

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205718Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Trade Name: AKYNZEO

Generic Name:
Netupitant palonosetron fixed-combination
capsule

Applicant Name: Helsinn Healthcare

Approval Date If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES / X / NO / ___ /

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

505(b)(1)

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

YES / X / NO / ___ /

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

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

d) Did the applicant request exclusivity?

YES / X / NO / ___ /

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

5 years

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

YES /___/ NO /X/

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

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

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

YES /___/ NO /X/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

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 / X / NO / ___ /

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

NDA#	022233	Aloxi (palonosetron HCl)	Approved
ANDA #	090713	Palonosetron hydrochloride (HCl)	Tentative approval
ANDA#	201533	Palonosetron HCl	Tentative approval
ANDA#	203050	Palonosetron HCl	Tentative approval

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.

NDA 205718 contains netupitant, a new chemical entity, in combination with palonosetron, a previously approved active moiety. Under the Agency's new interpretation described in the Agency's Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products, a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section

should be completed only if the answer to PART II, Question 1 or 2 was "yes."

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

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

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

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

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?

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the

application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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

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

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: Mary Chung
Title: Regulatory Project Manager

Name of Office/Division Director signing form: Donna Griebel
Title: Division Director

Appears This Way On Original



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

/s/

MARY H CHUNG
10/02/2014

DONNA J GRIEBEL
10/10/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205718 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: Akynzeo Established/Proper Name: netupitant/ palonosetron HCl Dosage Form: Capsule		Applicant: Helsinn Healthcare, SA Agent for Applicant (if applicable): August Consulting, Inc.
RPM: Mary Chung		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) 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)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <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) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:	
<i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>		
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>September 26, 2014</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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): New Molecular Entity
 (*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 type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• 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 type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<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 (<i>approvals only</i>)	<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>)	Action(s) and date(s)- Approval, 10/10/14
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 checked="" type="checkbox"/> Included 9/25/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 9/27/13
❖ 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 checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input 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 checked="" type="checkbox"/> Included 9/26/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 9/27/13
❖ 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 4/25/14, 7/16/14
❖ 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: 12/13/13 Review: 12/12/13
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 11/26/13 DMEPA: <input type="checkbox"/> None 1/19/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 5/13/14 OPDP: <input type="checkbox"/> None 5/06/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input type="checkbox"/> None 8/4/14 Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	11/26/2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ 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 type="checkbox"/> No <input 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 <u>May 14, 2014</u> If PeRC review not necessary, explain: _____ 	
<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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	9/26/14, 9/25/14, 9/23/14, 9/19/14, 9/15/14, 9/12/14, 9/11/14, 9/8/14, 9/3/14, 8/26/14, 8/14/14, 8/13/14, 8/6/14, 8/4/14, 7/25/14, 7/24/14, 7/14/14, 7/1/14, 6/26/14, 6/17/14, 6/13/14, 6/2/14, 5/30/14, 5/22/14, 5/19/14, 5/15/14, 5/13/14, 5/7/14, 4/24/14, 4/21/14, 4/16/14, 4/7/14, 3/27/14, 3/25/14, 3/13/14, 3/4/14, 2/14/14, 2/11/14, 2/3/14, 1/29/14, 12/30/13, 12/3/13, 11/7/13, 10/28/13, 10/22/13
<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) 	Not applicable
<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 checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 4/16/2013
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 7/20/2009
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 3/04/2014
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 6/11/2014
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	SPA Meeting 1/22/2010 SPA Meeting 7/15/2010 PeRC Meeting 5/14/2014
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 9/26/14
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 9/26/14
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 9/10/14
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None 5 templates, 9/10/14
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews 	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	9/6/14, 7/10/14
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input 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>)	See clinical review 7/10/14, page 28
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None PMHS Pediatric: 5/23/14 PMHS Maternal Health: 5/21/14 QT-IRT: 3/03/14 SEALD: 3/04/14, 4/24/14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 5/30/14
❖ 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 type="checkbox"/> None 7/25/14 (REMS not necessary review)
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 5/14/14
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 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
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 7/04/14
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/02/14
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
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/7/14, 6/27/14, 5/30/14
❖ 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 type="checkbox"/> No separate review 6/19/14
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 7/17/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/18/14, 6/19/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T primary review page 122 and Appendix
❖ 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	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None CMC: 9/17/14, 8/15/14, 5/30/14 Biopharmaceutics: 6/11/14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 10/2/13
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None Bioequivalence Study Inspection Report 5/30/14
❖ 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>)	7/21/14
<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>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: 7/23/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed: 4/29/14 <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)
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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 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 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 checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

MARY H CHUNG
10/14/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Friday, September 26, 2014 11:34:26 AM
Attachments: [NDA 205718 Akynzeo PPI Tracked Changes.pdf](#)
[NDA 205718 Akynzeo PPI Clean Copy.pdf](#)
[NDA 205718 Akynzeo PPI Clean Copy.docx](#)
[NDA 205718 Akynzeo PPI Tracked Changes.docx](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On September 25, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions to the Patient Information that are included as an enclosure.

We request that you resubmit labeling, the Patient Information, that addresses these issues as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
09/26/2014

From: Chung, Mary
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann@craig@august-consulting.com)
Cc: [Chung, Mary](mailto:Chung_Mary)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Wednesday, September 03, 2014 8:56:00 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

We note that your efficacy analyses covers the patient population up to age 55. Please provide efficacy analyses for the patient population up to age 65.

Please provide this information as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
09/26/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Wednesday, August 06, 2014 11:00:00 AM
Attachments: [NDA 205718 Akynzeo PI FDA Proposed Labeling 8-6-14 .pdf](#)
[NDA 205718 Akynzeo PPI FDA Proposed 8-06-14.pdf](#)
[NDA 205718 Akynzeo FDA Proposed Labeling- PI 8-6-14 Clean Copy.pdf](#)
[NDA 205718 Akynzeo PPI FDA Proposed 8-06-14 Clean Copy.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On July 29, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you perform an end-of-cycle SRPI review and make necessary revisions and edits, to ensure that your proposed labeling conform to the content and format regulations.

Please note that additional references have been made available at the [PLR Requirements for Prescribing Information](#) website (i.e., two SRPI videos).

We request that you resubmit labeling that addresses these issues by August 11, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
09/24/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Wednesday, September 24, 2014 12:46:06 PM
Attachments: [NDA 205718 Akynzeo PI FDA Proposed 9-24-14 Tracked Changes.pdf](#)
[NDA 205718 Akynzeo PI FDA Proposed 9-24-14 Clean Copy.pdf](#)
[NDA 205718 Akynzeo PI FDA Proposed 9-24-14 Tracked Changes.doc](#)
[NDA 205718 Akynzeo PI FDA Proposed 9-24-14 Clean Copy.doc](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On September 23, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

We request that you resubmit labeling that addresses these issues by September 25, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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MARY H CHUNG
09/24/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Wednesday, September 24, 2014 2:10:56 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed combination capsule received on September 27, 2013.

Additional reference is made to our proposed labeling revisions sent September 24, 2014. When you resubmit labeling that addresses these issues by September 25, 2014, please ensure the following labeling comment is also addressed.

Please remove the phrase [REDACTED] ^{(b) (4)} in the label and replace with “fixed combination.”

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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MARY H CHUNG
09/24/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Friday, September 19, 2014 11:18:09 AM
Attachments: [NDA 205718 Akynzeo FDA Proposed PI 9-19-14 Clean Copy.pdf](#)
[NDA 205718 Akynzeo FDA Proposed PI 9-19-14 Tracked Changes.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On September 17, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

We request that you resubmit labeling that addresses these issues by September 22, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
09/19/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, September 15, 2014 7:45:23 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

1. Treatment emergent AEs coded as cardiac disorders for Study 10-29 over multiple cycles (not just limited to cycle 1).
2. Troponin elevation patient counts/distribution in each of Study 08-18 and Study 10-29.
3. Summary of Ejection fraction changes, not taking into account troponin changes, separated out into each of Study 08-18 and Study 10-29.

Please provide this information as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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MARY H CHUNG
09/15/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Friday, September 12, 2014 5:06:24 PM
Attachments: [NDA 205718 Akynzeo FDA Proposed PI Track Changes 9-12-14.pdf](#)
[NDA 205718 Akynzeo FDA Proposed Clean Copy 9-12-14.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On August 18, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

We request that you resubmit labeling that addresses these issues by September 16, 2014 or before if possible.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
09/12/2014

From: [Chung_Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung_Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Friday, September 12, 2014 7:55:36 AM

Dear Dr. Lehmann,
Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following comments and recommendations related to the presentation of data in the ADVERSE REACTIONS section of your proposed labeling.

1. Given the differences in concomitant chemotherapy and comparator arms in the three trials, please present data separately for the 3 trials and provide a separate adverse drug reaction table for each of the three studies, (Study 1, Study 2, and multicycle safety study).
2. For Study 1 and Study 2 (those using palonosetron alone as the comparator), please start with a listing of all Treatment Emergent Adverse Events (TEAEs) above a cut-off of $\geq 2\%$ and for which the rate for drug exceeds the rate for palonosetron alone by 1%. In addition, you are welcome to propose an alternative cut-off for each of the trials that you believe is clinically relevant. This should be presented in the format provided below, rounding adverse event rates to the nearest whole number. (See further details in the following bullets).

Table 1: Study 1

Adverse Drug Reaction	Netupitant 300 mg Palonosetron 0.5 mg (N=X)	Palonosetron 0.5mg (N=X)
Headache	x%	x%
etc		
etc		

3. For the multicycle safety study (trial using aprepitant plus 5HT3 as the comparator), we recognize your concern about listing only those preferred terms with a higher frequency in the AKYNZEO arm than the comparator arm could be medically misleading and competitively unfair versus currently marketed antiemetics. For this study, please start with a listing of all TEAEs occurring above the cut-off of $> 2\%$ in both arms. In addition, as described above, you are welcome to propose an alternative AE rate cut-off that you believe is clinically relevant. This table should be presented in the format provided above, rounding adverse event rates to the nearest whole number. In conjunction with this table of ARs, please submit a summary table of the concomitant chemotherapy drugs by treatment arm (e.g. cisplatin: % Akynzeo %aprepitant; anthracycline: % Akynzeo % aprepitant). This will aid in the assessment of whether differences between arms in certain types of events might be attributed to differences in distribution of certain chemotherapy drugs between treatment arms.
4. As discussed, we disagree with defining adverse drug reactions as [REDACTED] (b) (4). [REDACTED] The rate of an identified adverse reaction is ordinarily derived from all reported adverse events of that type in the database used. Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations. We recognize that certain adverse events are typically related to chemotherapy (e.g., leukopenia, neutropenia, alopecia). We are concerned, however, that the potential for inhibitory effects of AKYNZEO on CYP3A4 enzyme activity could increase systemic exposure to chemotherapy agents which could lead to increased AEs typically associated with these chemotherapy agents.

You may define adverse reactions as described in #2 above (i.e., TEAEs occurring at $> n\%$ in the AKYNZEO arm and for which the rate for drug exceeds the rate for palonosetron alone by $x\%$). Alternatively, for each of the trials, you may propose a listing of TEAEs, along with a rationale, for removal from the tables as not being causally related to the study drug, such that the remaining items in the tables now represent your proposed adverse reactions (ARs).

Reference: Adverse Reactions labeling guidance:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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MARY H CHUNG
09/12/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Wednesday, September 10, 2014 5:36:22 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

(b) (4)

Reference is made to the revised Table 1 of the Full Prescribing Information:

Please create and submit a similar table above for the NETU-07-07 (for 300 mg arm), NETU-08-18, and NETU-10-29. Using TEAEs select the preferred term that is combination arm (300 mg) greater than control arm, after rounding to the whole number.

Please submit this information as soon as possible.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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Phone: 301-796-0260 /fax: 301-796-9904

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MARY H CHUNG
09/11/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, September 08, 2014 5:40:42 PM
Attachments: [Attachment-NDA 205718 Akynzeo Information Request 9-8-14.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

Please see the attached table. Please provide accurate numbers in all cells that are highlighted for NETU-07-07, NETU-08-18, NETU-10-29 and PALO-10-01.

Please provide this information as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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TABLE 2 - FREQUENCY OF PATIENTS WITH ABNORMAL VALUES FOR HEPATIC LABORATORY MEASUREMENTS TREATED PATIENTS IN PHASE 3 STUDIES*

	Netupitant / Palonosetron combination (300/0.50 mg) N= 1033		Palonosetron 0.50 mg oral N= 1095		Palonosetron 0.25 mg I.V. N= 369		Aprepitant plus palonosetron N= 104		Total N= 2601	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with at least a value >3*upper limit for AST	13	(1.3)	14	(1.3)	10	(2.7)	1	(1.0)	38	(1.5)
Patients with at least a value >5*upper limit for AST	0	0.0)	4	(0.4)	3	(0.8)	0	(0.0)	7	(0.3)
Patients with at least a value >10*upper limit for AST	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Patients with at least a value >3*upper limit for ALT	29	(2.8)	26	(2.4)	12	(3.3)	6	(5.8)	73	(2.8)
Patients with at least a value >5*upper limit for ALT	0	(0.0)	3	(0.3)	5	(1.4)	0	(0.0)	8	(0.3)
Patients with at least a value >10*upper limit for ALT	0	(0.0)	1	(0.1)	1	(0.3)	0	(0.0)	2	(0.1)
Patients with at least a value >3*upper limit for AST and >=2*upper limit for bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with at least a value >3*upper limit for ALT and >=2*upper limit for bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

*NETU 08-18; NETU 10-29; PALO 10-01
N= number of treated patients; n=number of patients with abnormal hepatic values
Percentages are calculated on the number of treated patients

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/s/

MARY H CHUNG
09/09/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, September 08, 2014 7:32:11 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

Please provide geriatric efficacy analyses (i.e., comparison of efficacy in patients < 65 years old vs. patients > 65 years old) for the following secondary endpoints.

- a. Acute phase for NETU-07-07
- b. Acute and overall phase for NETU-08-18
- c. Acute and overall phase for NETU-10-29
- d. Delayed phase and overall phase for PALO-10-01.

Please provide this information as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

MARY H CHUNG
09/08/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Tuesday, August 26, 2014 3:15:33 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

Please refer to your response to our May 30, 2014 information request submitted on June 5, 2014. Additional reference is made to the table titled "*NETU-07-07 Assessment of Violations at Site 120*" in this submission.

