the time of NDA submission.

Sponsor's response:

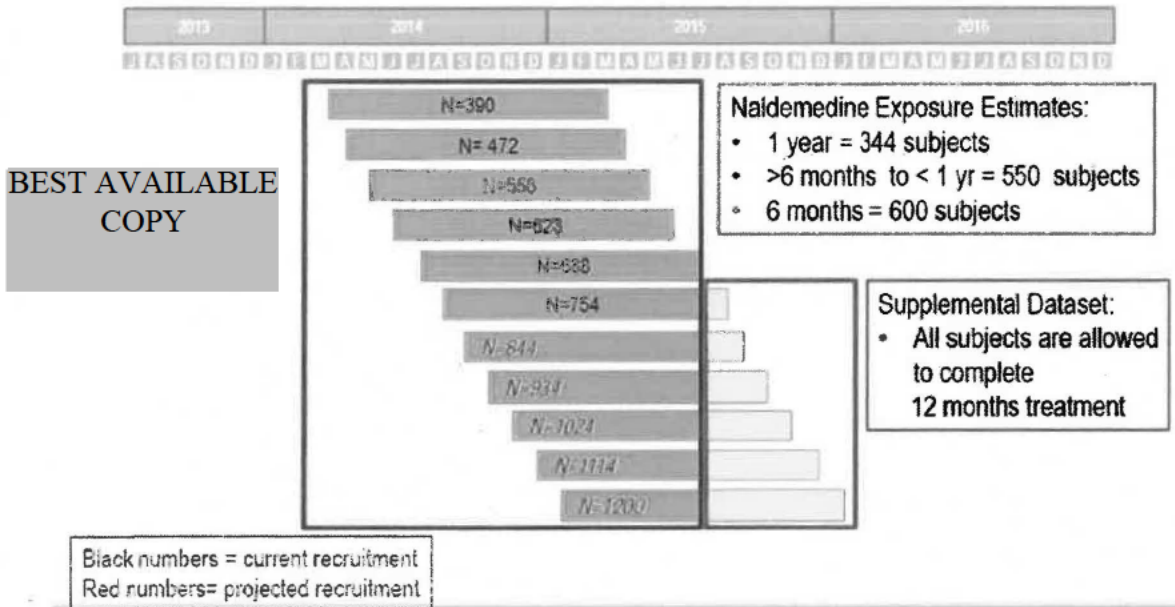
The Sponsor would like to clarify this question so that we can find an agreement that is consistent with the discussion held at the Type C meeting on September 18, 2014.

During that meeting, the Sponsor requested FDA's agreement with a proposal to reduce the sample size of Study 1326V9235 to 1200 subjects from 1500, given that after the June 11-12, 2014 AADP Advisory Committee, the requirement to rule out a certain level of cardiovascular risk was no longer required prior to approval, and 1200 subjects in Study 1326V9235 together with subjects from other studies in the program would ensure the number of subjects exposed would suffice to meet the ICH exposure guidance.

As described in the slideset included in the minutes from the Type C meeting, the Sponsor proposed to submit in the NDA a complete CSR for Study 1326V9235 submission dataset. The Submission Dataset will consist of 978 subjects (492 on naldemedine) with at least 6 months of treatment and 379 subjects (192 on naldemedine) with 1 year of treatment. As discussed at the meeting, subjects who had not completed a 52-week treatment at the end of the primary analysis period will continue to 12 months, and the data obtained beyond the primary analysis period would be considered supplemental (Supplemental Dataset) and this data would be submitted at the D120 safety update. (See Figure 1).

In summary, the NDA will include the CSR for Study 1326V9235 Submission Dataset and this data will be fully integrated into the ISS and ISE.

Figure 1. - NDA submission and supplemental datasets - Study 1326V9235



As captured in the minutes from the Type C meeting in September 2014, regarding the Safety Dataset for NDA submission, *the agency acknowledged that the expected number of Naldemedine exposed subjects at the time of NDA submission appeared reasonable because it was comparable to studies that other sponsors have conducted. The agency also expressed that they would like to see a complete dataset at the time of submission and agreed that the Sponsor would follow the patients and provide an update to the NDA after filing regarding safety. The agency suggested that details regarding the format of such submission would be discussed further at the pre-NDA meeting.*

During the meeting, FDA acknowledged that the Sponsor could end the study after the last subject had reached the 6-month visit, but recommended that the Sponsor continued Study 1326V9235 to ensure that the additional safety data was obtained, and the Sponsor concurred.

The Sponsor proposes to submit the safety data from the Supplemental Dataset at the time of the Day 120 safety update, as a summary, without updating the ISS, as was recommended during the Type C meeting by FDA.

Clarification question to the Agency: *The Sponsor believes that the proposed NDA safety package including the Submission Dataset as described above is sufficient and complete at the time of NDA submission and will meet the ICH exposure guidance. Does the agency agree?*

Question 6: *Shionogi only plans to submit in the NDA case report forms (CRFs) and serious adverse event (SAE) narratives for all SAEs reported for patients with OIC in chronic noncancer pain studies. Does the Agency agree?*

FDA Response to Question 6:

No, we do not agree. Based on a recent safety report received 4 September 2015 of a single case meeting Hy's law criteria, you should also submit narratives/clinical summaries for all reported cases of liver injury and/or hepatitis which occurred in clinical trials under this IND including the following information, as available:

- a clinical summary including laboratory test results and concomitant medications, from the time of enrollment in the relevant study to the most recent follow-up
- time course of AE from initiation of therapy, as well as any information on dechallenge and rechallenge, if available
- assessment of relatedness to naldemedine (S-297995)

In addition, you should summarize any cases meeting the Hy's law laboratory criteria for drug-induced liver injury (ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN at the same visit). Finally, you should provide summary tables describing abnormal liver related clinical lab values from each of your completed and ongoing studies. This should include:

ALT

- ULN to ≤ 3.0 xULN
- >3.0 xULN to <5 to ≤ 10 xULN
- >10 xULN

AST

- ULN to ≤ 3.0 xULN
- >3.0 xULN to <5 to ≤ 10 xULN
- >10 xULN

Bilirubin

- ULN to ≤ 2 xULN
- >2 xULN

Sponsor's response:

The Sponsor agrees to submit narratives/clinical summaries for all reported cases of liver injury and/or hepatitis which occurred in clinical trials under this IND. Given that the safety database will include a proportion of subjects from the clinical trials conducted in Japan in patients with cancer and opioid-induced constipation, and since those studies were not conducted under this IND, the Sponsor wants to confirm that narratives/clinical summaries for all reported cases of liver injury and/or hepatitis which may have occurred in those studies do not need to be submitted.

Does the agency agree?

