

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208587Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208587

SUPPL #

HFD # 161

Trade Name Endari

Generic Name L-Glutamine

Applicant Name Emmaus Medical, Inc.

Approval Date, If Known July 7, 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)(2)

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.

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:

c) Did the applicant request exclusivity?

YES NO

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

7 years orphan exclusivity

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?

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# 021667

Glutamine Oral (for solution)

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:

- **Study 10478:** A Phase II, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle β 0-Thalassemia
- **Study GLUSCC09-01:** A Phase III, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of L glutamine Therapy for Sickle Cell Anemia and Sickle β 0-Thalassemia

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"):

Study 10478
Study GLUSCC09-01

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 # Study 10478 YES NO
Explain:

Investigation #2

IND # Study GLUSCC09-01 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
Explain:

NO
Explain:

Investigation #2

YES
Explain:

NO
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: Michael Gwathmey, RN
Title: Regulatory Project Manager, DHP/OHOP
Date: July 7, 2017

Name of Division Director signing form: Ann Farrell, MD
Title: Division Director, DHP/OHOP

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/

MICHAEL V GWATHMEY
07/07/2017

ANN T FARRELL
07/07/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208587 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Endari Established/Proper Name: L-glutamine Dosage Form: 5 grams		Applicant: Emmaus Medical, Inc. Agent for Applicant (if applicable):
RPM: Michael Gwathmey, RN		Division: Division of Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<div style="background-color: yellow; border: 1px solid black; padding: 2px;">For ALL 505(b)(2) applications, two months prior to EVERY action:</div> <ul style="list-style-type: none"> 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) <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: 7/7/17 </p> <p><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></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>July 7, 2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> 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):
(confirm chemical classification at time of approval)

- | | |
|-------------------------------------------------------------|---------------------------------------------------|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> 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)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Burst Notification
❖ 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval; 7/7/17
-----------------------------------------------------------------------------------------	------------------

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 9/7/16
❖ 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>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 6/29/17
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Acceptability Letter: 2/27/17 Review: 2/27/17
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 11/22/16 DMEPA: 7/5/17, 6/23/17, 6/12/17, and 1/24/17 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 6/20/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None

Administrative / Regulatory Documents

❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	11/4/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ 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>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan designation</u> 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • 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>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> ❖ 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>) 	IR: , 7/6/17 (4), 7/3/17, 6/28/17(2), 6/27/17, 6/13/17, 6/9/17 (2), 6/8/17, 6/5/17, 5/31/17, 5/30/17, 5/19/17, 5/15/17, 5/12/17, 5/10/17, 5/1/17, 4/25/17 (2), 3/16/17, 3/7/17, 3/3/17, 2/28/17, 2/3/17, 1/27/17, 1/18/17, 11/29/16, 11/18/16, 11/14/16, 10/24/16, 10/19/17, 9/22/16
<ul style="list-style-type: none"> ❖ 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) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	6/11/14
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	4/20/09, 11/19/01
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	5/24/17
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	6/27/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	7/7/17
PMR/PMC Development Templates (<i>indicate total number</i>)	7/5/17
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Cosigned 6/7/17 review
• Clinical review(s) (<i>indicate date for each review</i>)	6/7/17 Joint Clinical and Statistical review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical/Statistical Review; see section 3.3 on page 23
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> 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>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	Review: 5/2/17 Letters: 5/5/17 (2), 4/20/17, and 4/19/17
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Cosigned 6/7/17 review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Cosigned 6/7/17 review
Statistical Review(s) (<i>indicate date for each review</i>)	7/6/17, 6/7/17 Joint Clinical and Statistical review

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).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Cosigned 5/31/17 review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Cosigned 5/31/17 review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	5/31/17
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review Cosigned 6/1/17 review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	6/1/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	6/6/17 (2)
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 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>)	6/19/17 Executive Summary: 6/15/17 Drug Substance: 2/7/17 Drug Product: 2/7/17 Labeling: 6/16/17 Process: 6/13/17 Facilities: 6/13/17 Memo EIR: 6/16/17 Final Risk Assessment: 6/15/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Refer to Executive Summary page 5
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

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

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	pending <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ 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	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	7/7/17
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

MICHAEL V GWATHMEY
07/11/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#)
Subject: RE: NDA 208587- PI Labeling
Date: Thursday, July 06, 2017 6:58:00 PM
Attachments: [NDA208587PICurrentVersionforEditsEM_rev FDA 070317_EM 070517_FDA 070617.doc](#)
Importance: High

Ms. Tran,

In reference to **NDA 208587 Endari (L-glutamine)**, the proposed labeling with the FDA's most recent edits/comments are attached. Using the same word document draft:

- Provide a response to the comments written by the Agency.
- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language in tracked changes. If necessary, edit but do not "reject" the FDA-proposed changes.
- With any input that you provide, please do so in tracked changes.

Please update and submit your revised labeling response to me via email (in track changes and in a clean version) by **12:00 am ET on July 7, 2017 (or earlier)** followed by an official submission to the NDA. The resubmitted labeling will be used for further labeling discussions.

Please acknowledge receipt of this email, and feel free to contact me if you have any questions.
Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

MICHAEL V GWATHMEY
07/06/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#)
Subject: FW: FW: NDA 208587- PI Labeling- *** URGENT RESPONSE REQUESTED
Date: Thursday, July 06, 2017 2:47:00 PM
Importance: High

Ms. Tran,

Regarding NDA 208587, we have an urgent request for the following information as stated below. Please provide a response as soon as possible, and let us know if you have any questions. Thank you.

TO APPLICANT:

There are minor discrepancies of the results (please see FDA's codes and my results). If you agree, please revise the numbers accordingly.

Also, since the recurrent event analysis is an exploratory analysis, FDA proposed to present the LWYY 95% CIs here to be more accurate (see below). Anderson and Gill method does not take account of the correlation and the LWYY method does, so it will be more accurate. One alternative is to present 95% CIs based on both Anderson and Gill (AG) and LWYY method.

The recurrent crisis event time analysis (Figure 1) yielded an intensity rate ratio (IRR) value of xx (with [\[A1\]](#) [\[A2\]](#) 95% CI= (xx,xx) based on Lin, Wei, Yang and Ying method based on an unadjusted model) in favor of Endari, suggesting that over the entire 48-week period, the average cumulative crisis count was reduced by 20% from the Endari group over the placebo group.

Here are my codes and results :





RESULTS:

Lin, Wei, Yang and Ying (2000) method

The PHREG Procedure

Model Information

Data Set WORK.DAT2

Dependent Variable TSTART Time to the recurrence

Dependent Variable TSTOP Time of the Kth recurrence

Censoring Variable event

Censoring Value(s) 0

Ties Handling BRESLOW

Number of Observations Read 875

Number of Observations Used 867

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
867	458	409	47.17

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	4720.908	4711.695
AIC	4720.908	4713.695
SBC	4720.908	4717.822

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	9.2128	1	0.0024
Score (Model-Based)	9.4170	1	0.0021
Score (Sandwich)	3.2790	1	0.0702
Wald (Model-Based)	9.3526	1	0.0022
Wald (Sandwich)	3.4951	1	0.0616

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio
trt	1	-0.28807	0.15409	1.636	3.4951	0.0616	0.750

Hazard Ratios for trt

Description	Point Estimate	95% Wald Robust Confidence Limits
trt Unit=1	0.750	0.554 1.014

Anderson and Gill model

The PHREG Procedure

Model Information

Data Set

WORK.DAT2

Dependent Variable TSTART

Time to the recurrence

Dependent Variable TSTOP Time of the Kth recurrence
Censoring Variable event
Censoring Value(s) 0
Ties Handling BRESLOW

Number of Observations Read 875
Number of Observations Used 867

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
867	458	409	47.17

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	4720.908	4711.695
AIC	4720.908	4713.695
SBC	4720.908	4717.822

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	9.2128	1	0.0024
Score	9.4170	1	0.0021
Wald	9.3526	1	0.0022

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
trt	1	-0.28807	0.09420	9.3526	0.0022	0.750

Hazard Ratios for trt

Description Point Estimate 95% Wald Confidence Limits

trt Unit=1

0.750

0.623

0.902

To Applicant: FDA can not confirm. Please provide a derived dataset for confirmation or SAS program for documentation purposes. Derived dataset is provided.

To FDA: The derived data set is provided along with the SAS program.

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/s/

MICHAEL V GWATHMEY
07/06/2017

From: Gwathmey, Michael
 To: "Lan Tran"
 Cc: Yutaka Niihara
 Subject: FW: NDA 208587- PI Labeling- *** URGENT RESPONSE REQUESTED
 Date: Thursday, July 06, 2017 1:15:00 PM
 Importance: High

Ms Tran,

Regarding NDA 208587, we have an urgent request for the following information as stated below Please provide a response as soon as possible, and let us know if you have any questions Thank you

- FDA performed a quick check of the acute chest pain syndrome (ACS) summary and still cannot get close results. Attached are FDA's codes and results for your information. FDA's codes are simple calculation for the summary which did not consider the time constraints. However, we do not expect to have such large discrepancies. Could you explain ? Or alternatively, please share with us the SAS codes that were used to perform the ACS summary.

Below are the codes and results:

** the following dataset was from [\\CDSESUB1\evsprod\NDA208587\0000\m5\datasets\ise\analysis\adam](#)

(b) (4)



chk sumacs

The FREQ Procedure

Table of TRT01P by sacs

Frequency	Percent	TRT01P(Planned Treatment for Period 01)	4	5	6	7	8	9	10	11	12	13	14	15	19	20	23	Total
		GLN	28	31	33	15	12	11	8	7	2	2	1	0	0	2	0	152
			12 17	13 48	14 35	6 52	5 22	4 78	3 48	3 04	0 87	0 87	0 43	0 00	0 00	0 87	0 00	66 09
			18 42	20 39	21 71	9 87	7 89	7 24	5 26	4 61	1 32	1 32	0 66	0 00	0 00	1 32	0 00	
			80 00	72 09	71 74	65 22	57 14	55 00	53 33	63 64	50 00	50 00	50 00	0 00	0 00	66 67	0 00	
		PLB	7	12	13	8	9	9	7	4	2	2	1	1	1	1	1	78
			3 04	5 22	5 65	3 48	3 91	3 91	3 04	1 74	0 87	0 87	0 43	0 43	0 43	0 43	0 43	33 91
			8 97	15 38	16 67	10 26	11 54	11 54	8 97	5 13	2 56	2 56	1 28	1 28	1 28	1 28	1 28	
			20 00	27 91	28 26	34 78	42 86	45 00	46 67	36 36	50 00	50 00	50 00	100 00	100 00	33 33	100 00	
		Total	35	43	46	23	21	20	15	11	4	4	2	1	1	3	1	230
			15 22	18 70	20 00	10 00	9 13	8 70	6 52	4 78	1 74	1 74	0 87	0 43	0 43	1 30	0 43	100 00

check % ACS

The FREQ Procedure

Table of TRT01P by dummy

Frequency	Percent	TRT01P(Planned Treatment)	dummy
-----------	---------	---------------------------	-------

Row Pct Col Pct	for Period (01)	1	Total
	GLN	152	152
		66 09	66 09
		100 00	
		66 09	
	PLB	78	78
		33 91	33 91
		100 00	
		33 91	
	Total	230	230
		100 00	100 00

run;

Michael Gwathmey, RN
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 Regulatory Health Project Manager
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/s/

MICHAEL V GWATHMEY
07/06/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Subject: NDA 208587- Item # 20 of the 356h form
Date: Thursday, July 06, 2017 12:33:00 PM

Ms. Tran,

This e-mail is in reference to NDA 208587. When completing item # 20 of the 356h form, we advise that you not identify NutreStore (NDA 021667) as the basis for your submission since you are not relying upon another applicant's NDA, but rather cross-referencing your own. Thank you and let me know if you have any questions.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
07/06/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#)
Subject: NDA 208587- PI Labeling
Date: Monday, July 03, 2017 3:19:00 PM
Attachments: [NDA208587PICurrentVersionforEditsEM_rev EM_6-19-17_FDA_062817_tracked_rev EM_062917_FDA_070317.doc](#)

Ms. Tran,

In reference to **NDA 208587 Endari (L-glutamine)**, the proposed labeling with the FDA's most recent edits/comments are attached. Using the same word document draft:

- Provide a response to the comments written by the Agency.
- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language in tracked changes. If necessary, edit but do not "reject" the FDA-proposed changes.
- With any input that you provide, please do so in tracked changes.

Please update and submit your revised labeling response to me via email (in track changes and in a clean version) by **4:00 pm ET on July 5, 2017 (or earlier)** followed by an official submission to the NDA. The resubmitted labeling will be used for further labeling discussions.

Please acknowledge receipt of this email, and feel free to contact me if you have any questions. Thank you.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
07/03/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Cc: [Yutaka Niihara](#)
Subject: NDA 208587 PI Labeling
Date: Wednesday, June 28, 2017 1:13:00 PM
Attachments: [NDA208587PICurrentVersionforEditsEM_rev EM_6-19-17_FDA_062817_tracked.doc](#)

Ms. Tran,

In reference to **NDA 208587 Endari (L-glutamine)**, the proposed labeling with the FDA's most recent edits/comments are attached. Using the same word document draft:

- Provide a response to the comments written by the Agency.
- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language in tracked changes. If necessary, edit but do not "reject" the FDA-proposed changes.
- With any input that you provide, please do so in tracked changes.

Please update and submit your revised labeling response to me via email (in track changes and in a clean version) by **12:00 pm ET on June 30, 2017 (or earlier)** followed by an official submission to the NDA. The resubmitted labeling will be used for further labeling discussions.

Please acknowledge receipt of this email, and feel free to contact me if you have any questions. Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
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/s/

MICHAEL V GWATHMEY
06/28/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#)
Subject: FW: NDA 208587- PMC Endari (L-glutamine)
Date: Wednesday, June 28, 2017 9:43:00 AM

Ms. Tran,

Regarding NDA 208587 and the post-marketing commitment, below is the most recent proposal:

PMC Description: Design and conduct a dose-finding trial in adult and pediatric patients with body weight less than or equal to 65 kg. The primary endpoint should be the increase in the ratio of NADH to total NAD levels from the baseline. The trial should have dose-finding and safety observation parts. The duration of evaluation for the dose-finding and safety observation should be justified in the protocol.
After the optimal dose is identified, the selected dose should be administered to adult and pediatric patients with body weight less than or equal to 65 kg for at least 24 weeks to assess safety and activity of the selected dose. The study population should include patients with renal and hepatic impairment.