For all major violations (i.e., violations with "impact on efficacy" indicated as major), please tabulate by each study arm and provide an explanation that addresses the following points:

- Why the major violation does not impact efficacy assessment
- For major violations with "violation details" indicated as ondansetron, please provide the dose and time of administration.
- For major violations with "violation details" indicated as metoclopramide, please provide the dose and time of administration.

For all violations with "violation details" indicated as dexamethasone, please provide an explanation on what is meant by the comment "more than 72 hours before day 1" study entry. For these violations, please indicate if the appropriate dose of dexamethasone was administered at the start of the study.

We request a response as soon as possible. Thank you.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
08/26/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, June 02, 2014 2:30:00 PM
Attachments: [NDA 205718 FDA Proposed Labeling PI 5-30-14 Clean Copy.doc](#)
[NDA 205718 FDA Proposed Labeling PI 5-30-14 Tracked Changes.doc](#)
[NDA 205718 FDA Proposed Labeling PI 5-30-14 Tracked Changes.pdf](#)
[NDA 205718 FDA Proposed Labeling PPI 5-30-14 Tracked Changes.docx](#)
[NDA 205718 FDA Proposed Labeling PPI 5-30-14 Clean Copy.docx](#)

Dear Dr. Lehmann,

Attached please find the Word versions of the NDA 205718 Akynzeo FDA proposed labeling sent 5/30/14.

- Attached are both the clean copy and the corresponding tracked changes version of the PI in Word. The tracked changes version of the PI is provided in both Word and pdf. The attached corresponding tracked changes version of the PI should replace the tracked changes version of the PI sent 5/30/14.
- The Word version of the PPI (clean and tracked changes) sent 5/30/14 are also attached.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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From: Chung, Mary
Sent: Friday, May 30, 2014 10:37 PM
To: Craig Lehmann (craig@august-consulting.com)
Cc: Chung, Mary
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On March 24, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by June 13, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

MARY H CHUNG
08/15/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Thursday, August 14, 2014 5:48:49 PM
Attachments: [NDA 205718 Akynzeo \(netupitant palonosetron\) Information Request 8-14-14.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

Please refer to Table 44 titled "*Hematology- Marked Abnormalities (Common Toxicology Criteria Grade 3 or 4) During Cycle 1- Safety Population (Cycle 1)*" on page 147 of NETU-08-18 Study Report submitted under module 5.3.5.1 NETU-08-18, Study Report Body, which is also attached with this correspondence.

Please provide the same table (i.e., same parameters tabulated in the same format) for NETU-08-18, NETU-10-29, NETU-07-07, and PALO-10-01 for the subset of patients treated with docetaxel.

Additionally, please provide the same table (i.e., same parameters tabulated in the same format) for NETU-08-18, NETU-10-29, NETU-07-07 and PALO-10-01 for the subset of patients treated with etoposide.

Please provide this information as soon as possible. Thank you.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
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Table 44: Hematology - Marked Abnormalities (Common Toxicology Criteria Grade 3 or 4) During Cycle 1 – Safety Population (Cycle 1)

Parameter	NETU/PALO FDC (N=725)		PALO alone (N=725)		Overall (N=1450)	
	N	(%)	n	(%)	n	(%)
Leukocytes: WBC decreased						
Number of patients with result	725		725		1450	
Any severe grade	80	(11.0)	72	(9.9)	152	(10.5)
Grade 3	65	(9.0)	66	(9.1)	131	(9.0)
Grade 4	15	(2.1)	6	(0.8)	21	(1.4)
Neutrophils: neutrophil count decreased						
Number of patients with result	725		725		1450	
Any severe grade	154	(21.2)	155	(21.4)	309	(21.3)
Grade 3	103	(14.2)	110	(15.2)	213	(14.7)
Grade 4	51	(7.0)	45	(6.2)	96	(6.6)
Hemoglobin: anemia						
Number of patients with result	725		725		1450	
Any severe grade	3	(0.4)	4	(0.6)	7	(0.5)
Platelets: platelet count decreased						
Number of patients with result	724		725		1449	
Any severe grade	3	(0.4)	1	(0.1)	4	(0.3)
Grade 3	3	(0.4)	1	(0.1)	4	(0.3)
Grade 4	0		0		0	

Source: [Section 14](#), [Tables 14.3.4.1.1.3.1.1 to 14.3.4.1.1.3.4.1](#), [Listing 16.2.8.1.1](#)

Percentages are based on the number of patients with any result for the respective time interval and parameter.

Abbreviations: FDC=Fixed-Dose Combination; N=Number of patients in group; n=number of patients with at least one abnormality; NETU=Netupitant; PALO=Palonosetron; WBC=White Blood Cells.

Marked abnormalities in blood chemistry parameters included hyperglycemia for 21 (2.9%) in the netupitant/palonosetron group and 19 (2.6%) patients in the palonosetron group, hyponatremia for 15 (2.1%) in the netupitant/palonosetron group and 10 (1.4%) patients in the palonosetron group, and hypokalemia for 3 (0.4%) in the netupitant/palonosetron group and 1 (0.1%) patient in the palonosetron group. Increases in the netupitant/palonosetron and palonosetron groups were reported for ALT (2 [0.3%] vs. 2 [0.3%]), AST (1 [0.1%] vs. 2 [0.3%]) and alkaline phosphatase (1 [0.1%] vs. 0). Increased creatinine was reported for one patient in the palonosetron group.

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/s/

MARY H CHUNG
08/14/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Wednesday, August 13, 2014 4:16:32 PM
Attachments: [NDA 205718 Akynzeo PI FDA Proposed Revisions 8-13-14.pdf](#)
[NDA 205718 Akynzeo PI FDA Proposed Revisions 8-13-14 Clean Copy.pdf](#)
[NDA 205718 Akynzeo PI FDA Proposed Revisions 8-13-14.doc](#)
[NDA 205718 Akynzeo PI FDA Proposed Revisions 8-13-14 Clean Copy.doc](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On August 8, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by August 15, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
08/13/2014

From: Chung, Mary
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann@craig@august-consulting.com)
Cc: [Chung, Mary](mailto:Chung_Mary)
Subject: NDA 205718 netupitant/palonosetron Information Request
Date: Tuesday, December 03, 2013 3:10:00 PM

Dear Dr. Lehmann,

Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information.

1. Biopharmaceutics: The formulation information for the slow dissolution profile batches (i.e., "slow batch") used to show the discriminating capability of the proposed dissolution method for Netupitant could not be located in the dissolution method development report (3.2.P.2.Pharmaceutical Development-Drug Product Dissolution Method Development (Intermediate Netupitant, Tablet)). Please provide this information or indicate where it is located in the submission.
2. Clinical Pharmacology: Please provide the assay validation for cardiac troponin levels (cTnI). If such information has been submitted, please indicate where it is located.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133

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/s/

MARY H CHUNG
08/07/2014

From: Chung, Mary
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@craig@august-consulting.com)
Cc: [Chung, Mary](mailto:Chung.Mary)
Subject: NDA 205718 Netupitant/Palonosetron Information Request
Date: Monday, October 28, 2013 12:37:00 PM

Dear Dr. Lehmann,

Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information. Please submit your response via email, and follow up with a formal submission to the NDA. Please submit your response by Tuesday October 29, 2013. If there are any questions or concerns, please contact me

- For the primary efficacy endpoints, provide a display and analysis of results by study site for each study (NETU-07-07, NETU-10-29, PALO-10-01). Please interpret and discuss the findings.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
08/07/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, August 04, 2014 11:20:16 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

Additional reference is made to study NETU-07-07. For investigators who did not provide financial disclosure forms please provide the below information.

- Please provide a list of these investigators.
 - o Please indicate whether they were primary or subinvestigators.
 - o Please indicate how many patients were enrolled at each of these investigators' site.
 - o Please indicate whether the sponsor provided compensation to these investigators for anything.

Please provide this information as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
08/04/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) PMR/PMC Comments
Date: Friday, July 25, 2014 12:47:43 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

Please see below the current list of Post Marketing Requirements (PMR) and Post Marketing Commitments (PMC) for this application. Please confirm your agreement with these requirements and commitments, including agreement with the proposed milestone dates. Where milestone dates are not provided, please provide us with your proposed dates for completion. We request that you provide your response by July 29, 2014.

PREA Post Marketing Requirements (PMR)

An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone.

Final Protocol Submission:	05/30/2015
Study/Trial Completion:	12/30/2015
Final Report Submission:	03/30/2016

A PK/PD dose finding study of netupitant to characterize netupitant PK/PD relationship for complete response in the delayed phase following oral administration of single dose of netupitant given concomitantly (in separate formulations) with oral single administration of palonosetron in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission:	11/01/2015
Study/Trial Completion:	04/30/2018
Final Report Submission:	09/30/2018

An adequate, well-controlled, double-blind, randomized, study to evaluate the safety and efficacy of a dose of the netupitant-palonosetron fixed dose combination compared to standard therapy in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission:	04/30/2019
Study/Trial Completion:	12/31/2021
Final Report Submission:	04/30/2022

Post Marketing Commitments (PMC)

In-vivo drug interaction study to evaluate the duration of inhibitory effects of

AKYNZEO on CYP3A4 enzyme activity beyond 4 days after AKYNZEO administration

Final Protocol Submission:	01/31/2015
Study/Trial Completion:	01/31/2016
Final Report Submission:	06/30/2016

In-vitro study to evaluate the potential of netupitant being a substrate for P-gp transporter in a bi-directional transport assay system.

Final Report Submission:	XX/XX/XX
--------------------------	----------

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
07/25/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Thursday, July 24, 2014 4:38:54 PM
Attachments: [NDA 205718 Akynzeo PI FDA Proposed 7-24-14 Tracked Changes.pdf](#)
[NDA 205718 Akynzeo PI FDA Proposed 7-24-14 Clean Copy.pdf](#)
[NDA 205718 Akynzeo PPI 7-24-14 Tracked Changes.pdf](#)
[NDA 205718 Akynzeo PPI FDA Proposed 7-24-14 Clean Copy.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On July 7, 2014 and July 15, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by July 29, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
07/25/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, July 14, 2014 12:08:24 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following comments on the burgopack label submitted April 25, 2014.

There is no place on the burgopack label that is specifically designated for Lot No. and Expiration Date. Specifically designate a place on the burgopack label where the lot number and expiration date will appear.

Please submit an updated burgopack label that addresses these comments to the NDA.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
07/14/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Tuesday, July 01, 2014 4:55:55 PM
Attachments: [NDA 205718 FDA Proposed Labeling 07-01-14 tracked changes.pdf](#)
[NDA 205718 FDA Proposed Labeling 07-01-14.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On June 17, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by July 8, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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MARY H CHUNG
07/01/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Thursday, June 26, 2014 11:30:19 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We are in the process of reviewing your application and have the following information request:

Since the netupitant component of Akynzeo increases the exposure of certain chemotherapeutic agents, we need information on patients who received docetaxel, etoposide, ifosfamide and cyclophosphamide and experienced SAEs and deaths. (i.e., For patients who had an SAE or death indicate which chemotherapeutic agents they received). Additionally, we need the grade of cytopenias and neutropenia, the need for dose adjustments, infections and grade III and IV diarrhea observed in these patients.

We request a response to this information request by July 2, 2014. Thank you.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133

Phone: 301-796-0260 /fax: 301-796-9904

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MARY H CHUNG
06/26/2014

From: Chung, Mary
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann@craig@august-consulting.com)
Cc: Chung_Mary
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) Information Request
Date: Tuesday, June 17, 2014 2:32:00 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We are in the process of reviewing your application and have the following information request:

The binding studies in your NDA do not contain substance P/NK-1 receptor binding data for metabolites M1, M2, or M3. Provide the affinities of the metabolites (M1, M2, and M3) for the recombinant human substance P/NK-1 receptor, if any such data is available.

We request a response to this Information Request by Tuesday June 24, 2014. Thank you.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133
Phone: 301-796-0260 /fax: 301-796-9904
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MARY H CHUNG
06/17/2014

From: Chung, Mary
To: [admin_assistant \(florence@august-consulting.com\)](mailto:admin_assistant@august-consulting.com); [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann@craig@august-consulting.com)
Cc: [Dario Ceriani](#); [Angioletta Navini](#); [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) Information Request
Date: Friday, June 13, 2014 9:05:00 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We are in the process of reviewing your application and have the following information requests:

For Study NETU-10-01, we noted inconsistent contents between the variables 'ARM' and 'ARMCD' in your response analysis dataset file (adresp.xpt). Please check the accuracy of these variables and explain the inconsistency. If any error is to be identified, you must explain how the error occurred and submit a revised data file. Furthermore, you should clarify if such an error has an impact on the efficacy and safety analyses results for this study.

We request a response to this Information Request by Thursday June 19, 2014. Thank you.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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Phone: 301-796-0260 /fax: 301-796-9904

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MARY H CHUNG
06/13/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) Information Request
Date: Friday, May 30, 2014 10:33:54 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We are in the process of reviewing your application and have the following information requests:

1. To further investigate the protocol violations found in Russian Site# 120 on the efficacy assessments for Study NETU-07-07, please perform the following sensitivity analyses for the complete response (CR) in all three phases (i.e., the delayed, acute and overall):
 - a. Excluding the patients with major protocol violations (including taking disallowed concomitant medications) in Site# 120
 - b. Excluding the patients with any protocol violations in Site 120
 - c. Including all patients in Site# 120 but treating the patients with major protocol violations (including taking disallowed concomitant medications) as “treatment failures”
 - d. Including all patients in Site# 120 but treating the patients with any protocol violations as “treatment failures”
 - e. Per-protocol analyses for the CR-delayed phase and -acute phase (including and excluding Site# 120)
2. If any of these analyses have already been submitted, please identify the location of these analyses results. Moreover, you should repeat the subgroup analyses by age, gender, race, and geographic regions, based on the analysis populations defined above, for the CR in all three phases.
3. We noted that following the outcome of a routine QA audit at the site 120 of NETU-07-07, an additional QA audit was conducted in August 2011 and a 100% re-SDV against the original patient charts was performed in September 2011.

In order for us to adequately assess the severity of violations, we need you provide updated information on each violation.