Narratives/ clinical summaries for reported cases of liver injury and/or hepatitis will include a clinical summary (including laboratory test results and concomitant medications, from the time of enrollment in the relevant study to the most recent follow-up), the time course of AEs from

initiation of therapy, as well as any information on dechallenge and rechallenge, if available, and the assessment of relatedness to naldemedine, as requested by FDA.

Additionally, the Sponsor will summarize any cases meeting the Hy's law laboratory criteria for drug-induced liver injury (ALT ≥ 3 x ULN and bilirubin ≥ 2 x ULN at the same visit). When assessing/describing these cases, the Sponsor plans to follow the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

The Sponsor also plans to provide summary tables describing abnormal liver related clinical lab values from each of the completed and ongoing studies, including:

ALT

- ULN to ≤ 3.0 xULN
- >3.0 xULN to <5 to ≤ 10 xULN
- >10 xULN

AST

- ULN to ≤ 3.0 xULN
- >3.0 xULN to <5 to ≤ 10 xULN
- >10 xULN

Bilirubin

- ULN to ≤ 2 xULN
- >2 xULN

Although the Sponsor acknowledges that assessment of the safety of naldemedine is a review issue, the Sponsor wants to reassure the FDA by providing a summary of the assessment of liver function in the completed Phase 3 studies in subjects with OIC and non-cancer chronic pain. In the three Phase 3 studies of naldemedine in subjects with OIC and chronic non-cancer pain (1326V9231, 1326V9232, and 1326V9235) minimal, non-significant changes in mean ALT, AST and bilirubin have been observed in subjects treated with naldemedine that were not different from placebo. In these same studies, the number of subjects meeting predefined limits of change from baseline¹ at any time during the study period were low and similar in the naldemedine group and the placebo group. No subjects in the naldemedine group met these same predefined limits of change for liver function tests at the last value obtained in the study.

Question 7: *Individual datasets for all Phase 3 studies in OIC patients with chronic noncancer pain and TQT study will be submitted to the Agency. Pooled SCS/SCE derived datasets (format and details of datasets provided below) will also be submitted.*

Does the Agency agree?

¹ Predefined limits of change: ALT >3 xULN, ALT >5 xULN, ALT >10 xULN, ALT >20 xULN; AST >3 xULN, AST >5 xULN, AST >10 xULN, AST >20 xULN; ALT or AST >3 xULN, ALT or AST >5 xULN, ALT or AST >10 xULN, ALT or AST >20 xULN; Total Bilirubin increase $>50\%$ and $>ULN$; ALT or AST >3 xULN and Bilirubin >2 xULN, simultaneously; Alkaline phosphatase increase $>50\%$ and $>ULN$

a. The naldemedine eCTD submission will contain 2 types (SDTM and ADaM) of datasets, both to be submitted in SAS Version 5 transport file format with corresponding documentation:

i. SDTM datasets (version 3.1.2) with define.xml documentation and the annotated CRF (acrf.pdf) for studies 1204V9219, 1314V9231, 1315V9232 and 1326V9235

ii. ADaM datasets with define.xml documentation will be provided for studies 1314V9231, 1315V9232 and 1326V9235

b. In addition, harmonized analysis datasets used for the SCE (1314V9231, 1315V9232) and SCS (1107V9221, 1314V9231, 1315V9232 and 1326V9235) will be provided

FDA Response to Question 7:

A1. Your approach is acceptable. Please also submit the study data review's guide

A2. Your approach is acceptable. Please also submit the analysis data review's guide. Regarding the analysis data for the TQT study (i.e., 1204V9219), although it is not a requirement, we request that you include them in the NDA submission to assist our review.

B. Your approach is acceptable.

Please also see our responses to Question 5 regarding the ISS and ISE. Please be sure to submit the data for the two pivotal Phase 3 studies, individually, for our review and analyses.

Sponsor's response:

The Sponsor will provide the following for the submission:

A1 and A2

Study	SDTM datasets	Study Data Reviewer's Guide for SDTM (SDRG.PDF)	aCRF.PDF	SDTM define.xml	ADaM datasets	Analysis Data Reviewer's Guide for ADaM (ADRG.PDF)	ADaM define.xml
1204V9219	✓	✓	✓	✓	✓		✓
1314V9231	✓	✓	✓	✓	✓	✓	✓
1315V9232	✓	✓	✓	✓	✓	✓	✓
1326V9235	✓	✓	✓	✓	✓	✓	✓
ISS*					✓	✓	✓
ISE**					✓	✓	✓

✓ = will be provided as part of the submission. The ADRG.PDF for the 1204V9219 is not available.

* = pooled data for 1107V9221, 1314V9231, 1315V9232, 1326V9235.

** = pooled data for 1314V9231, 1315V9232.

The data for the two pivotal Phase 3 studies, 1314V9231 and 1315V9232, will be submitted individually as described above.

Question 8: Programs (SAS code) for the analysis of the primary and key secondary efficacy endpoints for the two pivotal Phase 3 studies (1314V9231 and 1315V9232) will be submitted in ASCII (*.TXT) and PDF format. Does the Agency agree?

FDA Response to Question 8:

This is acceptable; however, in addition to the programs for analyzing the primary and secondary endpoints, please also submit your analysis programs that were used to derive the analysis data from the raw data to assist our review.

Sponsor's response:

For the two pivotal Phase 3 studies, the Sponsor will provide the SAS programs for creating the ADaM datasets that are used for the primary and secondary endpoints (from SDTM to specific ADaM) along with the analysis programs for the primary and secondary endpoints. Programs will be provided in ASCII (*.TXT) and PDF formats.

Question 9: Does the Agency agree with the clinical pharmacology package including population PK and PK/PD analyses and consider it to be sufficient for the filling of an NDA?

FDA Response to Question 9:

In general, the proposed Clinical Pharmacology package appears adequate for the NDA submission. Your Pop PK and PK/PD plan appears reasonable.

If the patient population, trial design and end point are same, we recommend you to pool the data from various trials to perform PK/PD analysis for efficacy and safety. For general expectations of submitting pharmacometric data and models, please refer to the following website,

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

The following additional Clinical Pharmacology aspects need to be addressed at the time of NDA submission:

- 1. Potential for drug interaction of naldemedine with gastric acid reducing agents (e.g., PPIs, H2-blockers, and antacids); please refer to agency meeting minutes dated March 15, 2013 in this regard.**
- 2. Drug-drug interaction potential of major metabolite(s) of naldemedine as pertaining to major drug metabolizing enzymes and transporters (DDI should be initially assessed in vitro; in vivo studies may be needed depending on the results of these studies).**
- 3. Bioanalytical method validation reports and study sample assay reports for review.**

Sponsor's Response to the Additional Comments on Clinical Pharmacology:

- 1. Potential for drug interaction of naldemedine with gastric acid reducing agents (e.g., PPIs, H2-blockers, and antacids); please refer to agency meeting minutes dated March 15, 2013 in this regard.**

The Sponsor will submit the bioanalytical method validation reports and study sample assay reports for review.