Schedule Milestones: Draft Protocol Submission: 1/2018
Final Protocol Submission: 4/2018
Study Completion: 7/2020
Final Report Submission: 12/2020

Please provide a response to me via email by **12:00 pm ET on June 30, 2017** (or earlier) followed by an official submission to the NDA. Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN

LCDR, U.S. Public Health Service
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Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Monday, June 19, 2017 7:06 AM
To: Gwathmey, Michael
Cc: Yutaka Niihara
Subject: Re: NDA 208587- PMC Endari (L-glutamine)

Dear Mr. Gwathmey,

In response to your email dated 09 June 2017, we submit our comments to the brief description of the necessary study's key trial elements and the proposed timelines for your consideration. Please advise if there is any additional information required as part of this submission at this point in time.

We plan to make a formal submission to the NDA by the end of this week.

Thank you for your continued help.

Sincerely,
Lan

On Fri, Jun 9, 2017 at 7:32 AM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:
Ms. Tran,

Please refer to the NDA 208587, L-glutamine that was received on September 7, 2016.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

- a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

- b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the

document room and us code the submission properly.

#1

NDA # 208587
Product Name: Endari (L-glutamine)

PMC Description: Design and conduct a 24-week dose finding trial in adult and pediatric patients with body weight lower or equal to 65 kg. The primary endpoint will be an increase in the ratio of NADH to total NAD levels from the baseline. The study design will include a comparison to the increase in the ratio of NADH to total NDA levels at baseline for patients with body weight higher than 65 kg administered a dose of (b) (4) per day. The trial will include analyses of safety and activity of the doses. The study population should include patients with renal and hepatic impairment.

PMC Schedule Milestones:	Draft Protocol Submission:	<u>MM/YYYY</u>
	Final Protocol Submission:	<u>MM/YYYY</u>
	Study Completion:	<u>MM/YYYY</u>
	Final Report	
Submission	MM/YYYY	

Please provide a response to me via email by **9:00 am ET on June 19, 2017** (or earlier) followed by an official submission to the NDA. Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
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Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
06/28/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Cc: [Yutaka Niihara](#)
Subject: NDA 208587- Carton/Container Labeling
Date: Tuesday, June 27, 2017 9:38:00 AM

Ms. Tran,

This e-mail is in reference to NDA 208587, regarding your June 22, 2017 carton/container package labeling submission. We recommend that the following be implemented prior to approval of this NDA 208587:

- I. Significantly reduce the font size of the "Rx Only" statement and relocate it away from the establish name and product strength information to improve the prominence and readability of other important information.

Please e-mail me a copy of the revised carton and container label by **4:00 pm ET June 29, 2017** (followed by an official submission to the NDA), and let me know if you have any questions. Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
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Food and Drug Administration
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Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
06/27/2017

From: Gwathmey, Michael
To: "Lan Tran"
Cc: Yutaka Niihara; Manitpisitkul, Wana
Subject: FW: FW: NDA 208587- Carton/Container Labeling Guidance.....
Date: Tuesday, June 13, 2017 2:44:00 PM

Ms. Tran,

This e-mail is in reference to NDA 208587, regarding your March 2, 2017 carton/container package labeling submission. We recommend that the following be implemented (to both carton and container packaging) prior to approval of this NDA 208587:

- I. Reduce the font size of the "Rx Only" statement and relocate it away from the product strength information to improve the prominence and readability of other important information.
- II. Replace the "Tradename" placeholder with the conditionally acceptability Proprietary Name.
- III. Align the product dosage form on the carton and container labels with the prescribing information. Replace [REDACTED] (b) (4) [REDACTED] with "L- glutamine oral powder".
- IV. Revise the mixing directions to "Mix the contents with cold or room temperature beverage or food immediately before dosing."

Please e-mail me a copy of the revised carton and container label by **4:00 pm June 19, 2017** (followed by an official submission to the NDA), and let me know if you have any questions. Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Gwathmey, Michael
Sent: Thursday, June 01, 2017 2:50 PM
To: 'Lan Tran'
Cc: 'Yutaka Niihara'
Subject: RE: FW: NDA 208587- Carton/Container Labeling Guidance.....

Ms. Tran,

In reference to your May 31, 2017 e-mail regarding the carton/container for NDA 208587, most of the recommendations were addressed in your submission dated March 2, 2017. We will have a few additional comments that we will be sending. In terms of the proposal for changing the carton dimension you may submit that now or wait until you receive our additional comments for the carton/container and submit it at the time of responding to that information request. Thank you and feel free to contact us with any additional questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
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Center for Drug Evaluation and Research
Food and Drug Administration
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301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Gwathmey, Michael
Sent: Thursday, June 01, 2017 8:26 AM
To: 'Lan Tran'
Cc: Yutaka Niihara
Subject: RE: FW: NDA 208587- Carton/Container Labeling Guidance.....

Ms. Tran,

Thank you for your questions below and we will have a response for you as soon as possible.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Wednesday, May 31, 2017 7:55 PM
To: Gwathmey, Michael

Cc: Yutaka Niihara

Subject: Fwd: FW: NDA 208587- Carton/Container Labeling Guidance.....

Dear Mr. Gwathmey,

Thank you for your email. I acknowledge receipt and we are currently working through the recommendations.

There are a few items we would like clarification on, particularly to A2, A3, A5, and A6. I would like to refer you to submissions to the NDA dated Feb 24, 2017 and Mar 2, 2017, Serial 0014 and 0015, respectively. We had submitted these in response to the recommendations made as noted in A2, A3, A5 and A6. Please see our questions in blue below.

2. Revise the strength on the PDP as currently presented it is not prominent.

Please advise if there is a specific manner in which this should be done.

3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of 1 unit and carton labeling of (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.

We had submitted NDC codes 42457- (b) (4) for the carton and container labels, respectively. Please advise if there is a specific manner in which this should be done

5. Remove bold font on manufacturer information as it takes reader's attention from important information such as proprietary and proper names, administration information and per packet strength.

Please advise if there is a specific manner in which this should be done.

6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

We included a bar code on the carton label but not the container label. Please advise if we should also add a bar code to the carton label.

On a separate but related note, we would like to propose different dimensions to the container carton. We would like to propose a 60 unit carton (b) (4). Please advise if it would be acceptable to submit those changes as part of our response to this request for information.

Please let me know if we can discuss live.

Sincerely,
Lan

On Wed, May 31, 2017 at 7:10 AM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:
Ms. Tran,

This e-mail is in reference to NDA 208587. Regarding your carton and container label, the Agency is providing **revised** recommendations that should be implemented prior to approval of this NDA:

A. Carton Label

1. Revise presentation of drug product established name on the PDP to be consistent with USP requirements: L-glutamine oral **powder**.
2. Revise the strength on the PDP as currently presented it is not prominent.
3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of 1 unit and carton labeling of (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.
4. Revise the statement (b) (4). E.g. “mix with cold or room temperature food or beverage”.
5. Remove bold font on manufacturer information as it takes reader’s attention from important information such as proprietary and proper names, administration information and per packet strength.
6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

B. Container Label

1. See A.1 through A.6.

Please acknowledge receipt of this e-mail, and let me know if you have any further questions. Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
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[301-796-8498](tel:301-796-8498)
Michael.Gwathmey@fda.hhs.gov

From: Gwathmey, Michael
Sent: Friday, January 27, 2017 12:57 PM
To: Yutaka Niihara
Cc: 'Lan Tran'; Fahnbulleh, Frances
Subject: NDA 208587- Carton/Container Labeling Guidance.....

Dr. Niihara,

This e-mail is in reference to NDA 208587. The Agency has reviewed your carton and container label, and we recommend the following be implemented prior to approval of this NDA 208587:

A. Carton Label

1. Revise presentation of drug product established name on the PDP to be consistent with USP requirements: L-glutamine powder for oral solution.
2. Revise the strength on the PDP as currently presented it is not prominent.
3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of 1 unit and carton labeling of [REDACTED] (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.
4. Revise the statement [REDACTED] (b) (4). E.g. “mix with cold or room temperature food or beverage”.
5. Remove bold font on manufacturer information as it takes reader’s attention from important information such as proprietary and proper names, administration information and per packet strength.
6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

B. Container Label

1. See A.1 through A.6.

Please acknowledge receipt of this e-mail, and let me know if you have any further questions. Thank you.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
06/13/2017

From: Gwathmey, Michael
To: "Lan Tran"
Cc: [Yutaka Niihara](#)
Subject: NDA 208587- PMC Endari (L-glutamine)
Date: Friday, June 09, 2017 10:32:00 AM

Ms. Tran,

Please refer to the NDA 208587, L-glutamine that was received on September 7, 2016.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.
2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:
 - a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
 - b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly.

#1

NDA # 208587
Product Name: Endari (L-glutamine)

PMC

Description:

Design and conduct a 24-week dose finding trial in adult and pediatric patients with body weight lower or equal to 65 kg. The primary endpoint will be an increase in the ratio of NADH to total NAD levels from the baseline. The study design will include a comparison to the increase in the ratio of NADH to total NDA levels at baseline for patients with body weight higher than 65 kg administered a dose of (b) (4) per day. The trial will include analyses of safety and activity of the doses. The study population should include patients with renal and hepatic impairment.

PMCSchedule Milestones:

Draft Protocol Submission:

MM/YYYY

Final Protocol Submission:

MM/YYYY

Study Completion:

MM/YYYY

Final Report Submission

MM/YYYY

Please provide a response to me via email by **9:00 am ET on June 19, 2017** (or earlier) followed by an official submission to the NDA. Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
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Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
06/09/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Cc: [Yutaka Niihara](#)
Subject: NDA 208587 Endari (L-glutamine) Labeling
Date: Friday, June 09, 2017 10:12:00 AM
Attachments: [NDA208587PICurrentVersionforEdits.docx](#)

Ms. Tran,

In reference to **NDA 208587 Endari (L-glutamine)**, the proposed labeling with the FDA's current edits/comments are attached. Using the same word document draft:

- Provide a response to the comments written by the Agency.
- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language in tracked changes. If necessary, edit but do not "reject" the FDA-proposed changes.
- With any input that you provide, please do so in tracked changes.

Please update and submit your revised labeling response to me via email (in track changes and in a clean version) by **9:00 am ET on June 19, 2017 (or earlier)** followed by an official submission to the NDA. The resubmitted labeling will be used for further labeling discussions.

Please acknowledge receipt of this email, and feel free to contact me if you have any questions.
Thank you.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
06/09/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Subject: NDA 208587: Carcinogenicity Assessment Document- Request for Waiver
Date: Thursday, June 08, 2017 7:31:00 AM

Ms. Tran,

This e-mail is in reference to NDA 208587, regarding SDN 20 and your waiver request: *"Does the Agency concur that based on the weight of evidence presented herein a waiver for conducting rodent carcinogenicity studies with L-glutamine is acceptable?"* Please be advised that yes, we concur. Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
06/08/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: "[Yutaka Niihara](#)"
Subject: NDA 208587: Information Request (due 4:30 pm ET, June 7, 2017)
Date: Monday, June 05, 2017 12:06:00 PM

Ms. Tran,

Regarding NDA 208587, we have a request for the following information as stated below. Please acknowledge receipt of this e-mail, and provide the necessary response/requested information by 4:30 pm ET June 7, 2017 (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

1. For subjects in your integrated safety dataset (Studies 10478 & GLUSCC09-01), please provide a breakdown of ethnicity as shown in the table below:

	Endari N = 187 n (%)	Placebo N = 111 n (%)	Total N = 298 n (%)
Ethnicity			
Hispanic			
Non-Hispanic			

2. We would like to explore the efficacy of Endari by ethnicity. Please provide a summary of baseline characteristics (age, HU use at baseline, study treatment group) and the clinical outcomes (number of crises at baseline, number of crises experienced during the study, duration of treatment, study discontinuation-Y/N) for Hispanic patients enrolled studies 10478 and GLUSCC09-01.

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MICHAEL V GWATHMEY
06/05/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#)
Subject: FW: NDA 208587- Carton/Container Labeling Guidance.....
Date: Wednesday, May 31, 2017 10:10:00 AM

Ms. Tran,

This e-mail is in reference to NDA 208587. Regarding your carton and container label, the Agency is providing **revised** recommendations that should be implemented prior to approval of this NDA:

A. Carton Label

1. Revise presentation of drug product established name on the PDP to be consistent with USP requirements: L-glutamine oral **powder**.
2. Revise the strength on the PDP as currently presented it is not prominent.
3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of 1 unit and carton labeling of (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.
4. Revise the statement (b) (4). E.g. "mix with cold or room temperature food or beverage".
5. Remove bold font on manufacturer information as it takes reader's attention from important information such as proprietary and proper names, administration information and per packet strength.
6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

B. Container Label

1. See A.1 through A.6.

Please acknowledge receipt of this e-mail, and let me know if you have any further questions. Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager

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Michael.Gwathmey@fda.hhs.gov

From: Gwathmey, Michael
Sent: Friday, January 27, 2017 12:57 PM
To: Yutaka Niihara
Cc: 'Lan Tran'; Fahnbulleh, Frances
Subject: NDA 208587- Carton/Container Labeling Guidance.....

Dr. Niihara,

This e-mail is in reference to NDA 208587. The Agency has reviewed your carton and container label, and we recommend the following be implemented prior to approval of this NDA 208587:

A. Carton Label

1. Revise presentation of drug product established name on the PDP to be consistent with USP requirements: L-glutamine powder for oral solution.
2. Revise the strength on the PDP as currently presented it is not prominent.
3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of 1 unit and carton labeling of (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.
4. Revise the statement (b) (4). E.g. "mix with cold or room temperature food or beverage".
5. Remove bold font on manufacturer information as it takes reader's attention from important information such as proprietary and proper names, administration information and per packet strength.
6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

B. Container Label

1. See A.1 through A.6.

Please acknowledge receipt of this e-mail, and let me know if you have any further questions. Thank you.