- a. Provide a table with all major violations per patient, per treatment group. This should be categorized into eligibly criteria violations, antiemetic concomitant medication violations, concomitant medication violations, failure to report adverse event, and “other” category.
- b. Provide detail information as much as possible for each violation in each patient and provide your assessment and conclusion if the violation would impact the efficacy evaluation or safety evaluation. Your assessment should be done with explanations for each violation that include each eligibility violation or each concomitant medication violation in each patient.
- c. Were the auditors who performed each audit and the 100% SDV in September 2011 blinded to study treatment assignment?

We request your response to this information request as soon as possible - June 3rd 2014 or before. Thank you.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133
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/s/

MARY H CHUNG
05/30/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Friday, May 30, 2014 10:36:54 PM
Attachments: [NDA 205718 FDA Proposed Labeling PI 5-30-14 Clean Copy.pdf](#)
[NDA 205718 FDA Proposed Labeling PPI 5-30-14 Clean Copy.pdf](#)
[NDA 205718 FDA Proposed Labeling PI 5-30-14 Tracked Changes.pdf](#)
[NDA 205718 FDA Proposed Labeling PPI 5-30-14 Tracked Changes.pdf](#)

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

On March 24, 2014, we received your updated proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by June 13, 2014.

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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/s/

MARY H CHUNG
05/30/2014

**PeRC PREA Subcommittee Meeting Minutes
May 14, 2014**

PeRC Members Attending:

Lynne Yao
Rosemary Addy
George Greeley
Jane Inglese
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Andrew Mulberg
Peter Starke
Shrikant Pagay
Kristiana Brugger
Freda Cooner
Kevin Krudys
Lily Mulugeta
Dianne Murphy
Adrienne Hornatko-Munoz

Agenda

NDA	205718	Akynzeo (netupitant_palonosetron) Deferral_Pediatric Plan	Prevention of acute and delayed nausea and vomiting associated with initial and repeat cycles of cancer chemotherapy, including highly emetogenic chemotherapy
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(b) (4)

Akynzeo (netupitant palonosetron) Deferral Pediatric Plan

- NDA 205718 seeks marketing approval for Akynzeo (netupitant_palonosetron) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat cycles of cancer chemotherapy, including highly emetogenic chemotherapy.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA goal date of September 26, 2014.
- The Division clarified that the sponsor is proposing a staged approach to the development of this combination product for use in pediatric patients:
 - Netupitant as a single oral agent will be studied with palonosetron (iv formulation given orally) .
 - The sponsor will attempt to develop an oral liquid formulation of the combination product to treat patients less than 6 years of age.
 - If the sponsor's attempts to develop an oral liquid formulation fails, the sponsor plans to develop an iv preparation of both products to be given concomitantly.
 - The sponsor is attempting to develop netupitant as an iv preparation for adult use. (b) (4)
- The PerC noted that development of an iv (b) (4) preparation, if attempts to develop an iv netupitant fails, cannot be required under PREA.
- *PerC Recommendations:*
 - The PerC agreed with a deferral for pediatric patients aged birth to less than 18 years because adult studies have been completed and the product is ready for approval.
 - The PerC recommended that the Division give the sponsor adequate time to develop a liquid formulation, but the Division should advise the sponsor that timeline for the remainder of the pediatric development program should be compressed.

- The PeRC advised that if the sponsor is unable to develop an age-appropriate formulation of this combination product, the deferral may be converted to a partial waiver.

(b) (4)





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/s/

JANE E INGLESE
05/27/2014

Tran-Zwanetz, Catherine

From: Craig Lehmann <craig@august-consulting.com>
Sent: Thursday, May 22, 2014 4:20 PM
To: Tran-Zwanetz, Catherine
Cc: Chung, Mary
Subject: RE: NDA 205718CMC IR #6

Thank you, Cathy! I will pass this on to the Sponsor at this time.

Best Regards,
Craig

From: Tran-Zwanetz, Catherine [<mailto:Catherine.TranZwanetz@fda.hhs.gov>]
Sent: Thursday, May 22, 2014 2:29 PM
To: Craig Lehmann
Cc: Chung, Mary
Subject: NDA 205718CMC IR #6

Hi Craig,

Here is another CMC IR: As part of our evaluation of the analytical procedures used in your specifications for drug substances and drug product, several of the procedures were performed in a laboratory. Regarding the analytical procedure for (b) (4) for Netupitant Drug Substance (AGC/166), the following observations were made:

1. The method specified (b) (4) The method did not meet system suitability under these conditions. The method was modified to use (b) (4) (b) (4) The modified method met system suitability requirements. It is suggested that the method be modified to allow for (b) (4) as needed to meet system suitability.
2. Peaks at (b) (4) and (b) (4) were detected in the sample solution. It is suggested that the peaks be identified in the method.

Please evaluate these observations and make any appropriate changes to analytical procedure AGC/166. Please report any changes to analytical procedure AGC/166 as an amendment to your NDA.

Thanks!

Cathy Tran-Zwanetz
Regulatory Project Manager
(301) 796-3877

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/s/

CATHERINE A TRAN-ZWANETZ
05/23/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 netupitant/palonosetron Information Request
Date: Monday, May 19, 2014 6:26:49 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We are in the process of reviewing your application and have the following Clinical Pharmacology information request (IR):

We acknowledge your response to our information request, in which you estimated the duration of CYP3A4 inhibitory effects based on dexamethasone C_{min} values. We noted that the C_{min} ratio is not reflective of the observed AUC ratio over time although a netupitant dose-dependence was observed. For example, AUC ratios were ~ 1.7 and ~ 2 on Day 1 and Day 4, respectively, while the corresponding C_{min} ratios were 7.6 and 3.4. Therefore, the estimation based on the linear regression of C_{min} ratios over time does not seem to be reasonable.

We request the following:

1. Compute the [I]/K_i values over time for netupitant and each of the metabolites that inhibit CYP3A4. Here, [I] is the plasma concentration of the analyte (parent drug or metabolite) at time t following oral administration of netupitant at the proposed dose. Please also sum up the [I]/k_i values at each time point. If the sum of [I]/k_i at the last time point is still >0.1, please estimate the concentrations of each analyte (parent and metabolites) at various time points until the sum of [I]/k_i is < 0.1. Present the results in a table and as a plot (i.e., time profiles of [I]/k_i for the parent drug, each metabolite, and the sum). Please also provide the raw data that support the plot in an xpt file.
2. We cannot locate the report for in vitro studies that evaluate time-dependent inhibition of CYP isozymes (i.e., studies with pre-incubation). If you have submitted such a report, please help us locate it. If not, please explain.
3. Estimate the times it takes to excrete various amount (80%, 90% and 95%, respectively) of the drug-related materials (parent drug and metabolites) from the body and describe your estimation method .

We request a response to #1 and #2 by May 21, 2014 and #3 by May 22, 2014. Thank you.

Regards,

Mary

Mary Chung, PharmD.

Regulatory Health Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133

Phone: 301-796-0260 /fax: 301-796-9904

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/s/

MARY H CHUNG
05/19/2014

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Thursday, May 15, 2014 1:20 PM
To: 'craig@august-consulting.com'
Subject: NDA 205718 CMC IR #5

My apologies for not including the NDA # in the original email.

From: Tran-Zwanetz, Catherine
Sent: Thursday, May 15, 2014 1:18 PM
To: 'craig@august-consulting.com'
Cc: Chung, Mary
Subject: CMC IR #5

Hi Craig,

Here is our latest information request:

Submit a revised drug product specification to sec. 3.2.P.5.1 of your NDA (for the Netupitant-Palonosetron Combination Capsule). The revised specification should include the acceptance criteria for dissolution for netupitant and palonosetron in the Combination Capsule provided in the Quality Information Amendment dated March 27, 2014.

Please provide this information by Friday, May 16, 2014 COB.

Thanks!
Cathy

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/s/

CATHERINE A TRAN-ZWANETZ
05/15/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Netupitant/palonosetron Information Request
Date: Tuesday, May 13, 2014 8:11:41 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We are in the process of reviewing your application and have the following Clinical Pharmacology information request (IR):

- Please clarify if you have evaluated the potential of netupitant being a substrate of P-gp transporter with net flux ratio determination. If you have, please assist us locating the study report.
- In your in vitro metabolism study, (study report 1003832), you have reported the enzyme kinetic parameters in microsome and rhCYP3A4. However, details of the experimental conditions for determination of kinetic parameters were not included in this study report. Please provide the details of the experimental conditions for these kinetic studies.

We request a response by May 15, 2014 12:00 PM EST. Please provide this information via email and submit to the NDA. Thank you.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
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/s/

MARY H CHUNG
05/13/2014

From: Barley, Stacy
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron: Clinical Pharmacology IR
Date: Wednesday, May 07, 2014 3:57:00 PM

Hello Craig,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 205718 Akynzeo.

We are in the process of reviewing your application and have the following Clinical Pharmacology information request (IR):

In Study NETU-06-07, the systemic exposure to dexamethasone was about two fold higher on day 4 after single dose administration of netu/palo combination on day 1. The duration of inhibitory effects on CYP3A4 was not studied longer than 4 days. Please provide how much longer the inhibitory effect is expected to last and propose a labeling language for concomitant CYP3A4 substrate in terms of the timing of co-administration without drug-interaction potential.

We request a response on May 8, 2014 by 4:00 p.m. EDT. Please email me with your response and cc Mary Chung (the Regulatory Project Manager).

Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

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stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
05/07/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Thursday, April 24, 2014 2:17:31 PM

Dear Dr. Lehmann,
For the below information request dated 4/24/2014 for NDA 205718 Akynzeo (netupitant/palonosetron), we are requesting that a response be submitted by April 30, 2014.

Regards,
Mary

From: Chung, Mary [<mailto:Mary.Chung@fda.hhs.gov>]
Sent: Thursday, April 24, 2014 10:10 AM
To: Craig Lehmann
Cc: Chung, Mary
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)

Dear Dr. Lehmann,
Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZE0, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013. We have the following requests for additional information.

1. In your *in vitro* metabolism study, (study report 1003832), please clarify if the hepatocytes and microsomes were characterized in respect to various metabolizing enzymes (including both phase 1 and phase2 enzymes) prior to use in the experiment. In addition, regarding the recombinant enzyme study to identify the CYP enzyme responsible for the metabolism of parent drug, please clarify if you have evaluated the potential of CYP1A2, 2B6 and 2C8 to metabolize the parent drug in the study.
2. In your *in vitro* inhibition study (study report 103907), please clarify if microsomes that were used in the experiment was characterized in respect to various CYP enzymes prior to use or if the experiment included positive controls with known inhibitors of various CYP enzymes to validate the test system.
3. As for the point estimate and 90% CI for Cmax and AUC ratio for the impact of hepatic impairment, please provide values in comparison to the combined control groups (n=18). While the values vary between control groups and the baseline, demographic factors are apparently similar enough to combine data for a control group.
4. We note that one healthy subject in Study NETU-10-10 has high systemic exposure close to the value observed in a patient with severe hepatic impairment. Please provide any potential intrinsic or extrinsic factors for the subject that may have affected the systemic exposure.
5. We note that in Study NETU-07-01, the median Tmax for digoxin is about 1 hr when the plasma concentration of netupitant is substantially lower than those at later time points. Provide an explanation, if any, whether this study can address the potential effects of netupitant on digoxin that was administered when netupitant concentrations are close to its peak concentration.

Please send an electronic copy of the response via email and also submit the response to the NDA.
Thank you.

Regards,

Mary

Mary Chung, PharmD.

Regulatory Health Project Manager

Division of Gastroenterology and Inborn Errors Products

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/s/

MARY H CHUNG
04/24/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, April 21, 2014 8:29:29 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule. Reference is also made to the pediatric plan you submitted for this application on April 4, 2014.

We have the following request for additional information. Please submit your response to this information request as an amendment to the pediatric section (1.9 Pediatric Administrative Information).

Section 1.9 Pediatric Administrative Information requires the following additional information:

1. Section 1.9.2 Pediatric Deferral: The sponsor should provide a statement requesting a deferral of pediatric studies for specific age groups (e.g., "Helsinn Healthcare is requesting a deferral of the submission of a pediatric assessment in children # to # years old.")
2. Section 1.9.2.1 Justification for requesting a deferral in children # to # years of age. (e.g., "Helsinn Healthcare is requesting a deferral of pediatric studies of [insert indication] in children # to # years of age for the following reasons...")
3. Section 1.9.2.2 Description of the planned studies (e.g., "Please refer to Section ##### for the Pediatric Plan, including a timetable for conducting and submitting the proposed studies.")
4. Section 1.9.2.3 Certification: The sponsor should certify that all statements made in this request for deferral of pediatric studies are true and correct, and that the information included is believed to adequately support the Request for a Deferral of Pediatric Studies.

Please submit this information to the NDA by Thursday April 24, 2014. Thank you.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

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MARY H CHUNG
04/21/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) Information Request
Date: Wednesday, April 16, 2014 12:14:48 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule.

We have the following request for additional information.

The ADSL file (“subject-level analysis data”) is not present in the eCTD submission (sequence #0000) under module 5.3.5.3 *ISS- Integrated Summary of Safety, Data Analysis Data, Analysis Dataset Legacy*.

Please make this file accessible through submission to the application. Thank you.

Regards,

Mary

Mary Chung, PharmD.
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MARY H CHUNG
04/16/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) - Labeling Comments
Date: Monday, April 07, 2014 9:11:17 AM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule.

We also refer to your carton and container label and instructions for opening diagram submitted September 27, 2013. We have reviewed the referenced material and have the following comments.

1. Burgopak Label and Carton Labeling

- a. The dosage form is not present. The established name presentation should include the active ingredient followed by the dosage form. Include the dosage form “capsules” on all labels and labeling immediately following the active ingredient presentation. Ensure the dosage form presentation is commensurate with the prominence of the active ingredient presentation.
- b. Increase the size and prominence of the established names on the container (blister pack) label and the carton label so that they are more comparable with those of the proprietary name. See 21 CFR 201.10(g)(2).
- c. The established name presentation uses a (b)(4) font against a white background which makes it difficult to read. Revise the font color to increase the prominence of the established name so that it is commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10 (g)(2).
- d. Change the equivalency statement on the front of the blister pack label and the carton label so that “HCl” is replaced with “hydrochloride” (the statement should read “0.56 mg palonosetron hydrochloride corresponding to 0.50 mg palonosetron free base”).
- e. Add the statement “See USP Controlled Room Temperature” to the end of the storage statement on the blister pack and carton label so that the entire statement reads: “Store at 20°C – 25°C (68°F - 77°F). Excursions permitted to 15°C - 30°C (59° - 86°F). See USP Controlled Room Temperature.”
- f. The components of the established name and strength “netupitant 300 mg, palonosetron 0.5 mg” appear blended together making each more difficult to differentiate. Revise the presentations of the established name and strength so that the established name appears on one line directly beneath the proprietary name and the strength appears on one line directly beneath the established name to increase legibility and differentiation of each, e.g.,
“Akynzeo”
“(netupitant and palonosetron) capsules”
“300 mg and 0.5 mg”
- g. Increase the prominence of the “Rx Only” statement on the blister pack and carton label. It should be at least as large and prominent as the NDC number.
- h. The (b)(4) located to the left of the proprietary name is prominent and may be misinterpreted as part of the proprietary name. Delete this (b)(4) or reduce the size of the (b)(4) and relocate away from the proprietary name.