Finally, the Sponsor would like to share with the FDA the top line results for Study 1326V9235 (Submission Dataset).

Attachments:

Table 14.1 – 4.1 Demographic and Baseline Characteristics

Table 14.3 – 1.1 Overall Summary of Treatment Emergent Adverse Events

Table 14.3 – 1.5 Incidence of Adjudicated Major Adverse Cardiovascular Events by Type and Opioid Dose Strata

Figure 14.2 – 1.1 Change in the Frequency of BMs per Week from Baseline to Each Visit

Shionogi Inc.
 Naldemedine (S-297995)
 Protocol:1326V9235
 Page 9 of 18
 Table 14.1-4.1 Demographic and Baseline Characteristics
 Safety Population

		Naldemedine 0.2 mg N=621	Placebo N=619	Total N=1240
Age (years)	n	621	619	1240
	Mean	53.4	52.7	53.0
	SD	11.68	10.55	11.13
	Min	20	21	20
	Median	54.0	53.0	54.0
	Max	80	79	80
Age Category (years), n (%)	<40	75 (12.1)	68 (11.0)	143 (11.5)
	>=40 to <65	445 (71.7)	475 (76.7)	920 (74.2)
	>=65	101 (16.3)	76 (12.3)	177 (14.3)
	>=75	22 (3.5)	10 (1.6)	32 (2.6)
Gender, n (%)	Male	238 (38.3)	217 (35.1)	455 (36.7)
	Female	383 (61.7)	402 (64.9)	785 (63.3)

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 Table 14.1-4.1 Demographic and Baseline Characteristics
 Safety Population

		Naldemedine 0.2 mg N=621	Placebo N=619	Total N=1240
Height (cm)	n	621	619	1240
	Mean	168.79	168.93	168.86
	SD	10.260	9.994	10.124
	Min	143.5	144.0	143.5
	Median	167.60	168.00	167.70
	Max	198.1	198.1	198.1
Body Weight (kg)	n	621	619	1240
	Mean	90.64	90.26	90.45
	SD	23.614	24.208	23.904
	Min	40.4	41.0	40.4
	Median	88.50	86.70	87.50
	Max	200.5	197.7	200.5

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Table 14.1-4.1 Demographic and Baseline Characteristics
 Safety Population

		Naldemedine 0.2 mg N=621	Placebo N=619	Total N=1240
BMI (kg/m ²)	N	621	619	1240
	Mean	31.68	31.45	31.56
	SD	7.603	7.650	7.625
	Min	16.0	15.1	15.1
	Median	30.50	30.30	30.40
	Max	68.2	68.2	68.2
BMI Category (kg/m ²), n (%)	<18.5	6 (1.0)	7 (1.1)	13 (1.0)
	>=18.5 to <25.0	93 (15.0)	96 (15.5)	189 (15.2)
	>=25.0 to <30.0	192 (30.9)	194 (31.3)	386 (31.1)
	>=30.0	330 (53.1)	322 (52.0)	652 (52.6)
Region, n (%)	North America	534 (86.0)	539 (87.1)	1073 (86.5)
	Rest of the World	87 (14.0)	80 (12.9)	167 (13.5)

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Naldemedine (S-297995)

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Table 14.1-4.1 Demographic and Baseline Characteristics

Safety Population

	Naldemedine 0.2 mg N=621	Placebo N=619	Total N=1240
Race, n (%)			
American Indian or Alaska Native	2 (0.3)	7 (1.1)	9 (0.7)
Asian	5 (0.8)	7 (1.1)	12 (1.0)
Black or African American	120 (19.3)	108 (17.4)	228 (18.4)
Native Hawaiian or Other Pacific Islander	2 (0.3)	1 (0.2)	3 (0.2)
White	492 (79.2)	496 (80.1)	988 (79.7)
Ethnicity, n (%)			
Hispanic or Latino	47 (7.6)	42 (6.8)	89 (7.2)
Not Hispanic or Latino	574 (92.4)	577 (93.2)	1151 (92.8)

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Shionogi Inc.
 Naldemedine (S-297995)
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 Table 14.3-1.1 Overall Summary of Treatment Emergent Adverse Events
 Safety Population

	Naldemedine 0.2 mg N=621		Placebo N=619		Difference of Proportion (95% Confidence Interval)
	n (%)	# of events	n (%)	# of events	
TEAEs	404 (65.1)	1466	423 (68.3)	1425	-3.3 (-8.5, 2.0)
ADRs	139 (22.4)	301	112 (18.1)	231	4.3 (-0.2, 8.8)
AE Leading to Discontinuation	38 (6.1)	74	30 (4.8)	46	1.3 (-1.3, 3.8)
SAEs	54 (8.7)	77	65 (10.5)	93	-1.8 (-5.1, 1.5)
SADRs	3 (0.5)	5	5 (0.8)	5	-0.3 (-1.2, 0.6)
SAEs Leading to Discontinuation	6 (1.0)	8	10 (1.6)	11	-0.6 (-1.9, 0.6)
Deaths	1 (0.2)	1	3 (0.5)	3	-0.3 (-1.0, 0.3)

ADRs were defined as TEAEs that were considered by the Investigator to be definitely, probably, or possibly related to IMP.

SADRs were defined as serious ADRs.

CIs based on normal approximation may not be reliable for small counts and should be interpreted with caution.

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Table 14.3-1.5 Incidence of Adjudicated Major Adverse Cardiac Events by Type and Opioid Dose Strata
 Safety Population

MACE Type	Naldemedine 0.2 mg			Placebo		
	30 - 100 N=396 n (%)	> 100 N=225 n (%)	Total N=621 n (%)	30 - 100 N=392 n (%)	> 100 N=227 n (%)	Total N=619 n (%)
Subjects with MACE	2 (0.5)	0	2 (0.3)	4 (1.0)	1 (0.4)	5 (0.8)
- Cardiovascular Death	0	0	0	2 (0.5)	1 (0.4)	3 (0.5)
- Myocardial Infarction	1 (0.3)	0	1 (0.2)	2 (0.5)	0	2 (0.3)
- Cerebrovascular Accident (Stroke)	1 (0.3)	0	1 (0.2)	0	0	0

MACE with the same type occurring more than once in a subject were counted once.

Dose of opioid was calculated using maintenance and breakthrough morphine equivalent dose. If any subjects were treated with <30 mg, the subjects were counted in '30-100'.