Michael Gwathmey, RN

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/s/

MICHAEL V GWATHMEY
05/31/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Cc: [Yutaka Niihara](#)
Subject: NDA 208587- Information Request due 4:30 pm ET, May 31, 2017
Date: Tuesday, May 30, 2017 12:19:00 PM

Ms. Tran,

Regarding NDA 208587, we have a request for the following information as stated below. Please acknowledge receipt of this e-mail, and provide the necessary response/requested information by 4:30 pm ET, May 31, 2017 (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Using the table shells below, please provide a summary of TEAEs and SAEs by baseline body weight for subjects in the safety population (Studies 10478 & GLUSC09-01)

TEAEs by baseline body weight

<i>Body weight category (kg)</i>	L-glutamine		Placebo	
	<i>Number of subjects</i>	<i>N (%) with = 1 TEAE</i>	<i>Number of subjects</i>	<i>N (%) with = 1 TEAE</i>
< 30				
30-65				
66-100				
>100				

SAEs by baseline body weight

<i>Body weight category (kg)</i>	L-glutamine		Placebo	
	<i>Number of subjects</i>	<i>N (%) with = 1 SAE</i>	<i>Number of subjects</i>	<i>N (%) with = 1 SAE</i>
< 30				
30-65				
66-100				
>100				

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MICHAEL V GWATHMEY
05/30/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#); [Wall, Laura](#)
Subject: NDA 208587- Information Request
Date: Friday, May 19, 2017 11:07:00 AM

Ms. Tran,

Regarding NDA 208587, we have a request for the following information:

- For all ACS events reported as TEAEs or SAEs in the safety population (studies 10478 and GLUSCC0901), please specify how many events (number (%), by treatment group) met the criteria for the protocol definition of ACS and were therefore also included in the primary efficacy endpoint analyses.

Please acknowledge receipt of this e-mail, and provide a response by **COB Monday May 22, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
05/19/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#); [Wall, Laura](#)
Subject: NDA 208587- Information Request (due COB Monday May 15, 2017)
Date: Monday, May 15, 2017 8:42:00 AM

Ms. Tran,

Regarding NDA 208587, we have a request for the following information:

- For Studies 10478 and GLUSCC0901, please clarify if acute chest syndrome events listed as Adverse events are also included in the primary efficacy endpoint.

Please acknowledge receipt of this e-mail, and provide a response by **COB Monday May 15, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
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MICHAEL V GWATHMEY
05/15/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Cc: [Yutaka Niihara](#)
Subject: NDA 208587 Information Request: Due by 4:00 pm ET Monday May 15, 2017
Date: Friday, May 12, 2017 12:59:00 PM

Ms. Tran,

Regarding NDA 208587, we have a request for the following information as listed below:

1. Please provide the reason for excluding children less than 5 years of age from enrollment in Study 10478 and Study GLUSCC09-01.
2. For Tables 9 and 10 in your Integrated Summary of Safety, please combine abdominal pain and abdominal pain, upper, into one category and provide an updated table.

Please acknowledge receipt of this e-mail, and respond by **4:00 pm ET Monday May 15, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
05/12/2017

From: Gwathmey, Michael
To: "[Lan Tran](#)"
Cc: [Yutaka Niihara](#)
Subject: FW: NDA 208587- Information Request
Date: Wednesday, May 10, 2017 12:49:00 PM

Ms. Tran,

Regarding NDA 208587, we have the following comments relating to your May 3, 2017 e-mail that was in response to our Information Request (IR) from May 1, 2017:

- **With regard to STAT Dataset and code submissions:**

Please note that STAT dataset and code submission do not meet the regulatory standard.

For your information, please see Page 13 in the following electronic data submission guidance. It is stated that "The SAS Transport Format (XPORT) Version 5 is the file format for the submission of all electronic datasets."

<https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm384744.pdf>

Also, please refer to row 23-29 in the following guidance. It is noted that we only accept SAS .xpt for data submission.

<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm2005545.htm>

In addition, we have a request for the following information relating to your May 3, 2017 e-mail that was in response to our IR from May 1, 2017 (to note, submission of additional datasets are not needed):

- **With regard to your response to Question 1 :**

It appears that the dataset ADSHER that you submitted on 1/23/2017 was a one record per patient data. In fact, a data set with one record per occurrence of crises per patient data including the variables specified in our previous requests, may be more helpful.

For your information, we have been using your intermediate dataset DS21 and the intermediate derived variable LAST48DT (defined a last48dt=min(w48dt,*/vsdt,*/exitdt,sd350dt)) as the cutoff date based on the SAS program submitted originally (d_pscs.sas) for our analyses.

The purpose of the SD350dt and w48dt in the derivation of LAST48DT in the dataset VISDT is not clear to us. We note that when we plot the data, the range of times exceeds 48 weeks. **Can you explain that?**

Please acknowledge receipt of this e-mail, and respond to the information request by **4:00 pm ET**

Friday May 12, 2017 (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
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/s/

MICHAEL V GWATHMEY
05/10/2017

From: Gwathmey, Michael
To: [Yutaka Niihara](#)
Cc: "Lan Tran"
Subject: NDA 208587- Information Request
Date: Monday, May 01, 2017 7:32:00 AM

Dr. Niihara,

Regarding NDA 208587, we have a request for the following information as listed below:

- In order to discuss the analyses based on the same dataset, we request that the derived data (include, but do not limit to cumulative count data age, HU use, pooled site variable, baseline crisis count data, duration on study,) that was used to perform your sensitivity analyses to be submitted. Please provide a lists of patient IDs who did not have any crisis count recorded in dataset ADJAE but you may have assigned it with a value (any value >=0)
 - . The assigned value should also be included in the list. We request that a SAS dataset of this list to be included as well.

Also, please note that we have been working on the analyses based on your intermediate dataset DS21 and derived dataset VISDT (shown on the primary analysis SAS codes t_PSCC.SAS submitted in the original submission). Based on those datasets, we are not able to come up with a total of 525 crises and 53250 days as you mentioned in the correspondence sent on 4/28. So, in addition to submit the derived dataset, the SAS codes that were used to derive this dataset should be submitted. Also, please inform us if there is any revisions of the original SAS codes.

Please acknowledge receipt of this e-mail, and respond by **4:00 pm ET Thursday May 4, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
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/s/

MICHAEL V GWATHMEY
05/01/2017

From: Gwathmey, Michael
To: [Yutaka Niihara](#)
Cc: "Lan Tran"
Subject: NDA 208587- Information Request
Date: Tuesday, April 25, 2017 4:40:00 PM

Dr. Niihara,

Regarding NDA 208587, we have a request for information as listed below:

**** Provide the following data for subjects in the safety population from Study GLUSCC09-01 only.**

	L-glutamine		Placebo	
	Treated with HU	Not treated with HU	Treated with HU	Not treated with HU
Subjects with \geq 1 TEAE, n (%)				
Sickle cell anemia with crisis				
Acute chest syndrome				
Subjects with SAEs, n (%)				
TEAE leading to withdrawal, n (%)				

Please acknowledge receipt of this e-mail, and respond by **12:00 pm Thursday April 27, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
04/25/2017

From: Gwathmey, Michael
To: [Yutaka Niihara](#)
Cc: "[Lan Tran](#)"
Subject: NDA 208587 Information Request
Date: Tuesday, April 25, 2017 11:46:00 AM

Dr. Niihara,

Regarding NDA 208587, we have a request for information as listed below. Please acknowledge receipt of this e-mail, and respond by **12:00 pm Friday April 28, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

** Please provide reasons of early drop-out for the following 24 patients:

Early drop-out patients with missing crisis count

Obs	PT	COHORT
1	01-102	1
2	02-102	1
3	02-503	1
4	03-107	1
5	04-504	1
6	05-102	2
7	07-101	1
8	07-502	2
9	07-503	1
10	08-503	1
11	09-512	1
12	10-101	1
13	10-502	2
14	10-503	1
15	13-101	1
16	16-103	1
17	16-104	1
18	16-105	1
19	16-502	1
20	21-504	1

21 21-507

22 25-102

23 28-502

24 30-103 2

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/s/

MICHAEL V GWATHMEY
04/25/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Cc: [Miller, Mara Bauman](#)
Subject: RE: NDA 208587 (Information Request- Patent Certification) - response to your questions
Date: Thursday, March 16, 2017 5:20:00 PM

Ms. Tran,

Regarding your questions that referred to the Information Request Letter (Patent Certification) that was sent on 3/7/17, please see the responses in below in **RED**:

I want to confirm whether we need to submit an updated 1.3.5.2 Patent certification to the NDA or if such certification should be made in the cover letter with a reference to the submission made on 2 March 2017. Also, moving forward, should a patent certification be included in all cover letters for our submissions? **Response: You will not need to submit an updated 1.3.5.2. form at this time. As stated in the Information Request Letter, you can include the relevant statement in the cover letter when responding to the IR, as well as in cover letters of future submissions.**

The certification that we will make is a Paragraph II Certification as per CFR 314.60 (f). The patent that covered the work in NDA 208587 is patent # US 5693671 A. Such patent expired on 4/30/2016. Further, to our knowledge the paragraph IV certification that we made is still correct. I am unclear if we need to include both certifications. Any guidance you can provide on this matter is greatly appreciated. **Response: Since there are no expired patents, Paragraph IV does not apply to this application. The Paragraph II certification is correct.**

Thank you and feel free to contact me with any additional questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Thursday, March 16, 2017 5:06 PM
To: Gwathmey, Michael

Subject: Re: NDA 208587 (Information Request- Patent Certification)

Dear Mr. Gwathmey,

Thank you for your email. Do you have an idea of when I can expect to hear back? I was hoping to formally submit our responses to the requests for information regarding morality and lab parameters on Friday and will be including a cover letter to such responses.

Sincerely,
Lan

On Wed, Mar 15, 2017 at 1:17 PM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:

Ms. Tran,

This e-mail is in reference to NDA 208587. Regarding your e-mail below from 3/13/17, we are reviewing your questions and will have a response for you soon. Thank you for your patience.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
[301-796-8498](tel:301-796-8498)
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [mailto:ltran@emmauslifesciences.com]
Sent: Monday, March 13, 2017 8:10 PM
To: Gwathmey, Michael
Cc: Yutaka Niihara
Subject: Re: NDA 208587 (Information Request- Patent Certification)

Dear Mr. Gwathmey,

As a follow-up to your email and letter, I would like to request clarification regarding the patent certification.

I want to confirm whether we need to submit an updated 1.3.5.2 Patent certification to the NDA or if such certification should be made in the cover letter with a reference to the submission made on 2 March 2017. Also, moving forward, should a patent certification be included in all cover letters for our submissions?

The certification that we will make is a Paragraph II Certification as per CFR 314.60 (f). The patent that covered the work in NDA 208587 is patent # US 5693671 A. Such patent expired

on 4/30/2016. Further, to our knowledge the paragraph IV certification that we made is still correct. I am unclear if we need to include both certifications. Any guidance you can provide on this matter is greatly appreciated.

Sincerely,
Lan

On Tue, Mar 7, 2017 at 1:50 PM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:
Ms. Tran,

Regarding NDA 208587, attached is an information request regarding patent certification (see the attached letter for more detail and information). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
[301-796-8498](tel:301-796-8498)
Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
03/16/2017



NDA 208587

**INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION**

Emmaus Medical Inc.
Attention: Yutaka Niihara, MD, MPH
Chairman and CEO
21250 Hawthorne Boulevard, Suite 800
Torrance, CA 90503

Dear Dr. Niihara:

Please refer to your New Drug Application (NDA) dated September 7, 2016, received September 7, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for L-glutamine powder, 5 grams.

We also refer to your amendment dated March 2, 2017. This amendment does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

- 1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

- 2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendment dated March 2, 2017.

If you have any questions, call me at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Michael Gwathmey, RN
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MICHAEL V GWATHMEY
03/07/2017

From: Gwathmey, Michael
To: ["Yutaka Niihara"](#)
Cc: ["Lan Tran"](#)
Subject: NDA 208587- Information Request (due 3/10/17)
Date: Friday, March 03, 2017 11:06:00 AM

Dr. Niihara,

Regarding NDA 208587, we have a request for the following information:

Please provide the following data regarding mortality outcomes for patients enrolled in in Studies 10478 and GLUSCC09-01 for NDA 208587.

1. Provide the death report forms for the 3 treatment emergent deaths that occurred in L-Glutamine treated patients in Studies 10478 and GLUSCC09-01.
2. Provide any evidence you have to show that the mortality rate observed in patients treated with L-Glutamine in your safety population is not greater than the expected mortality rate in this population.
3. Provide any information you may have collected on mortality outcomes for patients who discontinued study treatment.

Please acknowledge receipt of this e-mail, and provide a response by **Friday, March 10, 2017** (followed by an official submission to the NDA). Thank you and feel free to contact me if you have any questions

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
03/03/2017

From: Gwathmey, Michael
To: "Yutaka Niihara"
Cc: "Lan Tran"
Subject: RE: NDA 208587- Information Request (Due March 8, 2017)
Date: Tuesday, February 28, 2017 4:57:00 PM

Dr. Niihara,

A correction to the e-mail below: Please acknowledge receipt of this e-mail, and provide a response by **Wednesday March 8, 2017** (followed by an official submission to the **NDA**). Thank you.

Michael Gwathmey, RN

From: Gwathmey, Michael
Sent: Tuesday, February 28, 2017 4:54 PM
To: Yutaka Niihara
Cc: 'Lan Tran'
Subject: NDA 208587- Information Request (Due March 8, 2017)

Dr. Niihara,

Regarding NDA 208587, we have a request for the following information:

Please provide the following additional information to facilitate further review of NDA 208587:

1. Provide narratives for the following patients with serious AEs considered related to study treatment.

Study 10478: Patient 102EM005
GLUSCC09-01: Patients 21-101 and 08-503

2. Please provide narratives for the following patients noted to have potentially significant changes in blood chemistry parameters:

0901-17-501
0901-14-502
0901-04-101
0901-09-514

3. Provide table (see examples below) showing summary of common AEs and SAEs for patients with baseline renal and hepatic abnormalities (Grades 1-4) for patients in the safety population. Please provide separate tables for BUN, Cr, ALT, AST, GGT and Alkaline phosphatase.