2. Instructions for Opening Diagram

The written instructions for opening the Burgopak on the container label and in the

Instructions for Opening Diagram are adequate. However, we recommend revising the pictures accompanying the first two steps, “1. Press buttons A & B together,” and “2. Pull tab with other hand,” to depict the hand holding the Burgopak grasping the Burgopak from the rear rather than (b) (4) where the blister pack emerges.

We request that you resubmit the above mentioned material that addresses these comments by April 23, 2014.

If there are any questions, please contact me. Thank you.

Regards,

Mary

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MARY H CHUNG
04/07/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) Information Request
Date: Thursday, March 27, 2014 8:02:16 AM

Dear Dr. Lehmann,
Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information.

You have only provided descriptive complete response rates for Study NETU-07-07 excluding the 39 subjects from Russian site 120. You should repeat all the efficacy analyses, particularly for the primary and key secondary efficacy endpoints, with these subjects excluded.

We would appreciate receiving this information by Monday March 31, 2014.

Regards,
Mary

Mary Chung, PharmD.
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Division of Gastroenterology and Inborn Errors Products
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MARY H CHUNG
03/27/2014

From: Chung, Mary
To: "[Craig Lehmann](#)"
Subject: RE: NDA 205718 Akynzeo (netupitant/palonosetron) Pediatric Plan
Date: Thursday, March 13, 2014 7:41:00 PM

Dear Dr. Lehmann,

We are aware and acknowledge your comment that a FDAAA Pediatric Plan is applicable to this application. Please see below additional comments:

You claim that due to the nature of the dosage form and route of administration, the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients. You state that fixed dosing is not optimal in children due to varying weights and sizes of pediatric patients. However, other fixed dose combination drugs have been approved for pediatric patients.

Please note oral formulations for both palonosetron and aprepitant, the only approved NK1 antagonist, have postmarketing study requirements under the Pediatric Research Equity Act to conduct studies in pediatric patients. Therefore, a combination product comprised of these types of medications may limit pill burden, and improve compliance and convenience in the pediatric population as well as adults.

Please submit a pediatric development plan to this application as soon as possible. We would appreciate receiving this by March 26th 2014 or before.

Regards,
Mary

From: Craig Lehmann [<mailto:craig@august-consulting.com>]
Sent: Thursday, March 13, 2014 12:22 PM
To: Chung, Mary
Subject: RE: NDA 205718 Akynzeo (netupitant/palonosetron) Pediatric Plan

Dear Dr. Chung:

In reply to FDA's subject email below, Sponsor would like to provide the following information and also requests clarification.

Please note, as you are aware (please see FDA pre-NDA Minutes, Question #7), that Netupitant/Palonosetron NDA 205718 was submitted to FDA prior to the FDASIA Pediatric Study Plan (PSP) implementation date (5Jan2014), and therefore a FDAAA Pediatric Plan (not a FDASIA Pediatric Study Plan) is applicable.

Request for clarification. FDA's request in your email states that Sponsor's "(b) (4) request does not seem favorable". Sponsor is puzzled by this wording; FDA did not state that Sponsor's "(b) (4) request is denied and did not address whether a "(b) (4) might be feasible. An explanation would be appreciated because such clarification is important to help Sponsor prepare a

Pediatric Plan for applicable pediatric age groups. Please explain why the (b) (4) request does not seem favorable to FDA particularly regarding the various pediatric age groups (please note this request is consistent with FDA minutes of the pre-NDA meeting, Question #7 meeting discussion (page 12) where FDA stated, "FDA comments on the pediatric plan will be communicated to the sponsor during the NDA review period." Please provide clarification regarding this matter.

Best Regards,
Craig

From: Chung, Mary [<mailto:Mary.Chung@fda.hhs.gov>]
Sent: Wednesday, March 12, 2014 2:33 PM
To: Craig Lehmann
Subject: NDA 205718 Akynzeo (netupitant/palonosetron) Pediatric Plan

Dear Dr. Lehmann,
Upon review of your (b) (4) PREA (b) (4) request submitted with your NDA 205718 Akynzeo (netupitant/palonosetron), the granting of the (b) (4) request does not seem favorable. In light of this, please submit a pediatric development plan or a pediatric study plan to this application as soon as possible. We would appreciate receiving this by March 26th 2014 or before. Please refer to the April 16th 2013 Pre-NDA Meeting Minutes Question 7 for additional information.

If you could please provide us with your confirmation on this matter, it would be appreciated.

Regards,
Mary

Mary Chung, PharmD.
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MARY H CHUNG
03/26/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig_Lehmann_(craig@august-consulting.com))
Cc: [Chung, Mary](#)
Subject: NDA 205718 netupitant/palonosetron Information Request
Date: Tuesday, March 25, 2014 3:10:37 PM

Dear Dr. Lehmann,

Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information.

1. Please provide language describing clinical study PALO-10-01 to place in the clinical trials section of the label.
2. Please provide a copy of the nausea assessment as presented to the patient.
3. Please provide justification and any empiric evidence you have to support the cutoff points for evaluating nausea (i.e., maximum VAS < 5 mm for “no nausea” and maximum VAS < 25 mm for “no significant nausea”).

We would appreciate receiving this information by Friday March 28, 2014 if possible.

Regards,

Mary

Mary Chung, PharmD.
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mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
03/25/2014



NDA 205718

MID-CYCLE COMMUNICATION

Helsinn Healthcare SA
C/O August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Akynzeo (netupitant and palonosetron hydrochloride fixed-dose combination capsule).

We also refer to the teleconference between representatives of your firm and the FDA on March 4, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 4, 2014 10:00 AM to 11:00 AM EST

Application Number: NDA 205718

Product Name: Akynzeo (netupitant and palonosetron hydrochloride fixed-dose combination capsule)

Indication: Prevention of acute and delayed chemotherapy induced nausea and vomiting

Applicant Name: Helsinn Healthcare SA

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Mary Chung, Pharm.D.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director
Amy Eagan, M.D.	Deputy Director
Maria Walsh, RN, MS	Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Andrew Mulberg, M.D.	Deputy Director
Ruyi He, M.D.	Medical Team Lead
Nancy Snow, D.O., MPA	Medical Reviewer
David Joseph, Ph.D.	Pharmacology Team Lead
Ke Zhang, Ph.D.	Pharmacology Reviewer
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff
Mary Chung, Pharm.D.	Regulatory Project Manager

Office of Clinical Pharmacology

Sue-Chih Lee, Ph.D.	Team Lead
Insook Kim, Ph.D.	Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment/ Division of New Drug Quality Assessment II

Raymond Frankewich	Chemistry Reviewer
--------------------	--------------------

Division of Biometrics III

Freda Cooner, Ph.D.	Statistical Team Lead
---------------------	-----------------------

Pediatric and Maternal Health Staff

Erica Radden, M.D. Medical Reviewer
Denise Pica-Branco Senior Regulatory Project Manager

Office of Surveillance and Epidemiology/Division of Pharmacovigilance I

Christian Cao, MPAS, PA-C Safety Evaluator

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim Independent Assessor

APPLICANT ATTENDEES

Sergio Cantoreggi	Chief Scientific Officer
Ruben Giorgino, M.D.	Drug Development
Marco Palmas, M.D.	Clinical Development
Maria Elisa Borroni, M.D.	Clinical Development
Giorgia Rossi, MD.	Drug Safety (formerly Clinical Development)
Giuseppina Clerici, MD.	Drug Safety
Giada Rizzi	Statistics & Data Management
Cecilia Moresino	Statistics & Data Management
Claudio Pietra	Preclinical Development
Emanuela Lovati	Preclinical Development
Claudio Giuliano	Preclinical Development
Roberta Cannella	Technical Affairs
Fabiola Bambini	Technical Affairs
Angioletta Navini	Regulatory Affairs
Dario Ceriani	Regulatory Affairs
Fabio Trento	Project and Operation Controller

(b) (4)

Craig Lehmann Authorized Representative for the NDA

(b) (4)

(b) (4)

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

2.1 BIOPHARMACEUTICS

Based on the submitted dissolution data, we recommend that your dissolution specification for the intermediate product and the final product be as follows for product release and throughout the shelf-life:

Recommended Dissolution Specification

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume	Acceptance Criteria
Netupitant	Tablet/Combination Capsule	USP Paddle	100 rpm	0.07M Phosphate buffer pH 6.8 containing 1% sodium SDS	900 mL	(b) (4) in 45 minutes
Palonosetron	Capsule/Combination Capsule	USP Paddle	75 rpm	0.01 N HCL	500 mL	(b) (4) in 30 minutes

Please submit a correspondence to the application indicating your acceptance of our recommendation by April 3, 2014.

2.2 NONCLINICAL

Pregnancy category C appears to be appropriate for Akynzeo, based on our preliminary assessment of the fetal skeletal changes in the segment II developmental study in rabbits.

2.3 CLINICAL

There are no significant clinical concerns identified at this time and at this stage. Please see responses below to your questions.

3.0 INFORMATION REQUESTS

There are no new or outstanding information requests at this time.

4.0 MAJOR SAFETY CONCERNS/ RISK MANAGEMENT

There are no major safety concerns identified at this time, and at this stage we do not believe that a REMS is necessary to ensure the benefits outweigh the risks.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC Meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is June 11, 2014. In addition, please note the following projected milestone dates:

Labeling, PMR/PMC to Applicant:	June 4, 2014
LCM Background Package:	May 30, 2014
PDUFA Action:	September 26, 2014

7.0 ADDITIONAL DISCUSSION

Question 1

Please clarify what the Agency means by the statement in the April 16, 2013 pre-NDA meeting minutes that the approved labeling “will describe regimens that were studied,” and that “[t]he Division is moving beyond ‘HEC’ and ‘MEC’ classifications.” As discussed below, Helsinn has views regarding how the labeling of Akynzeo should describe the approved uses of the product and provide the information necessary for healthcare providers to make informed decisions regarding patient treatment. At the outset, however, it would be helpful for the agency to clarify what it intends for the labeling (*i.e.*, what changes, if any, are intended from the manner in which CINV antiemetics are currently labeled), and to explain what circumstances lead the agency to conclude that any such change is necessary or appropriate. Please provide clarification.

FDA Response:

We are considering alternative language for the indication statement such as prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy (CINV). The details of the chemotherapy regimens will be included in *Section 14.0 Clinical Studies* and AC therapy will not be described as MEC.

Question 2

Helsinn believes the indication statement in the approved labeling for Akynzeo should refer to “highly emetogenic cancer chemotherapy” (HEC) and [REDACTED] (b) (4)

[REDACTED] Helsinn also believes that, consistent with the agency’s statement that the labeling “describe regimens that were studied,” any concerns regarding the HEC/MEC classifications would be adequately addressed by the Clinical Studies section of the labeling (1) describing the patient populations studied with specific reference to each chemotherapy regimen, and (2) identifying the treatment guidelines that were the basis for classifying the studied chemotherapies as “highly” or “moderately” emetogenic. Does the agency agree? Please comment as needed.

FDA Response:

Please see response to Question 1.

Question 3

It is Helsinn’s view that, consistent with the NETU-08-18 SPA agreement, the data submitted with NDA 205,718 support approval for an indication of preventing acute and delayed nausea and vomiting in patients receiving either highly or moderately emetogenic chemotherapy. Helsinn believes that the revised categorization of AC chemotherapy under the 2011 ASCO guidelines does not change that conclusion with regards to moderately emetogenic chemotherapy. Recognizing that FDA has not yet completed its review of the Akynzeo NDA, does the agency agree that if the data demonstrate effectiveness, it will support approval of Akynzeo for both the HEC and MEC target indications?

FDA Response:

Please see response to Question 1.

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/s/

MARY H CHUNG
03/20/2014

From: [Chung_Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung_Mary](#)
Subject: NDA 205718 netupitant/palonosetron Advice/Information Request
Date: Thursday, March 13, 2014 11:36:23 AM

Dear Dr. Lehmann,

Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. Reference is also made to the revised labeling submitted December 20, 2013.

We have following recommendations for the placement of PK information throughout the submitted labeling. If these changes could be made to the labeling and submitted via email and to the NDA, it would be appreciated.

- 1) Section 5
 - o PK information should be moved to Sections 7 and/or 12.3
- 2) Section 7
 - Add subheadings in Section 7 (for example)
 - o 7.1.Effects of other drugs on Akynzeo
 - o 7.2 Effects of Akynzeo on other drugs
 - Add subheadings for (b) (4) in Section 12.3.
 - o Detailed PK study information should be moved from Section 7 to Section 12.3
- 3) Section 8.5-8.7
 - o Add subheadings for (b) (4) in Section 12.3.
 - o Detailed PK study information should be moved from Section 8 to Section 12.3
- 4) Section 12.3
 - o Organize ADME info by drug

Please see the Guidance for Industry: Drug Interaction Studies published February 2013 for more guidance.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Regards,

Mary

Mary Chung, PharmD.

Regulatory Health Project Manager

Division of Gastroenterology and Inborn Errors Products

Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133

Phone: 301-796-0260 /fax: 301-796-9904

mary.chung@fda.hhs.gov

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MARY H CHUNG
03/20/2014

From: Chung, Mary
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Subject: NDA 205718 netupitant/palonosetron Information Request
Date: Tuesday, March 04, 2014 4:27:00 PM

Dear Dr. Lehmann,
Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information.