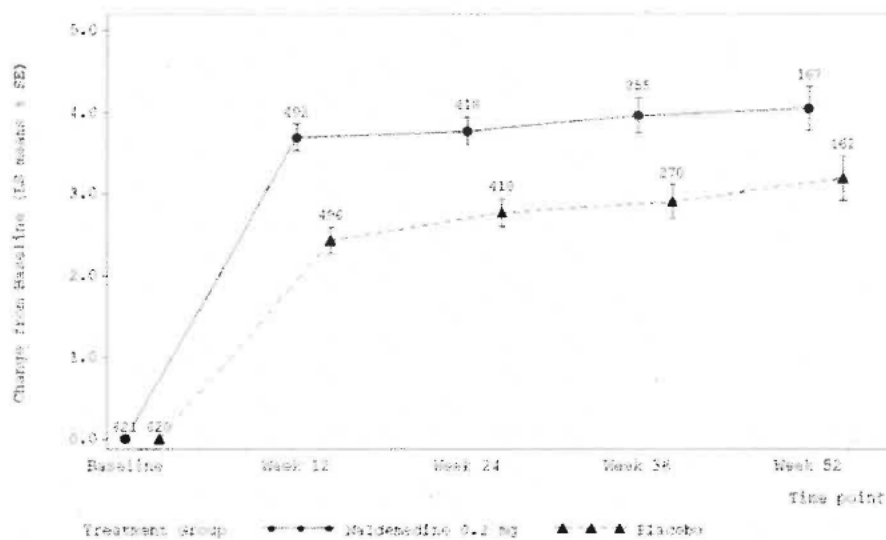
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Figure 14.2-1.1 Change in the Frequency of BMS per Week from Baseline to Each Visit (LS Mean $\pm$ SE)
 ITT Population



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Baseline was 14 consecutive calendar day qualifying period during the Screening Period.
 Frequency of BMS per week was calculated as the weekly average of observations in 7 days prior to each visit.
 Number of subjects at each visit is shown in the figure.
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/s/

JAMES B CARR
10/05/2015



IND 107475

MEETING MINUTES

Shionogi, Inc
Attention: Giselle Rose
Director, Regulatory Affairs
300 Campus Drive
Florham, NJ 07932

Dear Ms. Rose:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Naldemedine (S-297995) tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 19, 2013. The purpose of the meeting was to discuss the results of Phase 2 study (No. 1107V9221) titled "A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of S-297995 for the Treatment of Opioid-induced Constipation (OIC) in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy" and obtain concurrence on the path forward to support filing of a future NDA planned for 3rd quarter of 2015.

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

If you have any questions, call me, Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

Matt Brancazio, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2/Pre-phase 3

Meeting Date and Time: February 19, 2013 at 10:00 AM EST
Meeting Location: White Oak Building 22, Conference Room: 1421

Application Number: 107475
Product Name: Naldemedine (S-297995)
Indication: Treatment of opioid-induced constipation
Sponsor/Applicant Name: Shionogi, Inc.

Meeting Chair: Rob Fiorentino
Meeting Recorder: Matt Brancazio

FDA ATTENDEES

Robert Fiorentino, M.D., M.P.H., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products
Matt Brancazio, Pharm.D., Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Andrew Mulberg, M.D., Deputy Director, Division of Gastroenterology and Inborn Errors Products
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, Division of Gastroenterology and Inborn Errors Products
Matt Scherer, M.B.A. Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Freda Cooner, Statistical Reviewer, Division of Biometrics III
Dilara Jappar, Ph.D. Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III
Wes Ishihara, Chief Project Management Staff, Division of Gastroenterology Products
Farrokh Sohrabi, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products
George Greeley, Project Management Officer, Pediatric and Maternal Health Staff
Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, Pediatric and Maternal Health Staff

SPONSOR ATTENDEES

Kazuya Fukumura, Clinical Pharmacology and Pharmacokinetics, Shionogi & Co., Ltd
Toshinobu Iwasaki, Ph.D., Head Global Regulatory Affairs, Shionogi & Co., Ltd.
Hak-Myung Lee, Director, Biostatistics, Shionogi Inc.
Marc Lesnick, Vice President, US Regulatory Affairs, Global Development Projects, Shionogi Inc.
Pharis Mohideen, M.D., Vice President, Clinical Development, Shionogi Inc.

Gareth Morgan, Senior Vice President, Global Portfolio Management, Shionogi Inc.
Tsutae Den Nagata, M.D., Ph.D., FFPM, Chief Medical Officer, Shionogi & Co., Ltd.
Harald Reinhart, M.D., Senior Vice President, Clinical Development & Medical Affairs,
Shionogi Inc.
Giselle Rose, Director, Regulatory Affairs, Shionogi Inc.
Takuko Sawada, Senior Executive Officer, Shionogi & Co., Ltd.
Doreen Sekora, MPH, Senior Director, Clinical Development, Shionogi Inc.
Aileen Ward, Director, Clinical Development, Shionogi Inc.
Tomoyuki Yukizawa, MPH, Global Project Leader, Global Project Management, Shionogi &
Co., Ltd.

1.0 BACKGROUND

The purpose of this meeting is to discuss the results of Phase 2 study (No. 1107V9221) titled "A Randomized, Double-blind, Placebo-controlled, Parallel-group Study of S-297995 for the Treatment of Opioid-induced Constipation (OIC) in Subjects with Non-malignant Chronic Pain Receiving Opioid Therapy" and obtain concurrence on the path forward to support filing of a future NDA planned for 3rd quarter of 2015. Naldemedine (S-297995) is a peripheral opioid receptor antagonist for the treatment of opioid-induced constipation (OIC). Shionogi, Inc. submitted the type B meeting request on November 29, 2012, and was subsequently granted by the Division of Gastroenterology and Inborn Errors Products. IND 107475 was originally submitted on March 26, 2010. This is the first meeting between the agency and the sponsor related to this IND.

2. DISCUSSION

2.1. Clinical

Question 1: *Shionogi believes that proposed studies i.e., 2 pivotal studies in subjects not on laxatives, 1 study in subjects continuing on their laxative regimens, and 1 study in subjects with advanced medical illness (including pain related to cancer) are sufficient to characterize the efficacy of S-297995 to obtain the indication "Naldemedine for the treatment of OIC" in the label. Does the Agency concur?*

FDA Response to Question 1:

In general, your development program appears reasonable. However, determination of the adequacy of phase 3 trials in characterizing efficacy of S-297995 for the proposed indication will be a review issue. Also see Section 3 for additional clinical comments about your planned phase 3 trials.