For subjects with Grade 3 renal/hepatic abnormalities at baseline

	L glutamine			Placebo		
<i>PT</i>	<i>Events</i>	<i>Number of</i>	<i>Proportion</i>	<i>Events</i>	<i>Number of subject</i>	<i>Proportion</i>

For subjects with Grade 4 renal/hepatic abnormalities at baseline

	L glutamine			Placebo		
<i>PT</i>	<i>Events</i>	<i>Number of</i>	<i>Proportion</i>	<i>Events</i>	<i>Number of subject</i>	<i>Proportion</i>

For subjects with all grades of renal/hepatic abnormalities at baseline

	L glutamine			Placebo		
<i>PT</i>	<i>Events</i>	<i>Number of</i>	<i>Proportion</i>	<i>Events</i>	<i>Number of subject</i>	<i>Proportion</i>

Please acknowledge receipt of this e-mail, and provide a response by **Wednesday March 8, 2017** (followed by an official submission to the IND). Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
 LCDR, U.S. Public Health Service
 Regulatory Health Project Manager
 Division of Hematology Products
 Office of Hematology and Oncology Products
 Center for Drug Evaluation and Research
 Food and Drug Administration
 10903 New Hampshire Avenue, Bldg. 22, Room 3215
 Silver Spring, MD 20993
 301-796-8498
Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
02/28/2017



NDA 208587

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Emmaus Medical, Inc.
21250 Hawthorne Blvd.
Suite 800
Torrance, CA 90503

ATTENTION: Lan T. Tran, MPh
Chief Administrative Officer

Dear Mr. Tran:

Please refer to your New Drug Application (NDA) dated and received on September 7, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for L-glutamine Powder, 5 grams.

We also refer to your correspondence dated and received November 30, 2016, requesting review of your proposed proprietary name, Endari.

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

If any of the proposed product characteristics as stated in your November 30, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796- 0942. For any other information regarding this application, contact Michael Gwathmey, Regulatory Project Manager in the Office of New Drugs at (301)796-8498.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/27/2017

From: Gwathmey, Michael
To: ["Lan Tran"](#)
Subject: RE: NDA 208587/FDA Response to Clarification Question - Filing Letter: Response to your request to respond by 2/10/17
Date: Friday, February 03, 2017 7:24:00 AM

Ms. Tran,

This e-mail is in reference to NDA 208587, regarding the IR that was sent on 1/18/17. To follow up on the e-mail that I sent yesterday, please forward your response next week **as one package (to include all data tables)**. Thank you and contact me if you have any questions.

Michael Gwathmey, RN

From: Gwathmey, Michael
Sent: Thursday, February 02, 2017 4:34 PM
To: 'Lan Tran'
Subject: RE: NDA 208587/FDA Response to Clarification Question - Filing Letter: Response to your request to respond by 2/10/17

Ms. Tran,

Thank you for the e-mail and information. Concerning your questions regarding whether to send data tables as they become available versus sending the entire package once completed, I will ask the reviewers and let you know of their response as soon as possible.

Regards,

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Thursday, February 02, 2017 2:52 AM
To: Gwathmey, Michael
Subject: Re: NDA 208587/FDA Response to Clarification Question - Filing Letter: Response to your request to respond by 2/10/17

Dear Mr. Gwathmey,

Thank you for your time today. I wanted to confirm that we will not be able to submit the response by 2/3/17. We continue to work through preparing the information for submission and may not have the tables until at least Wednesday. We will then need to prepare all of the text summaries as requested. Apologies that this is taking longer than we had anticipated.

I have discussed with the team the possibility of perhaps providing the additional data tables as soon as they are available, to you. Please let me know if this may be helpful or if the preference is to receive the entire package once it is all ready. Nonetheless, we remain committed to providing the requested information as soon as possible.

Sincerely,
Lan

On Mon, Jan 30, 2017 at 2:35 PM, Lan Tran <ltran@emmauslifesciences.com> wrote:
Dear Mr. Gwathmey,

Thank you for your email. I've discussed this with the team and hope to have an update for you tomorrow regarding timing. I will try calling you tomorrow.

Thanks,
Lan

On Fri, Jan 27, 2017 at 12:00 PM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:
Ms. Tran,

This e-mail is in reference to NDA 208587, regarding the Information Request from 1/18/17 and your request to respond by 2/10/17. If there is any way possible to submit your response by **2/3/17**, that will be preferable. Thank you and contact me if you have any

questions. Michael Gwathmey, RN

From: Lan Tran [mailto:ltran@emmauslifesciences.com]
Sent: Thursday, January 26, 2017 6:52 PM
To: Gwathmey, Michael
Subject: Re: NDA 208587/FDA Response to Clarification Question - Filing Letter

Thank you, Mr. Gwathmey.

On Thu, Jan 26, 2017 at 3:41 PM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:
Ms. Tran,

In reference to NDA 208587, thank you for the e-mail and sorry I missed your call. Regarding your request (as stated below), I will forward the message to the reviewing team and contact you once I receive a response from them. Thank you and let me know if you have any further questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager

Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
[301-796-8498](tel:301-796-8498)
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Thursday, January 26, 2017 5:48 PM
To: Gwathmey, Michael
Subject: Re: NDA 208587/FDA Response to Clarification Question - Filing Letter

Dear Mr. Gwathmey,

As a follow-up to my voice mail, I wanted to confirm receipt of the email from Dr. Kolibab and also request an extension for the submission of the information. We did not see a formal deadline for the submission in the Day 74 letter.

We continue to work through integrating the data sets and hope to be able to provide the newly integrated safety data set which would include the legacy studies as well as appropriate tables and text. Although we originally had hoped to deliver such materials by tomorrow (1/27/17) we will need just a few more weeks pull everything together and would anticipate to be able to submit by 2/10. Please let me know if this will be acceptable.

Sincerely,
Lan

On Wed, Jan 18, 2017 at 7:20 AM, Kolibab, Kristopher <Kristopher.Kolibab@fda.hhs.gov> wrote:
Hello Lan,

Please refer to NDA 208587 and the follow up questions you sent below. We remind you the response is due by **Friday January 27, 2017**.

Please submit the following:

- 1. An updated integrated database to include the safety data from studies 8288, 8775, 10779, and 10511;**
- 2. New safety analyses/summaries; and**
- 3. Updates to Tables 1-23 in the Summary of Clinical Safety (in module 2.7.4) where applicable.**

Please confirm receipt of this message via email.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: [240-402-0277](tel:240-402-0277)

From: Lan Tran [mailto:ltran@emmauslifesciences.com]
Sent: Tuesday, January 17, 2017 3:42 PM
To: Kolibab, Kristopher
Cc: Gwathmey, Michael
Subject: Fwd: NDA 208587 - Day 74 Letter - Request for Clarification - Clinical Q1

Dear Dr. Kolibab,

My apologies for having to bother you while Mr. Gwathmey is away. However, I was wondering if you would be able to help with the question below.

Sincerely,
Lan

----- Forwarded message -----

From: Lan Tran <ltran@emmauslifesciences.com>
Date: Tue, Jan 17, 2017 at 12:11 PM
Subject: Re: NDA 208587 - Day 74 Letter - Request for Clarification - Clinical Q1
To: "Gwathmey, Michael" <Michael.Gwathmey@fda.hhs.gov>
Cc: Yutaka Niihara <yniihara@emmauslifesciences.com>

Hi Mr. Gwathmey,

I hope this email finds you well. I wanted to follow-up with you to check to see whether you've had an opportunity to review the email below to provide us with some clarification.

I wanted to add that we wanted to make sure that we understood whether you are expecting both an updated ISS data set that include all studies and an updated 2.7.4 with accompanying ISS tables or if just an updated ISS data set will suffice.

Thank you for your continued guidance.

Sincerely,
Lan

On Mon, Jan 9, 2017 at 5:38 PM, Lan Tran <ltran@emmauslifesciences.com> wrote:
Dear Mr. Gwathmey,

This email is in regards to the Day 74 letter. I was hoping to receive calcification to the sentence in bold and underline below which was excerpted from the letter.

"Clinical:

1. The integrated safety data submitted with your NDA application is inadequate because it does not include safety data from all clinical studies of L-Glutamine in patients with sickle cell anemia. For a chronically administered drug, the total number of patients exposed to L- glutamine seems small per ICH guidelines; therefore, safety data from all clinical studies trials of L-Glutamine in patients with sickle cell anemia need to be considered. **Please submit a revised integrated safety database and analysis and integrated summary of safety including the safety data from Studies 8288, 8775, 10779, and 10511.**"

In NDA 208587, our narrative portion of the integrated summary of safety is located in module 2.7.4, which approach we interpreted to be acceptable as per the 'Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document' dated April 2009 to be acceptable. Based on this, can you clarify the following?

Are you requesting that we:

- 1 a) Submit an updated integrated database to include the safety data from the aforementioned studies, and;
- 1 b) Submit new safety analyses/summaries, and;
- 1 c) Update module 2.7.4 to include safety data from all clinical studies of L-glutamine based on the "new" summaries, or;

2) Will submission of the integrated database suffice?

Thank you for your continued help.

Sincerely,
Lan

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/s/

MICHAEL V GWATHMEY
02/06/2017

From: Gwathmey, Michael
To: [Yutaka Niihara](#)
Cc: "[Lan Tran](#)"; [Fahnbulleh, Frances](#)
Subject: NDA 208587- Carton/Container Labeling Guidance.....
Date: Friday, January 27, 2017 12:56:00 PM

Dr. Niihara,

This e-mail is in reference to NDA 208587. The Agency has reviewed your carton and container label, and we recommend the following be implemented prior to approval of this NDA 208587:

A. Carton Label

1. Revise presentation of drug product established name on the PDP to be consistent with USP requirements: L-glutamine powder for oral solution.
2. Revise the strength on the PDP as currently presented it is not prominent.
3. When assigning National Drug Code (NDC) numbers, ensure the NDC number assigned to the inner label (container) and the outer label is appropriate. The container label of 1 unit and carton labeling of (b) (4) should have different NDC numbers. In addition, the NDC number is denoted by a placeholder. Please submit the NDC number.
4. Revise the statement (b) (4). E.g. "mix with cold or room temperature food or beverage".
5. Remove bold font on manufacturer information as it takes reader's attention from important information such as proprietary and proper names, administration information and per packet strength.
6. The drug barcode is often used as an additional verification before drug administration and/or dispensing. Therefore it is an important safety feature that should be part of the label when possible. We request you add a product barcode to the label.

B. Container Label

1. See A.1 through A.6.

Please acknowledge receipt of this e-mail, and let me know if you have any further questions. Thank you.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products

Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
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Michael.Gwatbmszy@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
01/27/2017

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, January 18, 2017 10:21 AM
To: 'Lan Tran'
Cc: Gwathmey, Michael
Subject: NDA 208587/FDA Response to Clarification Question - Filing Letter

Hello Lan,

Please refer to NDA 208587 and the follow up questions you sent below. We remind you the response is due by **Friday January 27, 2017**.

Please submit the following:

1. An updated integrated database to include the safety data from studies 8288, 8775, 10779, and 10511;
2. New safety analyses/summaries; and
3. Updates to Tables 1-23 in the Summary of Clinical Safety (in module 2.7.4) where applicable.

Please confirm receipt of this message via email.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Tuesday, January 17, 2017 3:42 PM
To: Kolibab, Kristopher
Cc: Gwathmey, Michael
Subject: Fwd: NDA 208587 - Day 74 Letter - Request for Clarification - Clinical Q1

Dear Dr. Kolibab,

My apologies for having to bother you while Mr. Gwathmey is away. However, I was wondering if you would be able to help with the question below.

Sincerely,
Lan

----- Forwarded message -----

From: Lan Tran <ltran@emmauslifesciences.com>
Date: Tue, Jan 17, 2017 at 12:11 PM
Subject: Re: NDA 208587 - Day 74 Letter - Request for Clarification - Clinical Q1
To: "Gwathmey, Michael" <Michael.Gwathmey@fda.hhs.gov>
Cc: Yutaka Niihara <yniihara@emmauslifesciences.com>

Hi Mr. Gwathmey,

I hope this email finds you well. I wanted to follow-up with you to check to see whether you've had an opportunity to review the email below to provide us with some clarification.

I wanted to add that we wanted to make sure that we understood whether you are expecting both an updated ISS data set that include all studies and an updated 2.7.4 with accompanying ISS tables or if just an updated ISS data set will suffice.

Thank you for your continued guidance.

Sincerely,
Lan

On Mon, Jan 9, 2017 at 5:38 PM, Lan Tran <ltran@emmauslifesciences.com> wrote:

Dear Mr. Gwathmey,

This email is in regards to the Day 74 letter. I was hoping to receive calcification to the sentence in bold and underline below which was excerpted from the letter.

"Clinical:

1. The integrated safety data submitted with your NDA application is inadequate because it does not include safety data from all clinical studies of L-Glutamine in patients with sickle cell anemia. For a chronically administered drug, the total number of patients exposed to L- glutamine seems small per ICH guidelines; therefore, safety data from all clinical studies trials of L-Glutamine in patients with sickle cell anemia need to be considered. **Please submit a revised integrated safety database and analysis and integrated summary of safety including the safety data from Studies 8288, 8775, 10779, and 10511.**"

In NDA 208587, our narrative portion of the integrated summary of safety is located in module 2.7.4, which approach we interpreted to be acceptable as per the 'Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document' dated April 2009 to be acceptable. Based on this, can you clarify the following?

Are you requesting that we:

- 1 a) Submit an updated integrated database to include the safety data from the aforementioned studies, and;
 - 1 b) Submit new safety analyses/summaries, and;
 - 1 c) Update module 2.7.4 to include safety data from all clinical studies of L-glutamine based on the "new" summaries, or;
- 2) Will submission of the integrated database suffice?

Thank you for your continued help.

Sincerely,
Lan

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

/s/

KRISTOPHER KOLIBAB
01/18/2017

From: Gwathmey, Michael
To: ["yniihara@emmausmedical.com"](mailto:yniihara@emmausmedical.com)
Cc: "Lan Tran"; Baird, Amy; Miller, Mara Bauman
Subject: NDA 208587- Information Request
Date: Tuesday, November 29, 2016 8:00:00 AM

Dr. Niihara,

In reference to NDA 208587 (L-glutamine), we have a request for the following information (for clinical site inspections):

1. Submit the following study subject data listing information for each clinical site listed below, **as a separated pdf file for each site.**

Study GLUSCC09-01:

- Site 14- Dr. Swayam Sadanandan,
- Site 2- Dr. Patricia Ann Oneal
- Site 21- Dr. Joseph Lasky

Study 10478:

- Site 101- Dr. Yutaka Niihara

- a) Study primary efficacy endpoint raw data (each component, including timing/duration of each event, and determination).
- b) Subject discontinuations (site, subject number, screening visit date, date of first dose/last dose, date of discontinuation, and the reason for discontinuation).
- c) Protocol deviation or violation
- d) Treatment compliance
- e) Concomitant medication list (i.e., non-study medications).
- f) All adverse events, both during treatment or post-treatment AEs (preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event [yes/no], death [yes/no]).