Our understanding is that RO0673189 is the Roche compound code for netupitant free base. However, there are several nonclinical study reports that identify the test article as RO0673189-008. Please provide the identity of RO0673189-008. If RO0673189-008 is a salt of netupitant, indicate whether the dose levels in nonclinical study reports are expressed as the free base or the salt.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133
Phone: 301-796-0260 /fax: 301-796-9904
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/s/

MARY H CHUNG
03/05/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 netupitant/palonosetron Information Request
Date: Friday, February 14, 2014 9:22:06 AM

Dear Dr. Lehmann,

Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information.

For Study NETU-07-07:

1. Provide more details and/or the program codes on your dynamic adaptive stratification algorithm used to allocate subjects to the five treatment groups.
2. For each subject, provide the probability of assignment to each of the five treatment groups at the time of the randomization. Provide a data set with this information.
3. Describe how the randomization scheme and codes provided in Appendix 16.1.7 of the clinical study report were used, and their role in your dynamic adaptive allocation.
4. Regarding the study site treatment kits:
 - a. Describe how the availability of treatment kits at the trial site affected the randomization and a subject's assignment, especially when the treatment kit was not available at the site.
 - b. Summarize the number of times a treatment kit was not available, both overall and by study site.
 - c. Describe the process used to ensure there were enough kits at a trial site and how it was possible for a trial to have an insufficient number of kits at the time a subject was assigned to a treatment.
5. Confirm that one-sided p-values for the primary efficacy analyses are presented in the currently submitted draft labeling and the study report.

For Study NETU-08-18: Provide the block size used in the randomization.

If there are any questions please contact me.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133

Phone: 301-796-0260 /fax: 301-796-9904

mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
02/14/2014

NDA 205718 CMC IR #3

Tran-Zwanetz, Catherine

Sent: Tuesday, February 11, 2014 12:23 PM

To: craig@august-consulting.com

Cc: Chung, Mary

Dear Dr. Lehmann,

Here is our latest information request:

Please provide a brief description of the analytical procedure for Elemental Impurities in the specification for the Netupitant Palonosetron Combination Capsule (AM32P52-20). Specific descriptions of the preparation of the sample and standard should be included.

Please let me know if you have any questions and confirm that you have receive this email.
Cathy

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/s/

CATHERINE A TRAN-ZWANETZ
02/11/2014

NDA 205718 another CMC IR

Tran-Zwanetz, Catherine

Sent: Monday, February 03, 2014 2:34 PM**To:** craig@august-consulting.com**Cc:** Chung, Mary

Dear Dr. Lehmann,

We have another IR for the NDA listed above, not related to the previous comment I sent earlier today.

In your flow diagram of the manufacturing process for intermediate netupitant tablet, you have proposed the following (b) (4) control: (b) (4) however, in your executed batch record (for lot number: 30004380), in (b) (4) the following statement has been written: (b) (4)

(b) (4) Thus, it is not clear which method is used for the (b) (4) control of (b) (4)

Please clarify and provide detailed analytical procedure for the analytical method to determine the (b) (4) for the (b) (4) control. And also please update NDA accordingly as well as email me.

Thanks!
Cathy

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/s/

CATHERINE A TRAN-ZWANETZ
02/03/2014

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Wednesday, January 29, 2014 4:17 PM
To: 'craig@august-consulting.com'
Cc: Chung, Mary
Subject: NDA 205718 Chemistry Information Request

Attachments: Picture (Metafile)

Dear Dr. Lehmann,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Akynezo (netupitant and palonosetron HCl) Fixed-dose combination Capsule received September 27, 2013. We have the following request for additional information.

Provide long-term freezer storage stability report for duration of bio-sample storage (studies NETU-09-07 and NETU-11-02) based on the "Bioanalytical Method Validation Guidance" under number 3 of section D of part IV page 7 shown below for Palonosetron component.

3. Long-Term Stability

The storage time in a long-term stability evaluation should exceed the time between the date of first sample collection and the date of last sample analysis. Long-term stability should be determined by storing at least three aliquots of each of the low and high concentrations under the same conditions as the study samples. The volume of samples should be sufficient for analysis on three separate occasions. The concentrations of all the stability samples should be compared to the mean of back-calculated values for the standards at the appropriate concentrations from the first day of long-term stability testing.

Please reply with this information by Friday, February 1 and let me know if you have any questions.

Thanks!

Cathy Tran-Zwanetz
Regulatory Project Manager
(301) 796-3877

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/s/

CATHERINE A TRAN-ZWANETZ
01/29/2014

From: [Chung, Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:Craig.Lehmann@august-consulting.com)
Cc: [Chung, Mary](#)
Subject: NDA 205718 netupitant/palonosetron Information Request
Date: Wednesday, January 29, 2014 9:37:49 AM

Dear Dr. Lehmann,

Reference is made to your NDA 205718 Akynzeo (netupitant and palonosetron HCl fixed-dose combination capsule) received September 27, 2013. We have the following request for additional information.

- For the exposure-response (PK/PD) analysis reported entitled “Population Pharmacokinetic and Pharmacodynamic Modeling and Simulation of Palonosetron in Pediatric Patients: Helsinn Healthcare SA Report PALO-07-34” dated August 8, 2007, please provide all the dataset used for the PK/PD analyses using WinBUGS. In addition, please provide a dataset from Study PALO-99-07 and Study 2330 with the same format as the dataset titled “popkpd-08oct2013.xpt.” A description of each data item should be provided in a Define.pdf file.
- For PopPK analysis, please explain why select subjects from PALO-10-20 where ADSL.PKSFL=“Y” and from PALO-99-07 where ADSL.PKFL=“Y” in dataset “popkpd-18sept2013.xpt”.

We would appreciate receiving this information by February 3rd, 2014 or before.

Regards,

Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5133
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
01/29/2014

Cuff, Althea

From: Cuff, Althea
Sent: Monday, December 30, 2013 12:36 PM
To: craig@august-consulting.com
Cc: Chung, Mary
Subject: NDA 205718 - Information Request

Dear Dr. Lehman;

We are reviewing the CMC section of Helsinn Healthcare SA's NDA 205718, please provide the following information by Monday January 20, 2014.

1. A detailed statistical report and syntax for the SAS program used to conduct the statistical analysis of the PK-parameters for studies NETU-09-07 and NETU-11-02.
2. Provide SAS transport file for SAS dataset in the following format (nine columns), the dataset you provided on November 8, 2013, is not in the requested format. You have not provided 2 datasets, one for each component of your product (Netupitant or Palonosetron). Secondly you have not simplified your entries for example under sequence column (A or B), under period column (1, 2, 3, 4), and under treatment column (T or R), etc.

Subject ID	Sequence	Treatment	Period	Cmax	AUClast	AUC inf
Tmax	T1/2					

Thanks, Althea

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/s/

ALTHEA CUFF
12/30/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205718

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Helsinn Healthcare SA
c/c August Consulting, Inc.
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Attention: Craig Lehmann, Pharm.D.
Authorized Representative

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) dated September 25, 2013, received September 27, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Netupitant and Palonosetron Hydrochloride Capsules, 300 mg/0.5 mg.

We also refer to your October 8, 2013, correspondence, received October 9, 2013, requesting review of your proposed proprietary name, Akynzeo. We have completed our review of the proposed proprietary name, Akynzeo and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 8, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Mary Chung, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/13/2013



NDA 205718

FILING COMMUNICATION

Helsinn Healthcare SA
C/O August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) dated and received September 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule.

We also refer to your amendments dated October 9, 2013, October 31, 2013, November 8, 2013, November 14, 2013 and November 21, 2013.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is September 26, 2014.

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 requirement/commitment requests by June 4, 2014. In addition, the planned date for our internal mid-cycle review meeting is February 12, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues and have the following requests as applicable:

1. Clinical Pharmacology
 - a. The $\Delta\Delta\text{QTcF}$ vs. time profile for moxifloxacin is inconsistent with our expectation because the $\Delta\Delta\text{QTcF}$ effect appears at the first available time point (1 hour post-dose). The rising phase of the moxifloxacin profile is missing. We would therefore like to evaluate the moxifloxacin induced $\Delta\Delta\text{QTcF}$ effect before hour 1. Please extract ECG data for moxifloxacin and placebo at 15 minutes and 30 minutes post-dose and the corresponding baseline for us to evaluate. Please submit this information by January 6, 2014.
2. Biostatistics
 - a. For the primary efficacy endpoints, provide analyses of gender, racial, and geriatric subgroups for each study (NETU-07-07, NETU-08-18, NETU-10-29, PALO-10-01). Please interpret and discuss the findings.

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.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights must be one-half page or less unless a waiver has been granted in a previous submission.
2. The Table of Content (TOC) should be in a two-column format.
3. The TOC subsection headings must be indented and not bolded. The word “action” in subsection 12.1 must be capitalized.
4. The numbers (b) (4) must be deleted from the TOC.
5. The Patient Counseling Information Section in the Full Prescribing Information must reference any FDA-approved labeling in Section 17 and indicate the type of FDA-approved patient labeling (i.e., Patient Information).
6. FDA-approved patient labeling must not be included as a subsection under section 17.

We request that you resubmit labeling that addresses these issues by January 6, 2014. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a (b) (4) of pediatric studies for this application. Once we have reviewed your request, we will notify you if the (b) (4) request is denied and a pediatric drug development plan is required.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

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

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/s/

BRIAN K STRONGIN

12/05/2013

Signing for Donna Griebel, Division Director

From: [Chung_Mary](#)
To: [Craig Lehmann \(craig@august-consulting.com\)](mailto:craig@august-consulting.com)
Cc: [Chung_Mary](#)
Subject: NDA 205718 Akynzeo (netupitant/palonosetron)
Date: Monday, September 08, 2014 8:08:27 PM

Dear Dr. Lehmann,

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AKYNZEO, netupitant and palonosetron hydrochloride fixed-dose combination capsule received on September 27, 2013.

We have the following request for additional information:

Reference is made to Table 1 of the Full Prescribing Information of the label. Please see below revised Table 1 based on Tables 2.3.1.1; 2.3.1.2; and 2.3.1.3. Please provide your confirmation of the below revised numbers.

(b) (4)

We request a confirmation by Tuesday September 9, 2014.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
09/09/2014

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Thursday, November 07, 2013 10:59 AM
To: 'craig@august-consulting.com'
Subject: IR Questions for NDA 205718

Dear Dr. Lehmann,

We are reviewing the CMC section of Helsinn Healthcare SA's NDA 205718, and have the following IR Questions:

1. Indicate whether or not the supplier of the capsule used for primary stability [REDACTED] (b) (4) is the same as the supplier of the capsule used for commercial distribution (white body / caramel cap). If the suppliers are different, confirm that the commercial supplier is [REDACTED] (b) (4) and provide the name and address of the other supplier.
2. Provide a more detailed LOA from [REDACTED] (b) (4) which indicates the specific location in its DMF for information describing empty hard gelatin capsule with white body / caramel cap (and, if appropriate, [REDACTED] (b) (4) [REDACTED]). The revised LOA should contain the date of the amendments containing the specific information.
3. If necessary, provide a separate LOA for the DMF of the supplier of the capsule used for the primary stability batches [REDACTED] (b) (4). The LOA should contain the date of the amendments containing the specific information.

Please respond to me via email, and submit a formal amendment to the NDA.

If you have any questions, please contact me.

Thank you,

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
CDER-ONDQA
301-796-1765

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/s/

REBECCA A MCKNIGHT
11/07/2013



NDA 205718

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Helsinn Healthcare SA
Attention: Dr. Craig Lehman
August Consulting, Inc.
515 Capital of Texas Highway, Suite 150
Austin, TX 78746
FAX: (512) 347-9375

Dear Dr. Craig Lehman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Akynzeo® (netupitant-palonosetron hydrochloride) Capsule.

We will be performing methods validation studies on Akynzeo® (netupitant-palonosetron hydrochloride) Capsule, as described in NDA 205718.

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

Method, current version

- Drug Substance: (b) (4) (AGC/166)
- Drug Substance: Related substances and identification by HPLC (ALC/146)
- Drug Substance: Assay by HPLC (ALC/147)
- Drug Product: Netupitant identification
- Drug Product: Assay of Netupitant
- Drug Product: Netupitant impurities
- Drug Product: Dissolution - Netupitant

Samples and Reference Standards

- 2 x 500 mg 14-NETU reference standard
- 400 mg (b) (4) reference standard
- 400 mg (b) (4) reference standard
- 50 mg (b) (4) reference standard
- 25 mg (b) (4) reference standard if available
- 500 mg Netupitant drug substance
- 150 Combination capsules (300 mg netupitant and 0.50 mg palonosetron)

Equipment

- 1 (b) (4)
- 1 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/22/2013



IND 073493

MEETING MINUTES

Helsinn Healthcare SA
C/O August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for netupitant and palonosetron hydrochloride fixed-dose combination capsule.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2013. The purpose of the meeting was to discuss the results of your phase 3 trials, the content and format of your planned eCTD NDA submission, your proposed labeling, and the schedule to submit your pediatric study plan.

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

If you have any questions, call me at (301) 796-796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: April 16, 2013; 9:00AM–10:00AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 073493
Product Name: netupitant and palonosetron hydrochloride fixed-dose combination capsule

Indication:

- 1) Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (CINV-HEC)
- 2) Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (CINV-MEC)

Sponsor/Applicant Name: Helsinn Healthcare SA

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Jagjit Grewal, M.P.H.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director
Victoria Kusiak, M.D.	Deputy Director
Maria Walsh, RN, M.S.	Associate Director for Regulatory Affairs

ODE III/Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Andrew Mulberg, M.D.	Deputy Director
Ruyi He, M.D.	Medical Team Lead
John Troiani, M.D., Ph.D.	Medical Reviewer
David Joseph, Ph.D.	Pharmacology Team Lead
Ke Zhang, Ph.D.	Pharmacology Reviewer
Jagjit Grewal, M.P.H.	Senior Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology III

Insook Kim, Ph.D. Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D. Chemistry Lead
Hitesh Shroff, Ph.D. Chemistry Reviewer
Deepika Arora Lakhani, Ph.D. Biopharmaceutics Reviewer

Office of Translational Sciences/Office of Biostatistics/Division of Biometrics III

Stephen Wilson, Ph.D. Director
Freda Cooner, Ph.D. Reviewer

Controlled Substances Staff

Katherine Bonson, Ph.D. Pharmacologist
Kristen Karlsen Pharmacy Student

Pediatric and Maternal Health Staff

Hari Sachs, M.D. Lead Medical Officer
Erica Radden, M.D. Medical Officer
Denise Pica-Branco, Ph.D. Senior Regulatory Health Project Manager

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim Independent Assessor

SPONSOR ATTENDEES

Helsinn Healthcare SA

Dr. Giorgia Rossi Manager, Corporate Clinical Development
Dr. Giuseppina Clerici Senior Manager, Safety Physician, Drug Safety Unit
Dr. Giada Rizzi Manager, Statistics & Data Management
Dr. Emanuela Lovati Manager, Research and Preclinical Development
Dr. Roberta Cannella Director, Technical Affairs
Dr. Fabiola Bambini Manager, Technical Affairs
Dr. Angioletta Navini Senior Manager, Regulatory Affairs
Dr. Sergio Cantoreggi Chief Scientific Officer
Dr. Richard Bourne Vice President, Regulatory Affairs, Helsinn Therapeutics US

Consultants



Dr. Craig Lehmann Authorized Representative, August Consulting, Inc.