Question 2: *a) Shionogi believes that the proposed responder definition of the primary efficacy endpoint is appropriate to support the proposed indication "Naldemedine for the treatment of OIC." Does the Agency agree?*

b) Does the Agency agree with the proposed (b) (4) for the missing imputation?

c) Does the Agency agree with the proposed [REDACTED] (b) (4)

d) Does the Agency agree with the proposed secondary endpoints?

FDA Response to Question 2:

a) **No, the Agency does not agree. As noted below, you should remove [REDACTED] (b) (4) during the Core phase.” In addition, your responder definition should be modified to demonstrate durability of response over the 12 week period by mandating that at least 3 of the responder weeks occur in the last 4 weeks of the 12-week trial.**

b) **No, we do not agree with the proposed [REDACTED] (b) (4) for the missing data imputation. For the primary analysis, all randomized subjects should be included, and any subjects with insufficient primary endpoint data should be treated as a “non-responder”. Moreover, if a subject has less than 4 days of diary entries for a week, they should be treated as “non-responder” for that week. The proposed [REDACTED] (b) (4) can be explored as a sensitivity analysis. To further address the issue of missing data, you should propose several sensitivity analyses. Details for handling missing data and the sensitivity analyses should be pre-specified in the protocol.**

Sensitivity analyses should include:

- **Observed case: exclude subjects from the analysis at a specific time point if the patient has insufficient data at that time point.**
- **Complete case: exclude subjects from the analysis at all time points if they had insufficient data at any of the time points of analysis.**
- **Worst case: subjects with missing observations at any of the time points of analysis are assumed to be “failed.”**
- **Per Protocol population.**
- **Model-based multiple imputation.**

c) **Please refer to the response to question 2-b above. Based on the missing data handling strategy stated, a responder is required to have a minimum of 9 weeks of completion.**

d) **Your proposed secondary endpoints appear reasonable, but secondary analyses of monthly responders for each month (e.g., responder for 3 out of 4 weeks) should also be presented. The secondary endpoints should be listed in the order of importance. If the secondary efficacy endpoints are not pre-specified or properly adjusted for multiplicity, the results of secondary endpoints would be considered exploratory and not suitable for any efficacy claims in the labeling.**

Meeting Discussion:

a) **Shionogi understands the Agency’s current recommendations to define a responder as a patient who is a responder for at least 9 out of the 12 weeks and at least three of those responder weeks must occur in the last 4 weeks of the 12 week study period.**

- b) **Shionogi understands that all subjects randomized would comprise the primary analysis population and the modified ITT would be a supportive analysis.**
- a. **For the worst case sensitivity analysis, if there are any missing data, that week would be considered a failure. For the primary analysis, at least 4 days of data are required to allow a response analysis for that week.**
 - b. **The Agency recommends the completion of a model-based multiple imputation.**

Question 4: *Does the Agency agree with the selection of the 0.2 mg dose once daily dose is to be used in Phase 3 studies for all study populations?*

FDA Response to Question 4:

The proposed dose for the phase 3 trials appears reasonable for the trials in adults with chronic non-cancer pain, assuming that the proposed tablet formulation used in phase 3 trials has a similar bioavailability and PK profile compared to the tablet formulation used in phase 2 trials.



Question 5: *Does the Agency concur with our choice of bisacodyl as the primary rescue medication?*

FDA Response to Question 5:

Your selection of bisacodyl as the primary rescue laxative appears reasonable. However, the protocols for trials that will allow subjects to continue on their usual laxative regimen during the double-blind phase should clearly delineate which laxatives are permitted and at what doses.

Meeting Discussion:

The Agency does not have any recommendations for excluding specific laxatives other than opioid antagonists. The Agency will accept the use of both electronic and paper diaries.

Question 6: *We believe the proposed clinical program will provide sufficient data and overall subject numbers to support the safety of S-297995. Does the Agency agree?*

FDA Response to Question 6:

We cannot agree that the planned safety evaluation will be adequate to support the NDA. Your planned phase 3 trials will need to be modified to address our concerns outlined below.

The effects of opioid withdrawal on the autonomic nervous system, including changes in hemodynamic parameters, could increase the risk of cardiovascular (CV) events. In a long term safety/efficacy trial of another peripheral mu-opioid receptor (MOR) antagonist (alvimopan) in patients with OIC, there were CV adverse events (AEs) observed. Further, in publically available postmarketing drug safety evaluations completed from July 2011 through December 2011, AE reports of drug withdrawal syndrome with use of methylnaltrexone were identified. In addition, we note that patients in previous trials investigating S-297995 had opioid withdrawal reported. Specifically, we note that there were seven patients with reported post-dose COWS scores >8 (1- and 3-mg dose groups) in the phase 2 trial 1007V9214. One of these patients in the 1 mg dose group reported opioid withdrawal syndrome AEs (e.g., severe stomach cramping and severe nausea) several hours after having the elevated COWS score. Further, a patient receiving the 0.3 mg dose had reported symptoms of diaphoresis, runny nose or tearing, and multiple episodes of diarrhea, nausea, and abdominal cramping within 24 hours post-dose. We further note that your product antagonizes opioid receptor subtypes (e.g., δ -delta) that are known to be present in the cardiovascular system and that are implicated in cardioprotection.

It is unclear if these withdrawal events represent a causal association with the drug or represent a background rate of withdrawal in patients taking opioids. However, given the potential for withdrawal, the above findings, and the elevated baseline risk for CV events in the OIC population (described in the literature), the Agency is concerned about a possible association between withdrawal due to the drug and CV events. Unless you can definitively demonstrate that your drug does not cause opioid withdrawal and does not have clinically meaningful interactions with opioid receptor subtypes in the cardiovascular system, you would need to do a premarketing randomized, controlled trial designed and powered to provide adequate assurance that there is not an increased risk of adverse CV events (MI, stroke and CV death) associated with your product.

Your phase 3 protocols should include a detailed plan to define, assess and centrally adjudicate all major adverse CV events. In addition to the CV events of MI, stroke, and death, the protocols should ensure that all subjects with chest pain or other symptoms typical of acute coronary syndrome (including symptoms that may overlap with opioid withdrawal) are adequately identified and evaluated (via cardiac enzymes, ECG, etc.). In patients with CV events, chest pain, and other symptoms typical of ACS, patient narratives and CRFs should be provided that include detailed information on the presence of withdrawal symptoms experienced by the patient.