2. Verify clinical site information and provide updated phone numbers and email addresses for these sites.

Clinical Investigator Sites for inspection	Study	Site#
Swayam Sadanandan, MD The Brooklyn Hospital Center, Brooklyn, NY Phone: Email:	GLUSCC0 9-01	14
Patricia Ann Oneal, MD, Howard University Hospital, Washington, DC	GLUSCC0 9-01	2

Phone: Email:		
Joseph Lasky, MD Lance Sieger, MD, Harbor-UCLA Medical Center, Torrance, CA Phone: Email:	GLUSCCO 9-01	21
Yutaka Niihara, MD Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center 1124 W Carson Street Torrance, CA 90502 Phone: Email:	10478	101

Please acknowledge receipt of this e-mail, and respond by **November 30, 2016**. Thank you and feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
11/29/2016



NDA 208587

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Emmaus Medical Inc.
Attention: Yutaka Niihara, MD, MPH
Chairman and CEO
21250 Hawthorne Boulevard, Suite 800
Torrance, CA 90503

Dear Dr. Niihara:

Please refer to your New Drug Application (NDA) dated September 7, 2016, received September 7, 2016, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for L-glutamine powder, 5 grams.

We also refer to your amendment dated October 18, 2016.

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 July 7, 2017.

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 June 9, 2017.

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

CLINICAL

1. The integrated safety data submitted with your NDA application is inadequate because it does not include safety data from all clinical studies of L-Glutamine in patients with sickle cell anemia. For a chronically administered drug, the total number of patients

exposed to L-Glutamine seems small per ICH guidelines; therefore, safety data from all clinical studies trials of L-Glutamine in patients with sickle cell anemia need to be considered. Please submit a revised integrated safety database and analysis and integrated summary of safety including the safety data from Studies 8288, 8775, 10779, and 10511.

2. In your pivotal Study GLUSCC09-01, a greater proportion of patients in the glutamine group did not complete the study. Please provide a table showing a comparison of the baseline characteristics for patients who completed 48-week treatment and those who discontinued treatment prematurely.
3. In Study GLUSCC09-01, the primary endpoint - sickle cell crisis includes acute chest syndrome however, ACS is also used as a separate secondary efficacy endpoint.
 - a. In your list of TEAEs and SAEs (ISS, Tables 7 & 9), please clarify if sickle cell anemia with crisis includes acute chest syndrome which is listed as a separate SAE.
 - b. To evaluate the impact of acute chest syndrome (ACS) on your primary efficacy analysis (controlling for region and hydroxyurea use), provide a separate efficacy analysis excluding ACS from your definition of sickle cell crisis.
4. Exchange blood transfusions and packed red blood cell transfusions occur frequently in sickle cell anemia patients and may alter the frequency of sickling crises in this population. Please provide a table show the frequency and percentage of exchange blood transfusions and PRBC transfusions by treatment group for your efficacy population.
5. In Study GLUSCC09-01, for the dataset XP, the variable XPTRT is labelled as "Reported Name of Procedure" however, in the annotated CRF, XPTRT is for blood product. Please explain this discrepancy.

CLINICAL PHARMACOLOGY

- You proposed a dosing regimen that could result in substantial increase in the exposure of L-glutamine in patients with relative lower body weight compared to patients with relative higher body weight within each proposed weight-based dosing tier. Please provide a summary of treatment emergent adverse events (TEAEs), serious AE's and TEAEs leading to study drug discontinuation in the L-glutamine and the placebo treatment groups by the following weight categories for review: 0 – 9.9 kg, 10 – 19.9 kg, 20- 29.9 kg, 30 – 39.9 kg, 40 – 49.9 kg, 50 – 59.9 kg, 60 -74.9 kg, and ≥ 75 kg.

PHARMACOLOGY/TOXICOLOGY

- In lieu of conducting carcinogenicity studies with L-glutamine in animals, you should submit a scientifically justified Carcinogenicity Assessment Document (CAD) and a carcinogenicity assessment waiver request.

BIOMETRICS

1. Based on the pre-specified primary efficacy analysis (controlling for region and hydroxyurea use), the result for the primary endpoint of sickle cell crises through Week 48 did not reach the pre-specified significance level of 0.045 (p-value = 0.0603). Additionally, the magnitude of the treatment effect is marginal.
2. The primary efficacy results were inconsistent among geographic regions, as shown by the large difference in results observed based on the stratified analyses adjusted for region and hydroxyurea use (p=0.063) versus results by the analysis adjusted for hydroxyurea use only (p=0.008) from study GLUSCC09-01.
3. Nearly one-third of randomized patients discontinued the study prior to Week 48, with notably more discontinuations from the L-glutamine group. A previous statistical review of the GLUSCC09-01 Protocol (dated 30 December 2009) indicated that “if the drop-out rate is similar in the two arms of the study, the proposed imputation method may be reasonable.” Since the drop-out rate is imbalanced, the impact of the imputation scheme for sickle cell crisis events in patients who discontinued prior to week 48 is not clear. Interpretation of the primary efficacy results will be a review issue.
4. To facilitate efficient review of the impact of imputation on your efficacy findings for study 10478 and GLUSCC09-01, please provide:
 - a. An efficacy analysis dataset that includes for each patient, the original counts (not altered or imputed) of sickle cell crises, hospitalizations, and ER/Medical Facility visits (i.e., the dataset used for the analyses presented at the October 27, 2016 Applicant Orientation Meeting).
 - b. A summary of the frequency of the observed number of crises (unaltered, and not imputed) by treatment group that distinguishes patients with missing data on number of crises from patients who had zero observed crises at withdrawal or at study end.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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 [Pregnancy and Lactation Labeling Final Rule](#) websites, which include

- 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 the following labeling issues and have the following labeling comments or questions:

1. Your prescribing information (PI) must comply with the Physician Labeling Rule (PLR) format. PLR format requires that the Highlights section be a minimum of 8-point font and in a two-column format with ½ inch margins on all sides and between columns and be contained within ½ page.
2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
3. A horizontal line must separate:
 - HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).
4. Headings in HL must be presented in order and include all categories (Contraindication section not present).
5. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”
6. The Drug Interactions subsection in HL is optional and may be deleted. Since you list (b) (4) here, we recommend deletion.
7. The TOC should be in a two-column format.
8. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
9. Your prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. Therefore, resubmit labeling in PLLR format by December 9, 2016. The submission should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be

located in Module 1. Refer to the *draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

10. Section 17: Patient Counseling: Please revise this section in accordance with the Patient Counseling Section of Labeling Guidance (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm368602.pdf>). This guidance recommends “the use of subheadings to organize and differentiate topics within the PATIENT COUNSELING INFORMATION section is recommended because they allow the reader to quickly identify the major concepts. Subheading titles should clearly identify the focus of each discussion (e.g., Acute Hepatic Failure rather than simply Hepatic), and a consistent formatting of the subheading titles (e.g., underlining or italicizing) is recommended.” Numbering is NOT recommended for these subheadings. A cross-reference should be inserted to direct the health care provider to the more detailed discussion elsewhere in labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 9, 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.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement

If you have any questions, call Michael Gwathmey, Regulatory Project Manager, at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
11/18/2016

From: Gwathmey, Michael
To: ["yniihara@emmausmedical.com"](mailto:yniihara@emmausmedical.com)
Cc: ["Lan Tran"](#); [Baird, Amy](#); [Miller, Mara Bauman](#)
Subject: NDA 208587- Information request
Date: Monday, November 14, 2016 8:57:00 AM

Dr. Niihara,

In reference to NDA 208587 (L-glutamine), please provide the following information for Study GLUSCC09-01:

1. Perform sensitivity analyses for the primary efficacy endpoint and key secondary endpoints based on alternative imputation methods.
2. Perform a sensitivity analysis for the primary efficacy endpoint/ other endpoints including count data based on the negative binomial (NB) and zero-inflated negative binomial methods. You may define the primary efficacy endpoint as an annualized rate using offset variables in the NB model (see SAS PROC GENMOD). The purpose of the analysis is to take consideration of the duration of the crisis assessments.
3. Perform a sensitivity analysis adjusting for baseline severity of sickle cell crises (number of crises in the last year [or 48 weeks] prior to study start) to estimate the mean number of annualized sickle cell crises.
4. Summarize differential drop-out patterns (either based on a single time point overtime or over 48 weeks) on the observed number of sickle cell crises by treatment group. Please note that a figure of such summary over time may be very helpful.

Please provide a response to item 1 no later than **December 2, 2016**. For all other items, provide responses no later than **December 16, 2016**. Thank you and let me know if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
11/14/2016

From: Gwathmey, Michael
To: "Lan Tran"; "yniihara@emmausmedical.com"
Cc: Baird, Amy; Miller, Mara Bauman
Subject: NDA 208587, L-glutamine: Information Request clarification
Date: Monday, October 24, 2016 3:32:00 PM

Ms. Tran,

This e-mail is with regards to NDA 208587 for L-glutamine, specifically your e-mail response/inquiry dated October 20, 2016:

- The review team requests option 2b proposed by the Applicant ("We can create the new sections and update the related sections that are affected such as Module 2.4 Nonclinical Overview, Labelling 12.1, references, etc. and create links from the associated sections...."). An extended period of time to complete the revisions is acceptable.

Please acknowledge receipt of this e-mail, and submit your response by COB November 21, 2016. Thank you and please feel free to contact me if you have any other questions.

Michael Gwathmey, RN

LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
301-796-8498
Michael.Gwathmey@fda.hhs.gov

From: Lan Tran [<mailto:ltran@emmauslifesciences.com>]
Sent: Thursday, October 20, 2016 4:35 PM
To: Yutaka Niihara
Cc: Gwathmey, Michael; yniihara@emmausmedical.com; Baird, Amy; Miller, Mara Bauman; Jim Hinson; Peggy Zorn
Subject: Re: FW: NDA 208587, L-glutamine: Information Request

Dear Michael,

Thank you for your email. We have received the information request and are fully committed to aiding the reviewers in their review of the application. We have reviewed the request and would like some clarification.

1) The FDA guidance M4E: CTD-Efficacy, the Summary of Clinical Pharmacology Mod 2.7.2, pg 18 allows for the summary of "clinical studies performed to evaluate human pharmacokinetics (PK) and pharmacodynamics (PD) and in vitro studies performed with human cells, tissues, or related materials (human biomaterials) that are pertinent to PK processes." Since our drug product is L-glutamine, an

endogenous product, we believed that 2.7.2 was the more appropriate placement of such human work, especially that which described the ADME or uptake (ie. cellular transfer) of L-glutamine. This information is readily viewable through those hyperlinks.

Given our intention, does the reviewer still want to us to revise Module 2, Section 2.6 Pharmacology tabulated and written summaries?

2) If the reviewer still wants us to revise Module 2, Section 2.6, that will require us to create the Sections 2.6.2 Pharmacology Written) and 2.6.3 (Pharmacology Tabulated), both of which do not exist in the application. There are two ways for us to proceed:

a) We can create a new section 2.6.2 and 2.6.3 that lists and summarizes the studies in labelling section 12.1. These new sections would be stand alone sections and not linked. We would not remove the existing information for the Clinical Pharmacology Section but duplicate it into the new sections. This would take us a little more time than you have allowed us (Oct 25). Or;

b) We can create the new sections and update the related sections that are affected such as Module 2.4 Nonclinical Overview, Labelling 12.1, references, etc and create links from the associated sections. This is more extensive and we would need to research exactly how long this will take for us to accomplish.

Thank you for your continued help.

Best,
Lan

On Wed, Oct 19, 2016 at 1:32 PM, Yutaka Niihara <yniihara@emmauslifesciences.com> wrote:
Mr. Gwathmey,

Thank you very much for the e-mail request.
We acknowledge the receipt of the e-mail of October 18th and will process the request promptly.
There will be a response from Ms. Lan Tran, our Chief Compliance Officer shortly.

Kind regards,

Yutaka

On Wed, Oct 19, 2016 at 1:05 PM, Gwathmey, Michael <Michael.Gwathmey@fda.hhs.gov> wrote:
Dr. Niihara,

Regarding NDA 208587 for L-glutamine received on September 7, 2016, we have the following request for information.

- Submit a revised Module 2 Section 2.6 Nonclinical Summary to include pharmacology tabulated and written summaries. Currently, the nonclinical studies to support Section 12.1 of the labeling are presented in Module 2 Section 2.7 Clinical Summary.

Please acknowledge receipt of this e-mail, and submit your responses by COB on October 25, 2016. Thank you and please feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
[301-796-8498](tel:301-796-8498)
Michael.Gwathmey@fda.hhs.gov

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Yutaka Niihara MD, MPH
Chairman and CEO, Emmaus Life Sciences, Inc.
[310-214-0065](tel:310-214-0065)
yniihara@emmauslifesciences.com

| |

Clinical Professor of Medicine, David Geffen School of Medicine at UCLA
Member, LA Biomed at Harbor-UCLA Medical Center

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/s/

MICHAEL V GWATHMEY
10/25/2016

From: Gwathmey, Michael
To: ["yniihara@emmausmedical.com"](mailto:yniihara@emmausmedical.com)
Cc: [Baird, Amy](#); [Miller, Mara Bauman](#)
Subject: FW: NDA 208587, L-glutamine: Information Request
Date: Wednesday, October 19, 2016 4:05:00 PM

Dr. Niihara,

Regarding NDA 208587 for L-glutamine received on September 7, 2016, we have the following request for information.

- Submit a revised Module 2 Section 2.6 Nonclinical Summary to include pharmacology tabulated and written summaries. Currently, the nonclinical studies to support Section 12.1 of the labeling are presented in Module 2 Section 2.7 Clinical Summary.

Please acknowledge receipt of this e-mail, and submit your responses by COB on October 25, 2016. Thank you and please feel free to contact me if you have any questions.