1.0 BACKGROUND

Helsinn Healthcare submitted a Type B, pre-NDA meeting request, dated November 12, 2013, for IND 73493 netupitant and palonosetron hydrochloride fixed-dose combination (FDC) capsule. The purpose of this meeting is to discuss results of their phase 3 trials, the content and format of their planned eCTD NDA submission, proposed labeling, and the schedule to submit the pediatric study plan. Palonosetron HCl is a 5-HT₃ receptor antagonist approved under the proprietary name Aloxi as oral capsule and intravenous injection formulations. Netupitant is a NK₁ receptor antagonist and new molecular entity. The proposed fixed-dose combination product is a hard gelatin capsule containing 300 mg of netupitant and 0.5 mg of palonosetron HCl. The FDC capsule is intended to be administered as a single oral dose one hour prior to highly and moderately emetogenic chemotherapies.

FDA granted the meeting in the correspondence dated November 28, 2012. On January 22, 2013, Helsinn requested that the meeting be postponed due to delays in receiving the phase 3 trial results from their CRO. Therefore, the meeting was rescheduled for April 16, 2013. Helsinn's meeting background package was received on March 18, 2013. FDA's preliminary comments were issued to the sponsor on April 12, 2013. On April 15, 2013, Helsinn provided responses to FDA's preliminary comments to facilitate discussion at the meeting.

Helsinn's clinical development program was previously discussed at the end-of-phase 2 meeting held on July 20, 2009. Subsequent to this meeting, a series of Special Protocol Assessment (SPA) requests were submitted by the sponsor and Type A SPA meetings were held on January 22, 2010 and July 15, 2010. Per discussions from these meetings, the below listed clinical studies were conducted to support the efficacy and safety of the fixed-dose combination capsule for the prevention of acute and delayed phases of CINV-HEC and CINV-MEC.

- NETU-07-07 (CINV-HEC): Superiority study comparing three single oral doses of netupitant (100 mg, 200 mg, 300 mg) each combined with 0.5 mg oral palonosetron HCl versus 0.5 mg oral palonosetron HCl in patients receiving a single cycle of HEC. An arm of oral aprepitant and I.V. ondansetron was included as an active comparator for exploratory purposes. This is the sole pivotal efficacy study in patients receiving HEC and also serves to demonstrate the contribution of the netupitant component to the FDC capsule. Complete Response (CR) overall was the primary endpoint of interest. However, Helsinn will include a post-hoc analysis utilizing CR delayed as the primary endpoint with secondary endpoint of CR acute and CR overall.
- PALO-10-01 (CINV-HEC): Non-inferiority trial comparing 0.5 mg oral palonosetron HCl to 0.25 mg I.V. palonosetron HCl in patients receiving a single cycle of HEC. Complete Response in the acute phase was the primary endpoint. This trial was conducted to establish the contribution of the oral palonosetron component in the FDC product for CINV-HEC. This trial is also used to demonstrate that oral palonosetron can be used as the comparator for CINV-HEC study NETU-07-07. FDA issued a SPA agreement correspondence for this trial protocol on November 3, 2010.
- NETU-08-18 (CINV-MEC): Superiority trial comparing netupitant and palonosetron HCl FDC capsule versus palonosetron HCl (b) (4) in patients receiving MEC. CR

delayed was the primary endpoint with CR acute and CR overall as secondary endpoints. This is the sole trial pivotal efficacy trial in patients receiving MEC (anthracycline/cyclophosphamide based). This trial will also provide repeat cycle safety data. FDA issued a SPA agreement correspondence for this trial protocol on November 3, 2010.

- NETU-10-29 (CINV-HEC/MEC): Randomized (3:1), double-blind, multi-cycle trial comparing the safety and efficacy netupitant and palonosetron HCl FDC capsule versus aprepitant and palonosetron HCl. The primary objective of this trial was to provide repeat cycle safety data for at least 6 cycles in more than 100 HEC and/or MEC patients (approximately 25% HEC and 75% MEC) exposed to the FDC capsule. A secondary objective of the trial was to descriptively evaluate the efficacy of the FDC capsule versus the aprepitant arm for the CR delayed, CR acute, and CR overall endpoints.

Helsinn will also provide safety data from study NETU-08-03 (an 8-week daily administration of netupitant alone in patients with overactive bladder), studies in analgesia, a PK study in cancer patients and hepatic patients. A thorough QT/QTc trial of the proposed fixed-dose combination product has been conducted. Furthermore, FDA issued correspondence on December 8, 2011 providing conditional acceptance on the proposed proprietary name AKYNZEO.

2.0 DISCUSSION

The format of these minutes provides for Helsinn's questions in regular typeface, followed by the Agency's April 12, 2013 responses in **bolded** print. Helsinn's April 15, 2013 comments are shown in *italic* print. The April 16, 2013 meeting discussion is presented in *italic and bolded* print.

2.1 CLINICAL/STATISTICAL PROGRAM

Question #1: Phase 3 efficacy study results: Efficacy results from phase 2/3 pivotal efficacy studies NETU-07-07 (HEC), NETU-08-18 (MEC), PALO-10-01 (HEC) are provided in Sections #8.1.1, 8.1.2 and 8.1.4 and Appendices #1 - 2. Sponsor plans to seek approval for the following target indication for AKYNZEO®:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

Sponsor believes that these MEC and HEC efficacy data are adequate to support the submission of the planned NDA for the target indication. Does the Agency agree? Please comment as needed.

FDA Response:

We agree that these studies can support submission of the planned NDA. Whether data from these studies support the proposed indications is a review issue. Please note that

NETU 08-18 is the sole MEC pivotal efficacy trial using AC therapy and AC chemotherapy was reclassified as HEC recently. If approved, labeling will describe regimens that were studied. The Division is moving beyond “HEC” and “MEC” classifications given the continual evolution of opinions in clinical medicine, particularly as new chemotherapy drugs are approved for marketing.

Sponsor Reply 4/15/13: Thank you for your response. Sponsor is concerned about the possibility of FDA changing the definition of the target indications since it can have substantial impact on drug use. The proposed indications were the basis of the phase 2-3 efficacy program as agreed with FDA during the SPA process and followed regulatory precedents. Please clarify FDA’s thinking regarding the indications and labeling implications and Sponsor’s options.

Meeting Discussion:

Helsinn indicated that they would prefer to maintain the original target indications. FDA replied that the approved label will describe the regimens that were studied. Final wording of the indications will be a review issue.

Question #2: Safety results and proposed content and format of the planned SCS and ISS: Safety results from Phase 2/3 studies NETU-07-07 (HEC), NETU-08-18 (MEC) and NETU-10-29 (HEC/MEC), including repeat cycle safety data from these later two studies, are summarized in Sections #8.1.1.5, 8.1.2.3 and 8.1.3.3, and Appendices #1, 2 and 3, respectively. PALO-10-01 safety results are not yet available at the time of this backgrounder but they will be integrated within the ISS. Section 8.3 describes the proposed content and format of the SCS and ISS for the NDA, which is consistent with previous FDA feedback (FDA ltrs 31May12 and 31Aug12, both provided in Appendix #10). Sponsor believes that the proposed SCS and ISS content and format are adequate to support the submission of the planned NDA. Does the Agency agree? Please comment as needed.

FDA Response:

We agree.

Sponsor Reply 4/15/13: Thank you for your response. No further discussion is needed.

2.2 BIOPHARM PROGRAM

Question #3: Biopharm/PK program in support of the planned NDA: For netupitant and for the FDC, biopharm/PK/PK-PD studies including ADME, food effect, drug interaction studies, PK studies involving elderly, PK studies involving hepatic impaired patients, PK studies involving the target CINV patient population, bioavailability and bridging bioequivalence studies as well as thorough QT/QTc, PET and apomorphine studies, all planned to be included in the AKYNZEO® NDA, are summarized in Section #9.0 and Appendix #7. For palonosetron, as agreed with the Agency at the EoP2 meeting, no ALOXI® study reports will be resubmitted in the AKYNZEO® NDA. In order to refer to the approved oral ALOXI® labeling information, the change of the

oral formulation of palonosetron was addressed in two BE studies NETU-08-12 and NETU-09-07, which bridged the approved ALOXI® oral formulation with the palonosetron component in AKYNZEO®. Therefore no biowaiver request is planned to be submitted. Sponsor believes that overall the biopharm/PK program is adequate to support the submission of the planned AKYNZEO® NDA. Does the Agency agree? Please comment as needed.

FDA Response:

Your clinical pharmacology program is acceptable for the submission of the AKYNZEO NDA provided that you also submit the transporter interaction studies for netupitant and its metabolites M1, M2, and M3 (NETU-12-81). The adequacy of the data will be determined during the NDA review. Please see the FDA “Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” (February 2012) for more information.

Sponsor Reply 4/15/13: Thank you for your response. We will submit NETU-12-81 in Module 5, as requested. Please note that transporter interaction studies are being conducted with netupitant, M1 and M3. Per the drug-drug interaction guidance (Dated February 2012): "The potential for drug interactions with metabolites of investigational drugs (metabolites present at > 25% of parent drug AUC) should be considered". Because exposure of M2 (AUC and C_{max}) was 7% compared to parent, M2 was not evaluated in NETU-12-81. In addition M2 is 15% as active as parent netupitant in preclinical models. Please comment as necessary.

Meeting Discussion:

Helsinn will also conduct an in vitro transporter study for M2. The study report will be included in the initial NDA submission.

Please submit all available safety and PK data in cancer patients analyzed by kidney function at the time of your NDA submission.

Sponsor Reply 4/15/13: Thank you for your response. Less than 5% of netupitant and netupitant related material (all radioactivity as extrapolated in human ADME study NETU-09-21) is excreted in urine. Less than 1% of netupitant (NETU-06-27) is eliminated unchanged in urine. Therefore any accumulation of netupitant or metabolites in renally impaired patients after a single dose would be negligible. Furthermore, based on the Guidance for Industry “Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling” issued in March 2010, the FDC is not intended to be administered chronically but as a single dose in repeated cycles of chemotherapy.

Since this was discussed during the End of Phase 2 meeting with FDA (19 Aug 2009; Question 14; see background package Appendix 10 page 39), no specific studies were performed to evaluate netupitant in patients with renal impairment. Renal impairment has no effect on the PK of palonosetron.

The pharmacokinetics of netupitant in cancer patients were investigated in Study NETU-10-09 and in the population PK study NETU-10-02 (in association with NETU-08-18 in MEC patients). Both these studies evaluated serum creatinine at screening and during the study. The effect of renal function on netupitant and metabolites PK was not evaluated in NETU-10-09. However, creatinine clearance (mL/min), calculated using the Cockcroft-Gault equation, is one of the covariates that will be evaluated for potential impact on the pharmacokinetics of netupitant (and its metabolites M1, M2 and M3) and palonosetron in the population PK study (NETU-10-02). Serum creatinine values were determined concurrently with each PK sampling session. This data will be included in the NDA.

In clinical practice, renal impairment limits the ability to administer cytotoxic chemotherapy. For this reason, patients with CrCl <60 ml/min were excluded in study NETU-08-18. While no specific renal exclusion criterion was applied in NETU-10-09, very few patients had serum creatinine above the normal range. Therefore only a limited number of renally impaired patients are expected to be included in the FDC safety database.

Please comment as necessary.

Meeting Discussion:

FDA acknowledged the sponsor's response. However, FDA noted that this will remain a review issue. In order to do appropriate labeling for renal impairment across the scope of renal impairment, a postmarketing special population safety study may be required.

We request that the study reports for in vitro studies using human materials be located in module 5 as well.

Sponsor Reply 4/15/13: Thank you for your response. We will submit in vitro studies using human materials in Module 5, as requested. No further discussion is needed.

We request that the clinical pharmacology summary is submitted using the provided template (see Attachment #1).

Sponsor Reply 4/15/13: Thank you for your response. We will submit the clinical pharmacology summary as requested. Please clarify if this document will replace CTD section 2.7.1 and/or 2.7.2 or if it will be in addition to CTD section 2.7.1 and/or 2.7.2. If in addition to 2.7.1 and/or 2.7.2, should it be located in Module 5.3.5.3?

Meeting Discussion:

FDA clarified that the Clinical Pharmacology Summary is not a replacement for module 2.7.1 or 2.7.2. The Clinical Pharmacology Summary document should be included in module 2 as an appendix.

2.3 PHARM/TOX PROGRAM

Question #4: Pharm/tox program in support of the planned NDA: Pharm/tox studies on netupitant and on the FDC are summarized in Section #10.0. Sponsor believes that pharm/tox program is adequate to support the submission of the planned AKYNZEO® NDA. Does the Agency agree? Please comment as needed.

FDA Response:

No, we do not agree. The draft label states under the section for

(b) (4)

These studies must be part of the pharm/tox list of preclinical studies that will be submitted in the NDA. Additionally, any abuse-related animal studies conducted with netupitant alone should be included in the NDA. If netupitant-alone studies were not conducted, you must provide a justification.