The trials should incorporate a thorough evaluation and analysis of opioid withdrawal at frequent enough intervals to estimate the incidence of potential opioid withdrawal

associated with S-297995. We recommend weekly COWS and daily subject opiate withdrawal scale (SOWS) assessments during the first two weeks of trial drug usage, in addition to the planned assessments for all phase 3 trials. The timing of the assessments also should take into consideration the pharmacokinetic properties of your drug. Also, analyze COWS and SOWS scores both with and without the abdominal pain question on the scale, as the MOR antagonist may cause abdominal pain. Additionally, the use of rescue medication (opioid and non-opioid) for pain must be captured and analyzed. Opioid dose must be recorded daily by the patient. In addition to the assessment of withdrawal, the protocol should include an analysis of the impact of S-297995 on the analgesic efficacy of the opioids used for chronic pain. This analysis may be based on changes in pain scores and opioid usage over the treatment periods of the studies.

Meeting Discussion:

- a) Sponsor asked if a 12-week period is adequate for assessing efficacy and durability of response. FDA said this is acceptable.
- b) Shionogi understands that all safety data should be submitted at the time of submission of the planned NDA. At the time of submission, there must have been an adequate number of events to have answered the cardiovascular safety questions.
- c) Shionogi understand that the number of events, not the number of subjects, is more relevant to the determination of sample size (i.e., hazard ratio of 2).
- d) Please see meeting discussion above (Question 6 letter c).
- e) Shionogi asked if it would be acceptable to submit an NDA for an OIC indication in non-cancer patients only. FDA said yes, this would be acceptable.

Question 7: *We have no significant concerns for cardiovascular risk based on the results of non-clinical and clinical (Phase 1 and 2) studies. It is not anticipated that there will be any significant ECG findings that will affect the need for additional ECG monitoring beyond the proposed ECG assessments in the Core Studies (#1-3). Does the Agency agree with our plans for ECG assessment?*

FDA Response to Question 7:

The Agency agrees with your plan for scheduled ECG assessments for phase 3 however you should also plan to collect unscheduled ECGs for specific adverse events as described in our response to Question 6.

2.2. ClinPharm

Question 8: *Does the Agency agree that PK data obtained from Phase 1 and Phase 2 studies are sufficient to support the NDA?*

FDA Response to Question 8:

No, we do not agree.

(b) (4)

(b) (4)

product. You should adequately characterize the PK profile of the to-be-marketed tablet formulation.

Question 9: *Does the Agency concur with our proposal to assess the effect of P-gp inhibitors in the Phase 3 studies?*

FDA Response to Question 9:

Yes, we agree. Please provide the PK data from these 7 patients who were co-administered with verapamil or azithromycin.

Question 10: *Does the Agency concur that S-297995 can be administered without regard to food during Phase 3?*

FDA Response to Question 10:

It is premature to answer this question without seeing the results of this planned BA/FE study with the to-be-marketed formulation (0.2 mg S-297995 tablet). If you conduct the food effect study with the to-be-marketed formulation before conducting phase 3 studies, and the result of this study indicates the absence of food effect, then you may administer S-297995 without regard to food during Phase 3 studies.

Question 11: *Does the Agency concur that the clinical pharmacology studies listed in this briefing document, performed to date and proposed, are sufficient to support an NDA application of S-297995?*

FDA Response to Question 11:

In addition to the studies performed to date and proposed, we will need to address the following:

- **You will need to adequately characterize the PK profile of the to-be-marketed product.**
- **Please evaluate the exposure-response relationship for both efficacy and adverse event.**
- **We note that most of your completed clinical pharmacology studies were conducted with healthy male subjects only. You should conduct your proposed clinical pharmacology studies in target population in both male and female subjects.**
- **Address the potential for drug interaction with gastric acid reducing agents (e.g., PPIs, H₂-blockers, and antacids).**
- **Please evaluate if your drug is CYP2B6 inducer.**
- **In addition to the proposed special population study, you will also need to compare the PK characteristics in following patients:**
 - **Male vs. female population**
 - **Elderly patients,**
 - **BMI (body mass index)**
- **Please assess if your proposed drug will have an effect on the efficacy of opioid**

Meeting Discussion:

- a) Shionogi reviewed the FDA response and will perform population PK analysis in phase 3 studies and will submit their protocols for FDA review in advance.
- b) Shionogi asked if the proposed clinical pharmacology studies are to be performed with healthy male and female volunteers. FDA said yes, this is acceptable.
- c) In regards to the last bullet in FDA's response to Question 11, Shionogi noted that the effect on the efficacy of opioids is already a secondary endpoint. Shionogi understands the need to assess the effect of naldemedine on opioid analgesia in the phase 3 program.

2.3. Pediatrics

Question 13: *Details of our pediatric study plan containing an outline of the proposed protocol along with a formal request [REDACTED] (b) (4) will be submitted to the IND by the end of 2013. Is this acceptable to the Agency?*

FDA Response to Question 13:

[REDACTED] (b) (4)

2.4. Statistics

Question 3: Does the Agency agree with the proposed randomization ratio and sample size calculation?

FDA Response to Question 3:

Yes, we agree with the proposed randomization ratio and sample size calculation for the submitted protocol; however as described in our response to Question 6, you will need to modify your development plan, which may require revisions to the sample size of your planned clinical trials.

3. ADDITIONAL FDA COMMENTS

3.1. Clinical

Regarding all four phase 3 trials:

- Within the protocols, indicate how long subjects will need to have met criterion #4 in order to be eligible for trial entry.

Regarding phase 3 trials in patients with chronic non-cancer pain (trials 1314V9231, 1315V9232, and 1316V9233):

- Patients must have a confirmed diagnosis of chronic non-cancer pain with documentation of the condition associated with chronic pain of at least 3 months duration. The underlying chronic pain condition for which they are receiving opioids must be documented at trial entry. Results of any diagnostic imaging or tests that support the chronic pain diagnosis should be included.
- Clarify exclusion criterion #7. This criterion excludes subjects with “significant abnormal laboratory test > 2 X ULN.” Define specifically which laboratory tests will be considered for this exclusion criterion and your rationale.

Regarding the two phase 3 trials in which patients will be allowed to continue their current laxative regimen during the double-blind phase (trials 1316V9233, 1317V9234):

- Clarify if patients not taking a “routine” laxative regimen will be permitted to enroll in these trials. If so, your trials may have some patients not taking a routine laxative regimen that has been prescribed to be taken with opioids in an effort to prevent or treat constipation, whereas others will be taking multiple laxatives on a schedule with their opioids, and remain constipated despite this regimen. If such a situation is possible, you should assure balance between arms in these two subpopulations and prospectively address this issue in the protocol.
- You have indicated that in these two trials, baseline usual laxative regimen is “any combination of laxatives taken by the subject on a consistent basis over the

past 28 days” and that will be maintained throughout the trial. The trial eligibility criteria should clearly specify what laxatives are permitted as part of the laxative regimen and use must be recorded daily by the patient.