Michael Gwathmey, RN
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Room 3215
Silver Spring, MD 20993
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Michael.Gwathmey@fda.hhs.gov

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/s/

MICHAEL V GWATHMEY
10/25/2016



NDA 208587

NDA ACKNOWLEDGMENT

Emmaus Medical Inc.
Attention: Yutaka Niihara, MD, MPH
Chairman and CEO
21250 Hawthorne Boulevard, Suite 800
Torrance, CA 90503

Dear Dr. Niihara:

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

Name of Drug Product: L-glutamine powder, 5 grams

Date of Application: September 7, 2016

Date of Receipt: September 7, 2016

Our Reference Number: NDA 208587

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 6, 2016 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). 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.

If you have any questions, call me at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Michael Gwathmey, RN
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MICHAEL V GWATHMEY
09/22/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 053841

MEETING MINUTES

Emmaus Medical, Inc.
Attention: Lan T. Tran, MPH
Chief Administrative Officer
Emmaus Medical, Inc.
20725 S. Western Ave., Suite 136
Torrance, CA 90501-1884

Dear Ms. Tran:

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

We also refer to the meeting between representatives of your firm and the FDA on June 11, 2014. The purpose of the meeting was to obtain the Division's feedback and guidance on the planned NDA so that it will be acceptable for review.

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 Linhua Tzeng, Regulatory Project Manager, at (240) 402-4619.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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: C
Meeting Category: IND

Meeting Date and Time: June 11, 2014; 1:00 PM – 2:00 PM EST
Meeting Location: White Oak Campus, Building 22, Conference Room: 1311

Application Number: IND 053841
Product Name: L-glutamine
Indication: Treatment of sickle cell disease
Sponsor/Applicant Name: Emmaus Medical, Inc.

Meeting Chair: Kathy Robie Suh, M.D., Ph.D.
Meeting Recorder: Linhua Tzeng, MS

FDA ATTENDEES

Division of Hematology Products (DHP)

Edvardas Kaminskas, M.D., Deputy Director
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader
Min Lu, M.D., M.P.H., Medical Officer
Nicole Verdun, M.D., Medical Officer
Lara Akinsanya, MS, Senior Regulatory Project Manager
Linhua Tzeng, MS, Regulatory Project Manager

Office of Clinical Pharmacology (OCP)

Gene Williams, Ph. D., Clinical Pharmacology Team Leader

Division of Hematology Oncology Toxicology (DHOT)

Haleh Saber, Ph.D., Supervisory Pharmacologist
Christopher Sheth, Ph.D., Pharmacologist

Office of New Drug Quality Assessment (ONDQA)

Janice Brown, MS, CMC Lead Product Quality

Office of Biostatistics, Division of Biometrics V (DBV)

Yuan Li Shen, Ph.D., Lead Mathematical Statistician

Qing Xu, Ph.D., Mathematical Statistician

Office of Manufacturing and Product Quality

Vipul Dholakia, Ph.D., Interdisciplinary Scientist - Chemist

SPONSOR ATTENDEES

Yutaka Niihara, M.D., M.P.H., President and CEO, Emmaus

Lan T. Tran, M.P.H., Chief Administrative Officer, Emmaus

(b) (4)

1.0 BACKGROUND

Emmaus Medical, Inc. requested a type B meeting with FDA on April 14, 2014, to obtain the Division's feedback and guidance on the planned NDA so that it will be acceptable for review. On May 2, 2014, FDA sent Emmaus Medical, Inc. a type C meeting granted letter.

On June 6, 2014, FDA emailed Emmaus Medical, Inc. preliminary responses to the questions contained in the meeting information package dated May 9, 2014.

2.0 DISCUSSION

Question 1: Has Emmaus provided sufficient information to adequately characterize the nonclinical pharmacology and toxicology of L-glutamine to support submission of this application?

Summary of Sponsor's position:

Emmaus has conducted extensive nonclinical pharmacologic research demonstrating the effects of L-glutamine's role in preventing cellular oxidative injury and reducing red blood cell endothelial adhesion in sickle red blood cells. As indicated in previous interactions with the Agency, Emmaus has not conducted any nonclinical toxicology studies with L-glutamine. However, subchronic and chronic toxicity studies in mice, rats and rabbits were performed in support of NDA 21,667, demonstrating limited toxicity in these species at the doses evaluated.

FDA Response to Question 1:

We agree that additional pharmacology/toxicology studies with L-glutamine are not needed, provided that you own (or have a written right of reference to) the data from the nonclinical studies performed in support of NDA 21667. The nonclinical data from studies submitted to NDA 21667 along with pharmacology studies conducted and relevant L-glutamine information from the scientific literature would support the proposed submission.

It is not clear whether the formulation and the manufacturing process are identical to the product under NDA 21667; please clarify. New impurities above the threshold described in relevant guidance documents, e.g. ICH Q3A/B, should be qualified or their levels be adequately justified.

Discussion:

No discussion occurred.

2.1. Clinical Pharmacology

Question 2: Has Emmaus provided sufficient information to adequately characterize the clinical pharmacology and pharmacokinetics of L-glutamine to support submission of this application?

Summary of Sponsor's position:

Emmaus has conducted studies in sickle cell disease patients demonstrating the effects of oral L-glutamine on red blood cell endothelial adhesion and on sickle cell oxidative stress. Additionally, Emmaus will summarize the extensive literature describing the pharmacokinetics of L-glutamine and Emmaus will reference NDA 21,667 in support of the sickle cell product NDA.

FDA Response to Question 2:

It appears acceptable. However, a final decision cannot be made until review of data submitted with your NDA.

Discussion:

No discussion occurred.

2.2. Clinical Efficacy and Safety

Question 3: Does the proposed content of the NDA provide sufficient efficacy and safety data for FDA to accept the NDA for review and to make a marketing approval decision?

Summary of Sponsor's position:

Because of the serious nature of the disease and the small population and unmet medical needs of sickle cell patients, Emmaus has received both orphan drug and fast-track designations for the development of L-glutamine for this indication. Emmaus has conducted a total of 8 clinical studies that included 266 subjects with sickle cell disease who were treated with at least 1 dose of L-glutamine. The Phase 3 (GLUSCC09-01) study compared L-glutamine to placebo(2:1 ratio) in reducing the number of sickle cell crises and the number of hospitalizations through 48 weeks of treatment. Findings from the Phase 2 comparative study (10478) provided further supportive

results. In addition to the safety data obtained from clinical studies conducted under IND 53,841, Emmaus also plans on referencing safety information provided under NDA 21,667 in support of this application. Emmaus believes that the totality of the existing clinical evidence supports a favorable benefit/risk evaluation and marketing approval for L-glutamine for the treatment of sickle cell disease.

FDA Response to Question 3:

The Agency is very interested in the development of agents for the treatment of sickle cell disease. However, based on the provided results of your Phase 3 trial, we have the following concerns for the proposed NDA submission:

- Based on the pre-specified primary efficacy analysis (controlling for region and hydroxyurea use), the result for the primary endpoint of painful sickle cell crisis through Week 48 did not reach the pre-specified significance level of 0.045.
- The primary efficacy results were inconsistent among geographic regions, as shown by the large difference in results observed based on the stratified analyses adjusted for region and hydroxyurea use ($p=0.063$) versus results by the analysis adjusted for hydroxyurea use only ($p=0.008$) from study GLUSCC09-01. The difference in median number of painful sickle cell crises ($=1$) is not clinically meaningful and is not consistent across regions. Provide possible explanations for the differences.
- About one-third of randomized patients discontinued study with significantly more discontinuations from the L-glutamine group. The impact of the imputation scheme for painful sickle cell crisis events in patients who discontinued prior to week 48 is not clear. The interpretation of study results will be difficult.
- As we previously recommended in the Type C meeting (11/5/12), an additional randomized controlled Phase 3 study must be conducted to support the proposed indication. Consider enrolling patients with a higher baseline VOC rate in your next Phase 3 trial to help with demonstrating a statistically significant difference in mean VOC rate in the study population.

Discussion:

The Sponsor explained that they anticipate that aberrant result in a single site in (Atlanta) accounts for the lack of statistical significance for the primary efficacy endpoint and concludes that the study should not have been stratified for region because patients and clinical practice in all of the regions were similar. Detailed analyses for comparability have not been done yet. Sponsor is convinced that the study overall shows a benefit. The Agency emphasized the above comments regarding the study and offered that the sponsor could submit the study report to the IND for review and comments to inform additional study for the indication. Sponsor commented that finding patients to enroll is difficult and this is an orphan disease.

Question 4: Does the FDA agree to our proposal for which datasets will be submitted with the NDA and our proposal regarding not conducting efficacy and safety analyses on a combined dataset?

Summary of Sponsor's position:

The initial proof-of-concept studies were open-label studies involving small numbers of subjects. Consequently, Emmaus plans to submit only the datasets for the Phase 2 and 3 studies. Additionally, since the Phase 3 study contained the large majority of subjects treated with L-glutamine in a controlled setting, Emmaus does not plan to submit a combined dataset. Additional analyses of efficacy and safety using a combined dataset would not be informative, since the large majority of the data would be coming from a single study. Furthermore, a finding of safety for L-glutamine in patients with short bowel syndrome has already been reached by the FDA in connection with NDA 21,667, and will be referenced in the new NDA. Emmaus plans to provide overviews and detailed summaries of efficacy and safety information from all of the clinical studies in sickle cell disease patients in the new NDA.

FDA Response to Question 4:

No. See response to Question 3.

For a NDA submission, the integrated safety analysis should be performed including all clinical trials in patients with sickle cell disease and the integrated summary of safety should be provided for review.

Efficacy analyses on a combined dataset should be performed to comprehensively examine the effectiveness data from individual clinical studies in patients with SCD. The analysis should be stratified by studies. The integrated summary of efficacy (ISE) must include an integrated summary of the data demonstrating substantial evidence of effectiveness for claimed indication.

Discussion:

No discussion occurred.

Question 5: Is it acceptable for Emmaus to submit datasets from the Phase 2 study and Phase 3 study to the NDA in their current format?

Summary of Sponsor's position:

Existing datasets from the Phase 2 study (protocol number 10478) and Phase 3 study (protocol number GLUSCC09-01) are available as SAS transport files with similar file structures. Emmaus does not plan to convert them to CDISC format for submission in the NDA.

FDA Response to Question 5:

- The sponsor should submit SDTM and ADaM formatted datasets.
- Datasets should have one and only one unique subject ID for each patient among all trials. Each dataset should contain a variable for study ID.
- The define.pdf file should contain the descriptions (including coding and definitions of the values) of variable in SAS data sets. For a given quantity, the same variable name should be used for all datasets (i.e., one definition, well-annotated, per variable).
- Please provide a simple and all-containing "Statistical Efficacy Analysis Data Set" for statistical reviewers, in SAS transport format. This should be a reviewer-friendly dataset without the need to merge datasets from demographics, baseline status, other prognostic variables, and efficacy variables, and should contain patient and site/investigator

identifications. We prefer one row of data for each patient, time, and treatment combination.

- There should be an instruction for the reviewer for the use of variables and flags to identify the set of analysis population. Please provide flags to identify, for example, (1) Intent-to-Treat patients set, (2) per-protocol population set and (3) safety population set.
- The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.
- Ensure the SAS dataset file name are consistent with those in the SAS programs that call them, so that the Agency can run the programs smoothly to verify the results / figures / tables reported in the submission.
- Please provide the location of the SAS datasets, the names of the variables used and the programs used to get every new value that will be appearing in the label.

Discussion:

No discussion occurred.

2.3. Chemistry, Manufacturing, and Control

Question 6: Does the FDA agree that the planned specifications will be adequate for drug substance release?

Summary of Sponsor's position:

Emmaus proposes to release the drug substance

(b) (4)

(b) (4)

FDA Response to Question 6:

No. The submitted information package is not sufficient to establish the acceptability of the tests, analytical methods and acceptance criteria in the proposed specification. We recommend that you address the following:

1. According to ICH Q6A, there are universal tests for a drug substance that the USP monograph for L-glutamine does not include, specifically a test for description and process and product related impurities. To support the proposed specification, we recommend that you establish the impurity profile (enantiomers, host cell protein, other amino acids, etc.) of the drug substance and a test for description.
2. Adopt an analytical method for assay that is discriminating (e.g. chiral column) and a method for impurities that is quantitative. The analytical method for impurities should be shown to be capable of detecting these compounds at appropriate levels of selectivity and sensitivity.
3. We remind you to revise the specification and report impurities according to ICH Q3A(R2).
4. Provide a justification why microbial limits are not included in the specification.

The drug substance obtained from the (b) (4) site has not been evaluated or approved for use in NDA 21-667 therefore its acceptability will be determined based on an evaluation of the information in (b) (4) DMF (b) (4) and the proposed NDA.

Discussion:

No discussion occurred.

Question 7: Does the Agency agree that the Sponsor's planned drug substance stability data will be adequate for the NDA submission?

Summary of Sponsor's position:

Emmaus plans to reference the long-term stability data from (b) (4) DMF (b) (4) which includes 36 months 25°C/60%RH on six lots and 6 months 40°C/75%RH on six lots. The stability studies use USP specifications and methods.

FDA Response to Question 7:

Yes, provided that following is met:

1. Stability protocol is modified according to the recommendations in the FDA response to question 6.
2. The holder is the same for DMF (b) (4) and (b) (4) and the method of manufacture of L-glutamine is the same at both (b) (4) sites.
3. Stability batches were manufactured at a minimum of pilot scale.
4. In order to use the (b) (4) batches to support the expiry of L-glutamine in the NDA, submit data demonstrating the equivalence of impurity profiles and physical properties of the drug substance manufactured at the (b) (4) and the (b) (4) sites.

We note that the submitted meeting package includes the results of an ICH Q1B light stress study, but does not include the results of force degradation or other stress studies. Include these additional studies in the NDA.

Discussion:

No discussion occurred.

Question 8: Does the FDA agree that the proposed tests will be adequate for drug product release and stability?

Summary of Sponsor's position:

Emmaus proposes to release the drug product and perform long-term stability studies using the following attributes and tests: Appearance (packet and contents), Assay by (b) (4) per the Glutamine, USP, monograph; Related Compounds by (b) (4) per the Glutamine, USP, monograph; Weight Variation; Loss on Drying; and Microbial Limits testing for Total Aerobic Microbial Count; Total Combined Yeast and Mold Counts; and absence of specified organisms.