Sponsor Reply 4/15/13: Thank you for your response. To comply with FDA's request at the End-Of- Phase 2 meeting held on July 20, 2009 (IND 073493, netupitant and palonosetron hydrochloride fixed-dose combination capsule), the Sponsor conducted the following studies (referenced in pages 70, 72 and 77 of this pre-NDA backgrounder):

- NETU-10-24 (in vitro pharmacology study to investigate the effects of netupitant and M1 in various in vitro receptor binding and uptake assay)
- NETU-10-16 (in vitro pharmacology study to investigate the effects of M1, M2 and M3 in various in vitro receptor binding and uptake assay)
- NEPA-12-71 Netupitant/Palonosetron Fixed Combination – Preclinical Abuse Liability Testing in Baboons (including NETU-11-12, PK-PD dose effect assessment of the time course of the behavioral effects of oral netu/palo and related blood levels, NETU-11-25 drug discrimination, NETU-11-24 IV netu/palo self-administration dose effect assessment, NETU-11-26 physical dependence and withdrawal assessment)

The Sponsor confirms that (a) these reports will be part of the pharm/tox list of preclinical studies that will be submitted in the NDA and (b) the proposed draft labeling “Drug Abuse and Dependence” section will include information from these drug abuse studies. No abuse-related animal studies were conducted with netupitant alone and a full justification will be provided in the NDA.

Meeting Discussion:

FDA acknowledged the sponsor's response, but noted that the justification for not conducting abuse-related animal studies with netupitant alone will be a review issue.

2.4 CMC PROGRAM

Question #5: Drug substance and drug product CMC program in support of the planned NDA: Section #11.0 describes drug substance information and proposed specifications, a follow-up evaluation of potentially genotoxic netupitant impurities, the proposed commercial drug product formulation including discussion of a novel excipient, provides an overview of planned drug product specifications, the stability data package, and an update on bridging Phase 3 combination capsule to the proposed commercial AKYNZEO® capsules. Sponsor believes that the CMC plan described in Section #11.0 is adequate to support the submission of the planned AKYNZEO® NDA. Does the Agency agree? Please comment as needed.

FDA Response:

Your proposed approach to drug substance and drug product specifications and stability testing is for the most part reasonable. However, at the time of your NDA submission, you must provide the following information:

- 1. Elemental impurities testing in accordance with USP <232> will need to be included in the drug product specification.**

Sponsor Reply 4/15/13: Thank you for your response. Information pertaining to evaluation of the finished drug product (combination product) in accordance with USP <232> will be included in the NDA. Specifically, the approach is consistent with that used for calculation of (b)(4) in that all components of the finished drug product will be evaluated and calculated. Helsinn will be using the summation option as stated in the pending USP <232> chapter. We would like to have your feedback at the meeting.

Meeting Discussion:

FDA agreed with the sponsor's proposal.

- 2. We note the absence of (b)(4) testing in the final product. When you submit your NDA, you will need to justify this.**

Sponsor Reply 4/15/13: Thank you for your response. Helsinn will provide a justification in the NDA concerning omitting (b)(4) testing on the finished drug product and would like to briefly discuss the approach at the meeting.

Meeting Discussion:

FDA did not agree with the sponsor's proposal. FDA noted that (b)(4) testing should be conducted on the finished product, not on the components of the finished product. (b)(4) testing or justification why testing is not required should be on the finished product.

- 3. In addition to providing specifications for your novel excipient, you will need to include a complete description of the manufacturing and testing procedures, either directly in the NDA, or in a referenced DMF.**

Sponsor Reply 4/15/13: Thank you for your response. No further discussion is needed.

We may have additional comments when we review your complete NDA submission.

Sponsor Reply 4/15/13: Thank you for your response. Helsinn will provide a complete dissolution development report for netupitant (contained in the intermediate tablet and in the finished combination product) in the NDA. Dissolution development report for palonosetron (contained in the intermediate softgel and in the finished combination product) will not be presented in the NDA as the method is the same as currently approved in NDA 22,233, for Aloxi (palonosetron HCl) 0.50 mg softgel. Dissolution profile data for palonosetron in the Intermediate Palonosetron Softgel and in the finished combination product will be presented in the NDA along with the specifications, method and method validation. We would like to discuss this further at the meeting.

Meeting Discussion:

Helsinn's proposal was partly acceptable. Helsinn must provide the specific reference to the oral palonosetron NDA for the dissolution method development section.

However, the sponsor will have to prove the discriminating abilities of the dissolution methods for both the APIs present in the combination product.

2.5 REGULATORY PROGRAM

Question #6: Palonosetron monotherapy (ALOXI®) data: As agreed with the Agency, Form 356h in the AKYNZEO® NDA will cross-reference to palonosetron I.V. (NDA 21-372) and oral palonosetron (NDA 22-233). IV and oral palonosetron study reports (pharm/tox, biopharm/PK, clinical safety or efficacy) will not be included in the AKYNZEO® NDA; as per FDA request, original electronic datasets that were part of oral ALOXI® NDA will be resubmitted. Sponsor will send them via FDA portal or on a CDrom but not included in the AKYNZEO® NDA. As described in Section #14.3, (b) (4)

These PIs are proposed to be located in Module 5.4 of AKYNZEO® NDA. Does the Agency agree with the proposed approach for (b) (4)

Please comment as needed.

FDA Response:

No, we do not agree. Please submit the original oral ALOXI datasets to the AKYNZEO NDA.

Sponsor Reply 4/15/13: Sponsor is concerned that the FDA eCTD software might generate a message error if Aloxi clinical datasets are submitted without including the corresponding study reports (please note that, as agreed, the Sponsor will not resubmit Aloxi clinical study reports in AKYNZEO NDA) and therefore the eCTD might not pass the validation at the FDA eSub Office.

Helsinn is currently corresponding with the FDA eSub Office to perform a test submission with an eCTD sample in the next couple of weeks and we will perform the test submitting the original Aloxi datasets in the eCTD, as requested. If the test is favorable, we will submit the original oral ALOXI datasets in the AKYNZEO NDA. If the test submission fails, we will contact the FDA GI Division to find an alternative solution in conjunction with the eSub Office. We would like to discuss this further at the meeting.

Meeting Discussion:

FDA agreed that the sponsor's proposal is acceptable.

Question #7: Planned approach for submitting the pediatric study plan: The planned approach for submitting the initial pediatric study plan for AKYNZEO® is described in Section #14.2. Due to the nature of the dosage form and route of administration (an oral fixed-dose combination), the Sponsor plans to submit a request for a (b) (4) in all age subsets of the paediatric population in CINV, on the (b) (4)

(b) (4) to facilitate the process of reaching agreement with FDA, the request for a (b) (4) is intended to be submitted to IND 73,493 a few weeks before the coming AKYNZEO® NDA submission, and then resubmitted in the AKYNZEO® NDA (planned by 3Q 2013). Does the Agency agree with the proposed approach? Please comment as needed.

FDA Response:

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 changes the timeline for submission of a Pediatric Study Plan and includes a timeline for the implementation of these changes. Because your End-of-Phase 2 (EOP2) Meeting occurred prior to November 6, 2012, the following apply to you regarding submission of a Pediatric Plan or a Pediatric Study Plan (PSP):

- **If you plan to submit your NDA prior to January 5, 2014, FDAAA rules still apply and your Pediatric Plan must be submitted with your application. There is no need to submit the Pediatric Plan to the IND. (Refer to Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm079756.pdf>). Alternatively, you may submit a PSP rather than a Pediatric Plan; however, a PSP should be submitted no later than 210 days prior to submission of your application;**

or

- **If you plan to submit your NDA on or after January 5, 2014, your Pediatric Study Plan (PSP) must be submitted no later than 210 days prior to submission of your application.**

A PSP must include the following:

- **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*). Appropriate juvenile animal toxicity studies will be needed to support the initiation of any pediatric studies.**
- **Any request for a deferral, partial waiver or waiver, along with supporting information. (Note: Although requests must be submitted with PSP, decisions on whether or not waivers and deferrals will be granted do not become final until approval.)**

A template is available to aid sponsors in formulating a Pediatric Study Plan:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>. In addition you may contact the Pediatric and Maternal Health Staff at 301 796-2200, or e-mail pdit@fda.hhs.gov.

Although not required for a Pediatric Plan submitted under FDAAA, the Pediatric Study Plan template contains elements that will assist FDA in reviewing a Pediatric Plan that is submitted under FDAAA.

It is premature to comment on the approval of a (b) (4) until the pediatric plan is reviewed. However, it is unlikely that a (b) (4) will be granted based on the provided rationale. Due to the nature of the dosage form and route of administration, you claim that the drug (b) (4)

However, you should submit epidemiologic and drug use data to support this claim. Oral formulations for both palonosetron and aprepitant, the only approved NK₁ antagonist, have postmarketing study requirements under the Pediatric Research Equity Act to conduct studies in pediatric patients. Therefore, a combination product comprised of these types of medications may limit pill burden, and improve compliance and convenience in the pediatric population as well as adults.

Furthermore, under PREA, you must demonstrate that reasonable attempts to produce a pediatric formulation have failed for the relevant pediatric subpopulations. If you are unable to develop a pediatric formulation for all of some of the relevant pediatric subpopulations, a full or partial waiver can be requested for this reason. You would need to provide data to support this claim for review by the Division, and if the waiver is granted, the submitted report would be publicly posted. Information on formulation development may be found in section V.C. of the “*Guidance for Industry: How to Comply with the Pediatric Research Equity Act*” (link above).

Sponsor Reply 4/15/13: Thank you for your very detailed response. The Sponsor plans to submit the NDA by August 2013 therefore we will submit a Pediatric Plan (not a PSP) in the NDA and we will not submit the pediatric plan to the IND. Please clarify the schedule for discussing and reaching an agreement with FDA on a Pediatric Plan during NDA review, and if a Pediatric Plan must be agreed upon before the NDA PDUFA decision date.

Meeting Discussion:

FDA stated that the pediatric plan will be evaluated during the NDA review period. An agreeable pediatric plan must be provided prior to the NDA PDUFA date. FDA comments on the pediatric plan will be communicated to the sponsor during the NDA review period.

Question #8: Draft Labeling: Draft labeling for AKYNZEO® is provided in Section #15.0. This draft labeling is representative of the proposed format and content of the information relevant to the FDC itself and/or to each single component. Does the Agency agree with the proposed approach? Please comment as needed.

FDA Response:

The format and content of your proposed draft labeling is not acceptable. Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- **Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.**
- **The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.**
- **The preferred presentation for (b) (4) in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see Warnings and Precautions (5.2)]".**

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

In addition, Section 9.0 Drug Abuse and Dependence of the drug label should include information from all abuse-related studies that were conducted.

Sponsor Reply 4/15/13: Thank you for your response. We will implement your recommendation in the PI. No further discussion is required.

Question #9: Proposed content and format of the planned NDA and approach to eCTD: The proposed draft Table of Contents (ToC) of the NDA is located in Appendix #17. The approach to the eCTD strategy is described in Section #8.4 (datasets) and Section #16. The initial NDA submission is planned to comprise all NDA components, i.e., per PDUFA V, no follow-up submissions are planned in the 30-day period after the initial NDA submission during FDA's review of the NDA unless FDA so requests. Sponsor believes that the proposed content and format of the planned NDA-eCTD is suitable for purposes of planning submission of the AKYNZEO® NDA. Does the Agency agree? Please comment as needed.

FDA Response:

No, we do not agree. Your NDA should include an Abuse Potential Assessment section. This section should be a compilation of all preclinical abuse-related studies that have been conducted (receptor binding with both drugs and active metabolites, self-administration study, drug discrimination study, physical dependence study), as well as a human abuse potential study (if conducted) and abuse-related adverse events observed in clinical studies. Each abuse-related adverse event observed in clinical studies should be presented in tabular form, with information about the study number, the onset, duration and severity of the event, and whether the event was drug-related. All events should be linked to their case report forms.

Sponsor Reply 4/15/13: Thank you for your response. The Sponsor confirms that summaries of drug abuse liability studies cited in Sponsor's response to Question 4, as well as any abuse-related adverse events observed in clinical studies, will be discussed in the Abuse Potential Assessment Section of the NDA. We confirm that each abuse-related adverse event observed in clinical studies will be presented in tabular form, with information about the study number, the onset, duration and severity of the event, and whether the event was drug-related and that all events will be linked to their case report forms.

The Abuse Potential Assessment section should provide a justification if a human abuse potential study was not conducted, based on abuse-related signals from preclinical and clinical studies. The draft "Guidance for Industry: Assessment of Abuse Potential of Drugs" (January 2010) should be referred to for information on where in the NDA the information on abuse should be located.

Sponsor Reply 4/15/13: No human abuse potential study was conducted. A justification will be provided in the Abuse Potential Assessment section of the NDA, as FDA requested.

After reviewing the guidance, the Sponsor still requests some clarification on which eCTD section this Abuse Potential Assessment Section should be located.

Meeting Discussion:

FDA provided Helsinn with a summary document indicating where abuse potential information should be located in the NDA (see Attachment #2).

In addition, we remind you to include a completed form FDA 3674 with your NDA submission. Also, your PREA (b) (4)/deferral requests, justification for the request(s), and your pediatric study plan should be included in Module 1 of the NDA.

Sponsor Reply 4/15/13: Thank you for your comment. Sponsor confirms a completed form FDA 3674 will be included. No further discussion is required.

Question #10: Administrative items associated with the planned NDA: Specific administrative matters involving the planned NDA are described in Section #13. These administrative matters include the planned NDA user fee, Sponsor's planned request for FDA confirmation of the acceptability of the proposed proprietary name (AKYNZEO®) and Sponsor's plan to include financial certification in the NDA for all applicable investigators in Phase 2/3 clinical studies NETU-07-07, NETU-08-18, NETU-10-29 and PALO-10-01. Does the Agency agree with the proposed approach? Please comment as needed.

FDA Response:

If your NDA is submitted in prior to October 1, 2013, your required user fee payment will be (b) (4)

Regarding your request for proprietary name review, we refer you the FDA "Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names" (February 2010). Your request for a proposed proprietary name review should be submitted as a separate submission to your NDA.

Sponsor Reply 4/15/13: Thank you for your comment. Recognizing that the original NDA Module 1 has a subsection for requesting proprietary names review, please clarify if the Sponsor's request for proposed proprietary name review should be submitted as general correspondence to the NDA shortly after NDA submission. Please clarify which submission method you prefer.

Meeting Discussion:

FDA stated that Helsinn may include their request for proprietary name review with the initial NDA submission in Module 1. The NDA should clearly indicate that the request for proprietary name review is included.

Your proposal to submit financial certification for investigators from the above listed studies is acceptable. We remind you that financial disclosure forms 3454 and/or 3455 must be signed by the applicant, not the designated US agent.

Sponsor Reply 4/15/13: Thank you for your comment. No further discussion is required.