- You should prespecify the differences from the usual laxative regimen that would constitute inconsistent use of laxatives during the screening period and double-blind phase. This pre-specification is important to minimize confounding of efficacy by changes patients may make to their usual laxative regimen during the double-blind phase.

Regarding the phase 3 trial in patients with pain from cancer or advanced medical illness (trial 1317V9234):

- We do not agree that data [REDACTED] ^{(b) (4)} will be sufficient to demonstrate durability of response as there is no comparator arm. Based on the proposed trial design, durability of response, if reflected in the Clinical Studies section of the label, could only be descriptive in nature.
- It is important to patients and healthcare providers that durability of response is established, and you must adequately evaluate this in the development program. In establishing durability of response in this population, you must consider and address the impact of rapid dose escalation of opioids on efficacy.
- The underlying pain condition for which patients are receiving opioids must be documented at trial entry.
- A full report of the on-going phase 2 trial of S-297995 in patients with cancer and OIC should be submitted for review and evaluation prior to initiation of the phase 3 clinical trial.

3.2 Stats

Statistical analysis plans (SAPs) should be finalized as much as possible, consistent with the protocols, and submitted with the protocols prior to the initiation of the clinical trials.

4.0 APPLICATIONS IN THE PROGRAM UNDER PDUFA V

Because your proposed product is a new molecular entity, your new drug application (NDA) will be subject to “the Program” under PDUFA V. You are strongly encouraged to have a pre-submission meeting, no later than 2 months prior to your planned submission, to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

5.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

6.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

7.0 ATTACHMENTS AND HANDOUTS
See attached sponsor slides.

Questions for Clarification

6) Overall Development Program

Given your significant comments, we plan to redesign the development program. At this time, we have the following additional questions:

- a) Is a 12-week period adequate for assessing efficacy and durability of response?
- b) Would 6 months safety data submitted at the time of NDA and data from the subsequent 6 months submitted during NDA review be acceptable?
- c) What would be the minimum number of subjects required in the Phase 3 safety database?
- d) For planning purposes, what is the acceptable Risk Ratio e.g., upper bound of 95% CI for risk ratio for cardiovascular events in our safety database to demonstrate product safety?

Additional question regarding the overall program:

We would like to focus on non-cancer OIC at this time. Would it be acceptable to submit an NDA for an OIC indication in non-cancer patients only?

2) Primary/Secondary Analysis

2 a) Regarding the comment “your responder definition should be modified to demonstrate durability of response over the 12 week period by mandating that at least 3 of the responder weeks occur in the last 4 weeks of the 12-week trial,” as an example, does it mean that if 3 weeks of response is seen in Weeks 7, 8, 9, and 10 for a subject who completes 10 weeks but discontinues after Week 10, are they still considered a responder?

Is 3 of the last 4 weeks a standard requirement for the indication?

2 b) We understand the intent-to-treat principle implies that the primary analysis should include all randomized subjects (ICH E9). Please clarify whether we may exclude from the set of all randomized subjects (1) any subject who took no trial medication and had no post-randomization data, or (2) any subject who took no trial medication for the efficacy analysis.

For the requested Worst case sensitivity analysis, is it correct that subjects with missing observations at any of the time points of analysis are assumed to be “failed” for that time point and not for the entire study?

Given the other sensitivity analyses to be performed, is the model-based multiple imputation essential?

5) Rescue meds / Current laxatives (3.1)

In the proposed add-on therapy studies, we are not excluding any laxatives. However, we will capture the laxatives and doses used and perform the necessary sensitivity analysis. Are there any laxatives that the Division has concerns if included?

IND No. 107475 Naldemedine (S-297995) Tablets
End of Phase 2 Meeting
February 20, 2013

Additional question regarding electronic diaries:

For certain regions participating in the global Phase 3 program, there are obstacles to the use of electronic devices. Would the use of a combination of electronic and paper diaries be acceptable?

2.2 Clin Pharm

11 a) Based on your comments, we will perform population PK analysis in Phase 3 studies and will submit our proposals for your review in advance.

11 b) For the 3rd bullet where you note that the proposed clinical pharmacology studies should be conducted in your proposed in target population in both male and female subjects, we would like confirmation that the proposed clinical pharmacology studies are to be performed with healthy male and female volunteers.

11 c) The effect on the efficacy of opioids is already a secondary endpoint. Since it is also noted as a Clin Pharm comment, can you please clarify?

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/s/

MATTHEW B BRANCAZIO
03/15/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208854

LATE-CYCLE MEETING MINUTES

Shionogi Inc.
Attention: Ting Chen
Senior Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated March 23, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Symproic (naldemedine) oral tablets 0.2 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 13, 2016.

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

If you have any questions, call LCDR Cheronda Cherry-France, Regulatory Project Manager at (301) 796-7295.

Sincerely,

{See appended electronic signature page}

Anil Rajpal, M.D., M.P.H.
Team Lead, DGIEP
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 13, 2016 at 9:00A.M. (EST)
Meeting Location: Teleconference

Application Number: NDA 208854
Product Name: Symproic (naldemedine)
Applicant Name: Shionogi Inc.

Meeting Chair: Anil Rajpal, M.D., M.P.H. Team Lead, DGIEP
Meeting Recorder: LCDR Cheronda Cherry-France

FDA ATTENDEES

Julie Beitz, M.D., Director, Office of Drug Evaluation III (ODEIII)
Amy Egan, M.D., Deputy Director, ODE III
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joette Meyer, Pharm. D. Associate Director for Labeling, DGIEP
Anil Rajpal, M.D., M.P.H., Team Lead, DGIEP
Lauren Weintraub, M.D., Medical Reviewer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Tracy Behrsing, Ph. D, Pharmacology Reviewer, DGIEP
Sue Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology III (DCPIII)
Sandhya Apparaju, Ph.D., Division of Clinical Pharmacology III
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)
George Kordzakhia, Ph.D., Statistical Reviewer, Division of Biometrics III (DBIII)
Ling Lang, Ph.D., Statistical Reviewer, Division of Biometrics III (DBIII)
Hitesh Shroff, Chemistry Team Leader, Office of Product Quality
Sarah Ibrahim, Ph.D., Chemistry Reviewer, Branch V, DNNDP II, ONDP
Katherine Bonson, Ph.D., Pharmacologist, Controlled Substance Staff (CSS/CDER)
Brian Strongin, Pharm. D. Chief Project Manager, DGIEP
Sukminder Sandhu, Medical Officer/Team Lead Division of Epidemiology, (DEPI)
Joel Weissfeld, Medical Officer, DEPI

EASTERN RESEARCH GROUP, INC.