FDA Response to Question 8:

No. Your meeting package did not include any information on the drug product degradants. We recommend that you address the following:

1. To support the proposed specification, we recommend that you obtain a profile of degradants that can form over time.
2. Adopt an analytical method for assay that is discriminating and a method for degradants that is quantitative. The analytical method for related substances should be shown to be capable of detecting drug product degradants at an appropriate level of selectivity and sensitivity.
3. We also recommend that the seal integrity be retained in the specification. Include next to the acceptance criteria for seal integrity that the test is performed in-process.
4. Include in-use compatibility studies to support the stability of the drug product in water and food (yogurt, applesauce, (b)(4)) over the maximum length of time the mixtures are stored.

Discussion:

No discussion occurred.

Question 9: Does the Agency agree that the planned drug product stability data will be adequate for the NDA submission?

Summary of Sponsor's position:

In the NDA, Emmaus will submit stability data on five pilot scale drug product lots manufactured using (b)(4) drug substance. At the time of submitting the NDA, the following stability results will be available: 0, 3, 6, 9, 12, 18, 24, 36, and 48 months at 25°C/60%RH corresponding to two different lots and 0, 1, 2, 3, and 6 months at 40°C/75%RH on two of these lots which utilized drug substance from (b)(4) plant. One of these lots was used for the Phase 3 study (protocol GLUSCC09-01). In addition, we will submit three lots with stability results available at 3, 6, 9, 12, 18, 24, and 36 months at 25°C/60%RH and 1, 2, 3, and 6 months at 40°C/75%RH, which utilized drug substance from (b)(4) plant. All three of these lots were used for the Phase 2 study (protocol 10478). All lots and storage conditions showed no change over the course of the stability studies to date.

FDA Response to Question 9:

Yes, provided that following is met:

1. Stability protocol is modified according to the recommendations in the FDA response to question 8.
2. Drug product in the primary stability studies should be manufactured by the proposed commercial process.
3. Perform in-use testing on primary batches as part of the formal stability studies at initial and final time points.

Discussion:

No discussion occurred.

Question 10: Does the FDA concur with the planned approach to process validation and post-approval stability?

Summary of Sponsor's position:

Because the composition of the drug product (with no excipients added); the packaging materials, dimensions and the fill size of the container closure; and manufacturing process for the sickle cell product are (b) (4) to those used in the already approved commercialized NutreStore[®] product, Emmaus is not planning to conduct process validation for the first three production size batches for the sickle cell product. However, Emmaus will conduct stability testing on the first commercial lot manufactured and one drug product lot per year, if a drug product lot is manufactured in that calendar year.

FDA Response to Question 10:

Regarding process validation, FDA cannot comment on the approach to (b) (4)

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished. The acceptability of the executed process performance protocol, supporting studies, and decision to commercially distribute product will be evaluated during an on-site inspection.

Please find more information in the Guidance for Industry, Process Validation: General Principles and Practices (January 2011).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Discussion:

No discussion occurred.

2.4. Regulatory

Question 11: Does the Agency agree to and find adequate our proposed Table of Contents for the NDA?

Summary of Sponsor's position:

The proposed table of contents for the submission can be found in Appendix A of this FDA meeting package. It includes all of the NDA sections and documents that the Sponsor believes will be necessary to allow the Agency to accept the NDA for review and reach a decision on marketing approval of the product.

FDA Response to Question 11:

See response to Question 3 regarding content.

From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below:

- Until eCTD v3.2. is implemented, FDA Form 3674 should reside under m1.2 cover letter section, with a clear leaf title.
- Providing a hyperlinked Reviewer's Guide with a high level overview of what is provided in modules 1-5, can be helpful to reviewers. The Reviewer's Guide is usually provided as a separate document under section m1.2, with a clear and descriptive leaf title.
- M1.12.17 will be available with eCTD v3.2 which is not yet being implemented. If v3.2. is implemented by submission date, then it is acceptable to use m1.12.17 otherwise, the document should reside under m1.2 section, with a clear leaf title.
- For archival purposes, sponsor should submit a pdf file of any labeling document submitted in word. Also, leaf title of word documents should include "word", so reviewers could quickly identify the word version of the document.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Case Report Forms need to be referenced under the appropriate study's STF, to which they belong, organized by site as per the specifications and tagged as "case report form". Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008).
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>

We agree with your plan to submit 2.7.2 Summary of Clinical Pharmacology studies. We appreciate that selected information will be lacking (i.e., not present in the NDA because it is not present for NutreStore or in literature), but the section 2.7.2 should 1) summarize what information is available (i.e. summarize the NutreStore and literature information submitted in the NDA), and 2) include the search strategies that produced conclusions that data are not available for the items where information is not provided in the NDA.

Discussion:

No discussion occurred.

Question 12: Emmaus plans to request a Priority Review of the L-glutamine NDA. Does the Agency believe that a request for Priority Review of the NDA is reasonable and likely to be granted?

Summary of Sponsor's position:

Emmaus believes that the information that will be provided in this application demonstrates that treatment with L-glutamine represents a clinically meaningful improvement over existing treatments for sickle cell disease. This drug development program was granted fast-track designation by the FDA on 7 January 2005, indicating the Agency's agreement that L-glutamine had demonstrated the potential to address an unmet medical need for a serious or life-threatening condition. The FDA also granted orphan drug designation on 1 August 2001, indicating the Agency's agreement that sickle cell disease is not only serious or life-threatening, but also rare.

FDA Response to Question 12:

The decision will be made at filing meeting after the NDA is submitted.

Discussion:

No discussion occurred.

Question 13: Does the Agency concur with the proposed Emmaus Pediatric Post-approval Study Plan?

Summary of Sponsor's position:

Emmaus has included pediatric patients 5 years of age and older in the clinical development program, particularly in the Phase 2 and Phase 3 studies. In total, Emmaus has treated 80 pediatric patients (5-18 years), with efficacy and safety outcomes similar to those in adults. Pediatric studies are not required since Emmaus has received orphan drug designation for L-glutamine in this indication. However, Emmaus plans to submit a Proposed Pediatric Study Request in order to obtain a Written Request from FDA to conduct a post-marketing clinical study in sickle cell disease patients aged 6 months to 5 years.

FDA Response to Question 13:

You need to submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting before your NDA submission. See Section 4.0 PREA REQUIREMENTS below for detailed instructions.

Discussion:

No discussion occurred.

2.5. Additional Comments

We emphasize that all stratification factors used in the randomization should be used as the stratification factors in the stratified analyses. The pre-specified pooled regions may be acceptable to be included in the stratified analyses adjusted for region.

In addition, in Phase 2 trial, ITT population should be used as the primary efficacy analysis population. The primary efficacy analysis result may be difficult to interpret due to the imbalances in baseline characteristics.

Based on these concerns, FDA considers the results provided in current submissions are, at the best, marginal and would request an additional study for future NDA submission.

3.0 PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor slides used as a reference at the meeting.

25 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KATHY M ROBIE SUH
07/02/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 53,841

Emmaus Medical, Inc.
Attention: Yutaka Niihara, M.D., M.P.H.
20725 S. Western Ave., Suite 136
Torrance, CA 90501-1884

Dear Dr. Niihara:

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

We also refer to the teleconference between representatives of your firm and the FDA on April 20, 2009.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

MEETING DATE: April 20, 2009
TIME: 2 PM – 3 PM (EST)
LOCATION: Conference Room 1415 (White Oak)
APPLICATION: IND 53,841
DRUG NAME: L-Glutamine.
TYPE OF MEETING: End of Phase 2 meeting

MEETING CHAIR: Rafel Rieves, M.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP):

Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Min Lu, M.D., M.P.H., Medical Reviewer
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Satish Misra, Ph.D., Statistics Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

Division of Oncology Drug Products (DDOP):

Edvardas Kaminskas, M.D., Medical Reviewer

Office of Orphan Products Development:

Erica McNeily, Regulatory Review Officer
Jeff Fritsch, Health Science Administrator

EXTERNAL CONSTITUENT ATTENDEES:

Emmaus Medical, Inc.:

Yutaka Niihara, M.D., M.P.H., President and CEO
Daniel R. Kimbell, Esq., Secretary and COO, Director of Business Development

Consultants:



BACKGROUND AND PURPOSE OF THE TELECONFERENCE:

The sponsor had an initial End of Phase 2 (EOP2) meeting with the Agency on November 19, 2001. At that time, the Agency recommended that the sponsor request a second EOP2 meeting following completion and analysis of the Phase 2 study. As the sponsor completed the Phase 2 study as well as the statistical analysis of the data, they submitted a follow up second EOP2 meeting request on March 2, 2009 to discuss the statistical analysis plan and design of the study. Also, the sponsor has an orphan drug designation for the treatment of sickle cell disease indication.

SUMMARY OF THE TELECONFERENCE:

In response to the questions in the March 18, 2009 background package, the following agreements were reached after the discussion. The format provides the firm's questions listed in the meeting background package in italics followed by DMIHP responses sent on April 17, 2009 in bolded font and the discussions during the teleconference in regular font.

Questions:

- 1. Demonstration of Safety - The Safety Evaluation in the Phase II study demonstrated that L-glutamine treatment for up to 48 weeks was as well tolerated as placebo by the sickle cell patient population, as evaluated by adverse events, clinical laboratory evaluations, and vital signs (n=70). 95% of the patients on L-glutamine reported adverse events compared to 91% of the patients in the placebo group, and 8% of the adverse events reported in the L-glutamine group were at least possibly attributable to the study medication compared to 9% possibly attributable to the placebo. There were no notable differences between the treatment groups in clinical laboratory evaluations or vital signs.*

If the Safety Evaluation performed at the end of our proposed Phase III study demonstrates similar results to the Phase II study, would the FDA concur that we have successfully demonstrated the safety and tolerability of L-glutamine for the treatment of sickle cell disease?

FDA Response:

Adequacy of the safety data to support product approval is a review issue. Based on the preliminary results you have included from your Phase 2 study, your approach to Phase 3 evaluation of safety appears acceptable.

The sponsor agreed to the Agency's response and had no further comments.

- 2. Demonstration of Efficacy - The Phase II study efficacy analysis demonstrated positive trends in favor of L-glutamine (versus placebo) for the primary efficacy endpoint (number of sickle cell crises) and many objective secondary endpoints, but was inconclusive in regards to most of the subjective endpoints. Based on these findings, we propose the following efficacy endpoints in the Phase III trial:*

Primary endpoint: **Frequency of painful sickle cell crises**
Secondary endpoints: **Frequency of hospitalizations for sickle cell pain**

*Frequency of emergency room (ER) visits for sickle cell pain
Hematological parameters*

Does the FDA concur that these efficacy endpoints are reasonable and sufficient?

FDA Response:

We recommend a more objective assessment parameter for use as the primary efficacy endpoint for your Phase 3 study, such as frequency of hospitalization for sickle cell crisis. Frequency of painful sickle cell crises is acceptable as a secondary efficacy endpoint. You should also note that regulatory approval generally requires demonstration of safety and efficacy of the drug in at least two clinical trials. We note that the trends reported for the primary and secondary efficacy endpoints in your placebo-controlled Phase 2 study do not reach statistical significance in most cases, calling into question the utility of the study as important support for approval of your product. The Phase 3 program must provide robust support for efficacy of the drug and demonstrate consistency between the primary efficacy endpoint and important secondary efficacy endpoints.

The sponsor understood the Agency's response but indicated that it was granted fast track designation for the indication of reducing painful crises in patients with sickle cell disease and asked if they could retain the fast track designation if they changed the primary endpoint to frequency of hospitalization for sickle cell crisis. Also, they asked if it would be possible to change the primary endpoint to hospitalization and emergency room visits (acute care with for example, administration of parenteral narcotics) since hospitalizations are rare.

The Agency responded that it will retain the fast track status since the designation is not tied to a specific design for the study. The study must address a serious aspect of sickle cell disease. The study should be designed to assess a treatment effect that reflects a potentially life-threatening vaso-occlusive complication of sickle cell disease. The Agency noted that the primary endpoint needs to be objective and clinically meaningful for treatment effect and to that end the sponsor should document clearly the cause of hospitalization and ER visit as related to sickle cell disease cause (such as acute chest syndrome).

- 3. **Duration of Study** - The Phase II study demonstrated the safety of daily L-glutamine treatment for one year with positive trends in efficacy noted after only 24 weeks.*

We propose that the Phase III study be designed with a duration of treatment for 24 weeks. Does the FDA concur with this proposal?

FDA Response:

Because sickle cell disease is a chronic condition, it is important that the efficacy evaluation of the drug be able to demonstrate a durable effect of the treatment upon important clinical outcomes of the disease. In your Phase 2 study there was variability between the efficacy results at week 24 and week 48. This suggests that the longer (48 week) treatment duration may be needed in the Phase 3 study to clearly establish efficacy.

The sponsor noted that the efficacy data of the 24 week were consistent and had a linear trend to the second 24 week data in the Phase 2 study, and that there would not be added value to do the 48 week study other than safety results. They indicated that the Phase 2 study population was difficult to follow up and most patients withdrew early on in the study and that they intend to improve compliance by limiting the number of patients with the Phase 3 study with better screening process, site selection and provide more support to the patients and training to the investigators. They noted that there was a higher rate of withdrawal in the placebo group but that the efficacy data were comparable between the 24 and 48 week, and proposed if a 6 month placebo-controlled study with an extension study would be acceptable. They stated that Hydroxyurea (HU) placebo-controlled study was a three year long study, however, the study was stopped after one and a half year due to efficacy reasons.

The Agency responded that since the treatment is life-long, the label will need to state how long the patients stayed on the drug (for maintenance and compliance). If compliance is an issue and patients are not taking the drug, then there would be a problem with durable treatment effects. The sponsor should make every effort for compliance and document the discontinuation reasons. Since the HU study was a three year study and L-glutamine has a better adverse reactions profile than HU, the sponsor should provide justifications of the L-glutamine study duration (of 6 months) in context with HU. The sponsor should include an interim analysis at 6 months with appropriate methodology in the statistical analysis plan.

4. ***Definition of Analysis Populations and Imputation of Missing Values*** - Two main reasons we feel we did not achieve statistical significance for some of our efficacy endpoints in the Phase II study were patient compliance regarding study medication dosing and the rate of early withdrawal from the study. The rate of withdrawal from the Phase II study was 55% in the full analysis set. Of those patients who withdrew, 40% were withdrawn after being dosed for four weeks or less. The high rate of withdrawal equated to a high proportion of imputed values in the critical statistical analyses. Based on these occurrences we propose the following analysis populations and imputations in the Phase III trial:

- a) ***Safety population***: all patients who are enrolled and take at least one dose of study medication.
- b) ***modified Intent-To-Treat (mITT) population***: all patients who are enrolled, take at least one dose of study medication, and have been dosed for at least 6 weeks (25% of total treatment exposure).
- c) ***Per-Protocol (PP) population***: all patients who are enrolled, have been dosed for at least 12 weeks (50% of total treatment exposure), and who have taken at least 75% of the study medication over the course of their participation.
- d) ***Missing value imputation***: For the mITT population, missing values for the primary and secondary endpoints (crises, hospitalizations, and ER visits) will be imputed with the mean value for the completed patients regardless of treatment group. For the PP population, missing values for the primary and secondary endpoints will be imputed according to the individual patient's frequency rate at the date of withdrawal, rounded up to the next whole integer.

Does the FDA concur with these population definitions and methods of missing value imputation?

FDA Response:

The high withdrawal rate and the large amount of missing data for your Phase 2 study are concerning. For your proposed Phase 3 study, the primary efficacy analysis should be conducted using a true intention-to-treat population, that is, all patients randomized. All randomized patients should be followed for study outcomes, regardless of compliance with study medication. Every effort must be made to protect the study blind and to ensure compliance with study medication and procedures. An evaluable analysis, such as you describe for the mITT population may be done as a secondary analysis. You may also conduct sensitivity analyses with imputation of missing values to assess the impact of protocol violations on the results of the study. Your full plan for analysis of the study data should be submitted in the Statistical Analysis Plan prior to initiating enrollment in the study.

5. *Sample Size* - Based on the analysis populations described above, we propose an enrollment of up to 150 patients with the intent of having at least 72 patients who meet the PP definition. A sample size of 72 patients (36 per treatment group if randomized in a 1:1 ratio) will provide 80% power with a 5% significance level to detect a 2.0 difference in the treatment group means for frequency of painful sickle cell crises assuming a standard deviation of 4 (based on data from the Phase II study).

Does the FDA concur with the proposed sample size?

FDA Response:

The proposed sample size appears to be inadequate. Please consider the high dropout/noncompliance rate as exhibited in Phase 2 results. It appears that this is a repeated measure design with possible recurrence of sickle cell anemia during the treatment duration. This should be incorporated in the design and analysis of the trial including sample size determination. The sample size of the study should be recalculated based on a more objective primary efficacy endpoint (such as, hospitalizations). Based on the results of your Phase 2 study, where there were considerably fewer hospitalizations than painful crises, the proposed sample size appears much too small.

The sponsor stated that they compared the number of crises per patient in the 24 week duration for the two groups and summarized (mostly fell between 0 and 5).

The Agency recommended that comparisons should be based on non-parametric methods including a comparison of distribution of events, rank-sum test, and other suitable methods. The Agency also recommended that analyses at the interim of 24 week and at the end of study (with same endpoints) would be more appropriate, and re-iterated that the sponsor should make every effort for patient follow up.

6. *Randomization Ratio* - In order to increase the number of patients in the L-glutamine treatment group and also based on the Phase II study trend of a lower rate of withdrawal for patients on L-glutamine versus placebo (with withdrawal rates of 48% in the L-glutamine

group and 62% in the placebo group), we are also considering implementing a 2:1 or 3:1 L-glutamine:placebo randomization schema.

Does the FDA concur with this rationale?

FDA Response:

Your proposal for an unbalanced randomization is acceptable.

7. **Randomization Stratification**– *The randomization for the Phase III study will be stratified by investigational site and use of hydroxyurea. Stratification for hydroxyurea usage will confirm that the efficacy analysis results are based on L-glutamine treatment and not dependent upon concomitant hydroxyurea use.*

Does the FDA concur with the randomization stratification?

FDA Response:

Stratification by investigational site and use or non-use of hydroxyurea is acceptable.

The sponsor agreed to the Agency's response and had no further comments.

8. **Sufficiency of a Single Phase III Study** - *It is our goal to design and implement a single multi-site Phase III study that would allow us to submit an NDA upon study completion and statistical analysis, provided that the analysis clearly demonstrates the efficacy and safety of L-glutamine in the treatment of sickle cell disease. The safety data is also supported by the fact that L-glutamine is already available on the market for the treatment of short bowel syndrome (NDA 021667 held by ██████████^{(b) (4)} approved 6/10/04) at a recommended daily dose equivalent to the highest dose used in our Phase II study and has a safety profile comparable to that noted in our Phase II safety evaluation.*

Does the FDA concur with this plan?

FDA Response:

See response to question 2. Please see “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998” on why two studies are recommended and what otherwise would be needed. The adequacy of a single study to support approval of a new indication will be determined by its ability to support the efficacy claim based on strength of the results. Internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results will be considered in the evaluation. There is a risk in performing a single study that may not have convincingly positive results.

The sponsor agreed to the Agency's response and had no further comments.

9. **Treatment Protocol** - *Safety has been demonstrated for L-glutamine use up to 48 weeks and the efficacy analysis has shown a statistically strong trend favoring a lower frequency of*

painful crises, hospitalizations, and ER visits in the L-glutamine group. This project has 'Orphan Drug' status, and due to the relatively small target population, only large sickle cell treatment centers will be used in the phase III trial. This means that a number of patients with sickle cell disease who do not live near large sickle cell treatment centers will not have an opportunity to participate. We feel that the drug meets the criteria listed under CFR 312.34 and would like to use L-glutamine for the treatment of sickle cell disease under a treatment protocol so that the sickle cell population that will not be able to participate in the Phase III trial will still have access to L-glutamine.

Given these facts, we request that L-glutamine be made available under a treatment protocol for the treatment of sickle cell disease during conduct of the Phase III efficacy and safety studies. Does the FDA concur with this proposal?

FDA Response:

At this time and based on the available clinical data from your Phase 2 study, it is not clear that a treatment protocol is appropriate. However, you may submit a proposal for review.

The sponsor noted that the L-glutamine is approved for the treatment of short bowel syndrome and that they are concerned of the off-label use. They stated that their rationale for the treatment protocol is to collect data.

The Agency responded that typically, drugs are made available for treatment use during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, the drug may be made available during the Phase 2. The sponsor should consider a single arm, open-label study rather a treatment protocol.

Additional comments:

- **Please provide discussion and justification for the L-glutamine dose selected for your Phase 3 study.**
- **The final protocol for your Phase 3 study should be submitted for review.**

Linked Applications

Sponsor Name

Drug Name / Subject

IND 53841

NIIHARA YUTAKA MD

L-GLUTAMINE

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

/s/

HYON-ZU Z LEE

05/12/2009



IND 53,841

Hope Therapeutics
Attention: Yutaka Niihara, M.D.
Executive Manager
P.O. Box 0401
Montrose, CA 91021-0401

Dear Dr. Niihara:

Please refer to the meeting between representatives of your firm and FDA on November 19, 2001. The purpose of the meeting was to gain understanding of the processes/requirements, guidances, data management, labeling requirements, and good manufacturing practices for the submission of a New Drug Application (NDA) for L-glutamine for the treatment of sickle cell disease.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 19, 2001
Time: 12 nn-1:30 pm
Location: Parklawn Building, Potomac Conference Room
Application: IND 53,841 L-glutamine

Type of Meeting: End-of-phase II Meeting

Meeting Chair: Kathy Robie-Suh, M.D., Ph.D.

Meeting Recorder: Karen Oliver, RN, MSN

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Reviewer
Ann Farrell, M.D., Medical Reviewer
Ruyi He, M.D., Medical Reviewer
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist
Liang Zhou, Ph. D., Chemistry Team Leader
Karen Oliver, RN, MSN, Regulatory Health Project Manager

Office of Clinical Pharmacology and Biopharmaceutics, HFD-870

Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics, HFD-715

Thomas Permutt, Ph.D., Mathematical Statistician, Team Leader

Division of Orphan Drugs, HF-35

Janet Whitley, Ph.D.

External Constituent Attendees and titles:

Hope Therapeutics

Yutaka Niihara, M.D., Executive Manager
Daniel R. Kimbell, Esq., Director of Technology and Licensing

(b) (4)

Background:

On September 11, 2001, the sponsor submitted a request for an End-of-Phase II meeting to discuss L-glutamine for the treatment of sickle cell disease. The drug has orphan drug designation for the desired indication. On September 11 and October 29, 2001, they submitted background information for the meeting.

Meeting Objectives:

- To gain understanding of the NDA processes/requirements and FDA expectations.
- To gain understanding of guidances, data management, labeling requirements, and good manufacturing practices.

Discussion Points:

In response to the sponsor's specific questions in their March 1, 2000 background package, the following agreements were reached after discussion. The format provides the sponsor's questions (1-3), followed by the Agency's response in bolded lettering.

The sponsor presented 8 overheads during the meeting (see submission dated November 19, 2001).

1. We are planning to study 60 patients in excess of a 60-week period in randomized, crossover double blind study, as set forth in the IND. Statistical analysis will be performed on the following clinical endpoints:
 - Frequency of painful crisis
 - Exercise tolerance
 - Number of hospital days due to painful crises
 - Emergency room visits due to painful crisis.
 - Frequency of acute chest pain.

Given the outlined statistical plan, and assuming the defined clinical endpoints are convincingly attained, does the Agency agree that the proposed trial would be sufficient for licensure?

- **No. We believe that additional studies will be required (see "Additional Agency Observations/Comments/Recommendations" below).**

2. We are planning to outsource the manufacturing of the Product to (b) (4) and outsource the packaging into individual dose foil packets to an FDA approved packager. Will this meet FDA standards in conducting clinical research?
- **Refer to 21 CFR 312 (7) for the sufficient amount of Chemistry, Manufacturing and Controls information (drug substance, drug product, labeling, and environmental assessment) needed to conduct a Phase II and Phase III clinical study under the IND.**
 - **Provide information regarding study drug packaging that facilitates dose adjustment.**
 - **Provide information regarding patient dosing instructions.**
 - **Provide information on how patient comprehension of dosing regimen will be verified.**
 - **Provide the following updated Chemistry, Manufacturing and Control (CMC) information to this IND including:**
 - a. **Drug Substance (b) (4) or cross reference to DMF(s);**
 - b. **Drug Product (formulation, etc);**
 - c. **proposed Specifications for Drug Substance and Drug Product;**
 - d. **detailed packaging information and packager or cross reference to DMF(s); and**
 - e. **proposed stability protocols for Drug Substance and Drug Product.**
 - **It is inadequate to propose Phase III/pivotal clinical studies based on only a COA of Drug Substance (refer to CMC guidance on CDER Web site <http://www.fda.gov/cder/guidance/guidance.htm>)**
 - **It is recommended that you should request a CMC EOPII meeting.**
3. Aside from the clinical outcome and safety data, we are planning to study physiological and biochemical affects of L-glutamine in sickle cell patients for academic reasons. For NDA application, do we need to submit physiological and biochemical data aside from the data on clinical endpoints?
- **Yes, it is appropriate to submit the physiological and biochemical data to the NDA application. This information will add to the general, overall knowledge of the drug, and may provide, indirectly, additional information regarding drug safety.**

Additional Agency Observations/Comments/Recommendations

- **The study, as proposed, would be a proof of concept study, i.e., the design would not provide sufficient safety and efficacy information to fully support the drug.**
- **Submit data on all previous studies (both adult and pediatric patient population) conducted to explore the safety and/or efficacy of the drug.**
- **Both adult and pediatric patients may be included in studies conducted with the drug.**
- **Provide safety data from all pediatric patient clinical exposures to L-Glutamine, regardless of indication for use or disease entity. Include information on dose and duration of exposure, where available.**
- **Provide available pre-clinical pharmacology and toxicology data for L-Glutamine.**
- **The proposed dose of glutamine, i.e. 30 g/day, would be in excess of the recommended upper limit of 12.4% of the average daily intake of protein (refer to 21 CFR 172.320). Prolonged administration of glutamine raises clinical safety concerns of elevated hepatic transaminases, possible exacerbation of hepatic encephalopathy, potential neurotoxicity and tumor growth promotional effects (Buchman, A.L., Am J. Clin. Nutr. 74:25-32, 2001). To address these concerns, we recommend chronic toxicity study in nonhuman primates and study in tumor promotion models.**
- **Provide justification for the proposed dosing regimen.**
- **Regarding the proposed study, consider the following:**
 - a. **Consider including additional dosing regimens.**
 - b. **Consider deleting exercise tolerance as an endpoint. The method for assessing this parameter must be standardized and relationship to clinically meaningful benefit must be established. Consider “sickle cell painful crises” as the primary endpoint and the other proposed endpoints as secondary.**
 - c. **Consider a multiple-failure-time analysis to make use of information on the timing as well as the number of events.**
 - d. **Provide a fixed follow-up period.**
 - e. **Attempt to secure objective baseline data on the patients prior to enrollment in the study, i.e. frequency of crises, intensity of crises, etc. rather than relying on patient memory via questionnaire.**
 - f. **Determine how confounders (e.g., use of concomitant medications) in the study will be minimized and/or adjusted for in the study.**
 - g. **Consider expanding the enrollment criteria to include a broader patient population, e.g., patients on hydroxyurea.**
 - h. **Discuss prospective initiatives to track patients during this long study protocol.**
 - i. **Describe, prospectively in the protocol, how patients lost to follow-up will be included in the analysis.**

- **After completion of the study proposed, and analysis of the study data, consider requesting an End-of-Phase II meeting with the Agency and/or submitting a Phase III protocol as a 45-Day Special protocol for Agency review and comment. Please refer to *Guidance for Industry Special Protocol Assessment (Draft Guidance)*.**
- **Submit all the biopharmaceutics primary data for L-glutamine to the IND for Agency review including bioavailability, food effect, dose proportionality, and single and multi-dose effect.**
- **The NIH study and the proposed study could provide supportive data for a Phase III study to support the proposed indication.**
- **Further comments on the Phase III study (design, statistical analysis plan, sample size) will be forthcoming upon submission and review of the proposed Phase II study results.**

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

/s/

Karen Oliver
1/14/02 03:16:09 PM