 ^{(b) (6)} (Independent Assessor)

APPLICANT ATTENDEES

Ting Chen, M.S., Vice President, Regulatory Affairs, Shionogi Inc.
Toshihiro Wajima, PhD, Senior Director, Head of Clinical pharmacology & Pharmacokinetics, Shionogi & Co., Ltd.

Tohko Arai Manager, Drug Safety Evaluation, Research Laboratory for Development, Shionogi & Co., Ltd.

Toshiyuki Kanemasa, Associate Principal Scientist, Discovery Research Laboratory for Core Therapeutic Areas, , Shionogi & Co., Ltd.

Bin Cai, Ph.D., Sr. Director, Global Observational Research & Epid, Shionogi Inc.

Masaaki Wada, Senior Director, Head of Analytical Chemistry Department, Analytical R&D Center, CMC R&D Division, Shionogi & Co., Ltd.

Tomoyuki Yukizawa, MPH, Global Project Leader, Global Project Management, Shionogi & Co., Ltd.

Sayo Hashimoto, CQPV, Shionogi & Co., Ltd.

1.0 BACKGROUND

NDA 208854 was submitted on March 23, 2016 for Symproic(naldemedine), 0.2 mg tablets.

Proposed indication: treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

PDUFA goal date: March 23, 2017

FDA issued a Background Package in preparation for this meeting on December 1, 2016.

2.0 DISCUSSION

1. Introductory Comments : Welcome, Introductions, Ground rules, Objectives of the meeting (5 minutes) By LCDR Cheronda Cherry-France

2. Discussion of Postmarketing Requirements/Postmarketing Commitments (10-15 minutes) By Dr. Sukminder Sandhu, Dr. Anil Rajpal/Cross Discipline Team Lead, & Dr. Lauren Weintraub/Clinical Reviewer

- A postmarketing requirement (PMR) for major adverse cardiovascular events (MACE) is being considered. Note that the PMR would reflect class-based thinking for the peripherally acting mu opioid receptor antagonists (PAMORAs).

Discussion: FDA stated that this is a class-wide safety issue and it is still under review at this time.

3. Statement : Abuse Potential Assessment (5 minutes)By Katherine Bonson, Ph.D., Pharmacologist, Controlled Substance Staff (CSS/CDER)

CSS confirms that all necessary information for assessment of abuse potential was submitted in the NDA for naldemedine. The studies are generally well-designed to provide the data that are necessary to determine whether naldemedine has abuse potential.

Since naldemedine is a derivative of thebaine, it is currently a Schedule II drug under the Controlled Substances Act (CSA). If naldemedine is determined by CSS to not have abuse

potential, FDA will prepare an Eight Factor Analysis (8FA) (as required under the CSA) that contains all data showing that the drug has no abuse-related signals and provides a recommendation that it should be decontrolled. Following review and concurrence by the National Institute on Drug Abuse (NIDA), the 8FA will be sent to the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS). If the ASH concurs with the recommendation to decontrol naldemedine, the 8FA will be transmitted to the Drug Enforcement Administration (DEA). The DEA is the final authority regarding whether a drug can be decontrolled from the CSA. Thus, prior to DEA action, all evaluations regarding scheduling are considered to be pre-decisional and cannot be shared outside of HHS and DEA.

Discussion: FDA stated that Section 9 of the label can be eliminated.

4. Review Plans, Wrap-up and Action Item (2 minutes) by Dr. Anil Rajpal/Cross Discipline Team Lead & Dr. Lauren Weintraub/Clinical Reviewer

- Review is ongoing.

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/s/

ANIL K RAJPAL
12/14/2016



NDA 208854

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Shionogi Inc.
Attention: Ting Chen
Senior Director, Regulatory Affairs
300 Campus Drive
Florham Park, NJ 07932

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symproic (naldemedine) oral tablets 0.2 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for **December 13, 2016**. Attached is our background package, including our agenda, for this teleconference.

Please email me a list of your attendees at cheronda.cherry-france@fda.hhs.gov, at least five days prior to the scheduled teleconference.

If you have any questions, call LCDR Cheronda Cherry-France, Regulatory Project Manager, at (301) 796.7295.

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 13, 2016 at 9:30 AM-10:30 AM (Eastern Standard Time)

Meeting Location: Teleconference and call-in information:
Toll free: 1-855-828-1770
Follow the instructions that you hear on the phone.
Cisco Unified Meeting Place meeting ID: 745 192 338

Application Number: 208854

Product Name: Symproic (naldemedine)

Indication: treatment of opioid-induced constipation in adult patients with chronic non-cancer pain

Applicant Name: Shionogi

FDA ATTENDEES (tentative)

Julie Beitz, M.D., Director, Office of Drug Evaluation III

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)

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Katherine Bonson, Ph.D., Pharmacologist, Controlled Substance Staff (CSS/CDER)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal

date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No Substantive Review Issues have been identified to date.

3. Abuse Potential Assessment

CSS confirms that all necessary information for assessment of abuse potential was submitted in the NDA for naldemedine. The studies are generally well-designed to provide the data that are necessary to determine whether naldemedine has abuse potential.

Since naldemedine is a derivative of thebaine, it is currently a Schedule II drug under the Controlled Substances Act (CSA). If naldemedine is determined by CSS to not have abuse potential, FDA will prepare an Eight Factor Analysis (8FA) (as required under the CSA) that contains all data showing that the drug has no abuse-related signals and provides a recommendation that it should be decontrolled. Following review and concurrence by the National Institute on Drug Abuse (NIDA), the 8FA will be sent to the Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS). If the ASH concurs with the recommendation to decontrol naldemedine, the 8FA will be transmitted to the Drug Enforcement Administration (DEA). The DEA is the final authority regarding whether a drug can be decontrolled from the CSA. Thus, prior to DEA action, all evaluations regarding scheduling are considered to be pre-decisional and cannot be shared outside of HHS and DEA.

4. Advisory Committee Meeting

An Advisory Committee meeting is not planned.

5. REMS or Other Risk Management Actions

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (LCDR Cheronda Cherry-France)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Postmarketing Requirements/Postmarketing Commitments – 10-15 minutes (Dr. Anil Rajpal/Cross Discipline Team Lead & Dr. Lauren Weintraub/Clinical Reviewer)

A postmarketing requirement (PMR) for major adverse cardiovascular events (MACE) is being considered. Note that the PMR would reflect class-based thinking for the peripherally acting mu opioid receptor antagonists (PAMORAs).

3. Review Plans, Wrap-up and Action Item –5 minutes (Dr. Anil Rajpal/Cross Discipline Team Lead & Dr. Lauren Weintraub/Clinical Reviewer)

Review is ongoing.

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

/s/

DONNA J GRIEBEL
12/01/2016