3.0 ADDITIONAL FDA COMMENTS

3.1 The following biopharmaceutics information must be included at the time of the NDA submission:

- a. **Dissolution Test**: The dissolution method report supporting the selection of the proposed dissolution test(s) should be provided in the NDA. Note that the selected dissolution method must be suitable for both the active ingredients otherwise two methods must be developed. The dissolution report should include the following information:
 - i. Solubility data for both the drug substances covering the pH range of 1 ^{(b) (4)}  ;
 - ii. Detailed description of the dissolution test(s) being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method(s) as the optimal test for the proposed product (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a ^{(b) (4)}  was used, the data supporting the selection of the type and amount of ^{(b) (4)}  should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (i.e., 15, 20, 30, 45, & 60 minutes) and cover at least ^{(b) (4)}  of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;
 - iii. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and
 - iv. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test(s) as well as the supportive validation data for the dissolution method(s) (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
- b. **Dissolution Acceptance Criteria**: For the setting of the dissolution acceptance criteria of your proposed drug product, the following points should be considered:
 - i. The dissolution profile data (i.e., 15, 20, 30, 45, & 60 minutes) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your proposed drug

product [i.e., specification-sampling time point and specification value].

- ii. The *in vitro* dissolution profile should encompass the timeframe over which at least (b) (4) of the drugs are dissolved or where the plateau of drugs dissolved is reached, if incomplete dissolution is occurring.
- iii. The selection of the specification time point should be where $Q =$ (b) (4) dissolution occurs. However, if you have a slowly dissolving product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q =$ (b) (4) dissolution occurs.
- iv. The dissolution acceptance criteria should be based on average *in vitro* dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criteria for your proposed product will be made during NDA review process based on the provided data.

3.2 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Helsinn will submit contents of their NDA submission as outlined in the meeting background package and as per discussion at the pre-NDA meeting. Specifically, FDA and Helsinn agreed that the initial NDA submission will include the *in vitro* transporter study of the M2 metabolite, (b) (4) testing or justification as to why testing is not needed for the finished product, and the dissolution method information as discussed at the pre-NDA meeting. No unsolicited information will be submitted subsequent to the initial NDA submission.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

- A preliminary discussion on the need for a REMS was held and it was concluded that FDA does not anticipate the need for a REMS at this time.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

3.3 MANUFACTURING FACILITIES

To facilitate our inspectional process, at the time of your NDA submission we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application.

Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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

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

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

Corresponding names and titles of onsite contact:

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

Meeting Discussion

Helsinn agreed to provide the manufacturing facilities information as requested.

4.0 ATTACHMENTS AND HANDOUTS

Attachment #1 – Clinical Pharmacology Summary Aid

Attachment #2 – Location of Abuse Potential Information in NDA

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics

(Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent

terminal t_{1/2} and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in.

Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant

metabolites after single doses and multiple doses at steady-state [C_{max} , t_{max} , AUC, $C_{max,ss}$, $C_{min,ss}$, $C_{max,ss}/C_{min,ss}$, $t_{max,ss}$, $AUC_{0-\tau}$, CL/F, V/F and $t_{1/2}$ (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max} , C_{min} , CL/F and $t_{1/2}$ of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, t_{max} , $t_{max,ss}$, C_{max} , $C_{max,ss}$ and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as

parent drug and metabolites?

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose

proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether C_{max} and C_{min} of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of

distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on Cl_{cr} for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine

impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.7 Extrinsic Factors

2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to K_m , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ($[I]$). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the $[I]/K_i$ ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of

interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

- 2.7.8 Does the label specify co-administration of another drug?**
- 2.7.9 What other co-medications are likely to be administered to the target population?**
- 2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

- 2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**
- 2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?**
 - 2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**
 - 2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?**
- 2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.
- 2.8.4 Was the bioequivalence of the different strengths of the to be**

marketed formulation tested? If so were the strengths bioequivalent or not?

- 2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

MR product (if an IR is already marketed)

- 2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?**

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C_{max}, AUC and C_{min} of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

- 2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?**

- 2.8.8 What is evidence that MR formulation displays less variability in C_{max}, AUC and C_{min} than IR formulation?**

- 2.8.9 Does the MR product show dose dumping *in vivo*?**

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

- 2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?**

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

- 2.8.11 Are the MR and IR products marketed simultaneously?**

If the intention is to market both the MR and IR products, indicate how patients

are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries

2.4 Nonclinical Overview

This section should include a brief statement outlining the non-clinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the non-clinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

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

/s/

JAGJIT S GREWAL
05/09/2013



IND 073493

MEETING MINUTES

Helsinn Healthcare SA
C/O August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for netupitant and palonosetron HCl fixed-dose combination capsule.

We also refer to the meeting between representatives of your firm and the FDA on July 15, 2010. The purpose of the meeting was to discuss the FDA responses, dated May 14, 2010 and June 18, 2010, to your request for special protocol assessment of revised MEC clinical protocol NETU-08-18 and HEC clinical protocol PALO-10-01.

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

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Special Protocol Assessment (SPA) Meeting

Meeting Date and Time: July 15, 2010; 1:00PM – 2:00PM EST
Meeting Location: FDA – White Oak Campus
10903 New Hampshire Avenue, Building #22
Silver Spring, MD 20993

Application Number: IND 073493
Product Name: netupitant and palonosetron HCl fixed-dose combination capsule
Indication:
1) Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (CINV-HEC)
2) Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC)

Sponsor/Applicant Name: Helsinn Healthcare SA

Meeting Chair: Nancy Snow, D.O., M.P.A.
Meeting Recorder: Jagjit Grewal, M.P.H.

FDA ATTENDEES

Division of Gastroenterology Products

Donna Griebel, M.D.	Director
Nancy Snow, D.O., M.P.A.	Acting Medical Team Leader
John Troiani, M.D., Ph.D.	Medical Reviewer
Jagjit Grewal, M.P.H.	Regulatory Project Manager

Division of Biometrics III

Milton Fan, Ph.D.	Acting Team Leader
Freda Cooner, Ph.D.	Reviewer

SPONSOR ATTENDEES

Helsinn Healthcare SA

Dr. Angioletta Navini	Manager, Regulatory Affairs
Dr. Fabio Trento	Senior Manager, Project and Operation Controller
Dr. Giada Rizzi	Manager, Statistics and Data Management
Dr. Giorgia Rossi	Manager, Corporate Clinical Development
Dr. Maria Elisa Borroni	Manager, Corporate Clinical Development
Dr. Marco Palmas	Head of Corporate Clinical Development
Dr. Sergio Cantoreggi	Chief Scientific Officer
Dr. Dario Ceriani	Director, Regulatory Affairs
Dr. Steven Grunberg	Clinical Oncology Consultant

Dr. Craig Lehmann

Authorized Representative/Consultant

1.0 BACKGROUND

Reference is made to the Helsinn's request for special protocol assessment of revised clinical protocol NETU-08-18 (CINV-MEC) dated March 30, 2010, and FDA's "No Agreement" response dated May 14, 2010. Further reference is made to Helsinn's request for special protocol assessment of clinical protocol PALO-10-01 (CINV-HEC) dated May 4, 2010, and FDA's "No Agreement" response dated June 18, 2010. The sponsor's SPA submissions proposed the following phase 3 clinical trials:

1. NETU-08-18 (CINV-MEC): Superiority trial comparing oral palonosetron HCl + netupitant (0.5mg/300mg) combination capsule versus FDA-approved Aloxi (palonosetron HCl) capsule 0.5 mg in patients receiving moderately emetogenic cancer chemotherapy. Complete Response in the delayed phase (25-120 hours) during cycle 1 is proposed as the primary endpoint. Patients have the option to participate in at least 4 chemotherapy cycles.
2. PALO-10-01 (CINV-HEC): Non-inferiority trial comparing Aloxi (palonosetron HCl) capsules 0.5 mg to Aloxi (palonosetron HCl) I.V. 0.25 mg, given in combination with dexamethasone, in patients receiving highly emetogenic cancer chemotherapy during cycle 1 only. Complete Response in the acute phase (0-24 hours) is proposed as the primary endpoint. This trial is incorporated to establish the contribution of the oral palonosetron component in the combination product for CINV-HEC.

As previously discussed at the January 22, 2010 SPA meeting, Helsinn intends to utilize the completed phase 2 study NETU-07-07 to demonstrate the contribution of the netupitant component to the treatment effect of the combination product. NETU-07-07 is a superiority study comparing three single oral doses of netupitant (100 mg, 200 mg, 300 mg) each combined with 0.5 mg oral palonosetron HCl versus 0.5 mg oral palonosetron HCl in patients receiving highly emetogenic cancer chemotherapy. The FDA-approved oral EMEND (aprepitant) regimen was also included an active comparator for exploratory purposes.

Helsinn submitted Type A meeting requests dated May 20, 2010 to discuss the FDA responses to the sponsor's requests for special protocol assessment of revised clinical protocol NETU-08-18. FDA granted Helsinn's meeting requests in the letter dated June 3, 2010. In subsequent conversation with the sponsor, FDA agreed to also discuss the SPA "No Agreement" response for clinical protocol PALO-10-01 at the same scheduled meeting.

Helsinn's meeting background package dated June 30, 2010 proposed revisions to their development program to include the following:

1. NETU-08-18 (CINV-MEC): Patients have the option to participate in a multiple-cycle extension if they fulfill the enrollment criteria. Treatment randomization and double-blind for the initial cycle will continue through the repeated cycles. A pre-defined

number of cycles is not planned and patients may stay on the trial consistent with their scheduled sequence of repeat cycle chemotherapy.

2. PALO-10-01 (CINV-HEC): Patients have the option to enroll in an open-label safety extension. All patients in the open-label extension will receive a single oral dose of the proposed fixed-dose combination. A pre-defined number of cycles is not planned. Efficacy data will be collected but will only be descriptively summarized.

FDA preliminary comments were sent to the sponsor on July 13, 2010. On July 15, 2010, Helsinn provided their replies to the FDA preliminary responses and a slide handout proposing further program revisions to facilitate discussion at the meeting. Helsinn's revised development program can be found on slide #8 of the attached slide set and includes a new double-blind, randomized, controlled safety study (NETU-10-XX) in addition to providing safety data from a phase 2 study in overactive bladder patients (NETU-08-03).

2.0 DISCUSSION

The format of these minutes provides for Helsinn's original SPA questions in regular typeface, followed by the Agency's "No Agreement" responses in **bolded** print. Helsinn's follow-up questions/comments to the FDA responses, as listed in their June 30, 2010 meeting background package, are indented and in *italic* print. FDA's responses dated July 13, 2010 are indented and shown in **bolded** print. Helsinn's July 15, 2010 replies to FDA's preliminary responses are further indented and presented in *italic* print. The July 15, 2010 meeting discussion is presented in *italic and bolded* print.

2.1 SPECIFIC QUESTIONS FOR PROTOCOL NETU-08-18 (MEC)

Original NETU-08-18 Specific Question #1: Study Design, Objectives and Endpoints.

Protocol NETU-08-18 is proposed to be a multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified, parallel design involving 2 arms: the netupitant 300 mg plus palonosetron 0.5 mg fixed combination capsule (hereafter designated as the Combination) versus oral Aloxi (palonosetron HCl) 0.50 mg. After completion of Cycle-1, patients will have the option to participate in a Multiple-Cycle Extension within NETU-08-18 if they fulfill enrolment criteria.

The primary objective of NETU-08-18 as stated in section 2 of the protocol (located in section 3.0 of this submission) and section 4.1 of the Statistical Analysis Plan (SAP; located in section 4.0 of this submission) is to compare the efficacy of the Combination given with oral dexamethasone versus oral Aloxi (palonosetron HCl) 0.5 mg given with oral dexamethasone in terms of complete response in the delayed phase (25-120 hours) in Cycle-1. Section 12.1 of the SAP states that the primary efficacy objective is to demonstrate the superiority of the Combination to oral Aloxi 0.5 mg in terms of CR in the 25-120 hour interval (the delayed phase).

The primary efficacy endpoint as stated in section 6.1.1 of the protocol is the proportion of patients with complete response (CR, defined as no emesis and no rescue medication) in the delayed phase (25-120 hours after MEC administration) in Cycle 1. This primary endpoint and

design, as per FDA/OMP feedback, will be able to isolate the netupitant effect within the combination, since the NK₁ receptor antagonist is expected to be effective in the delayed phase of emesis, while the 5-HT₃ receptor antagonist oral palonosetron has been proven to be effective in the acute phase (Aloxi® softgel capsules 0.5 mg are approved for “*Moderately emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses*”).

Key secondary efficacy endpoints are CR in the acute (0-24 hours) and overall (0-120 hours) phases in Cycle-1 as described in section 6.1.2 of the protocol and in section 12.2 of the SAP. As described in Section 1.3 of this submission, the proposed target indication for the fixed dose combination is “prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. The palonosetron component is effective in the acute phase and the netupitant component is effective in the delayed phase of nausea and vomiting”

(b) (4)

(b) (4)

- Please confirm the acceptability of the proposed NETU-08-18 design, objectives and endpoints as described in the above cited sections of the protocol and SAP for purposes of demonstrating efficacy in support of the MEC target indication (Section 1.3). Please comment as needed.

Reference is made to FDA’s minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see questions #1B #1C and #2 (CINV MEC) and relevant FDA’s answers and meeting discussion. Reference is also made to FDA’s letter dated March 8, 2010 (at Appendix #4), containing FDA Office of Medical Policy (OMP) feedback, see item #2 (MEC).

FDA Response to Original NETU-08-18 Question #1: We cannot provide agreement for such a general question. Per the FDA Guidance for Industry – Special Protocol Assessment, you should include “focused questions concerning specific issues regarding the protocol, protocol design (including proposed size), study conduct, study goals, and/or data analysis for the proposed investigation.” Please see the responses to the specific questions below.

Sponsors NETU-08-18 Follow-up Questions regarding Original Sponsor’s Question #1: Consistent with the above FDA feedback, the Sponsor’s Original Question #1 is now divided into Follow-up Specific Questions #1A, #1B, #1C, #1D, #1E provided below.

- Please confirm that Sponsor’s Follow-up Specific Questions #1A, #1B, #1C, #1D and #1E below are sufficiently focused for FDA to provide a reply in the planned follow-up SPA request submission for protocol NETU-08-18, and if appropriate for you at this time, please provide replies to help us address any outstanding matters in the next SPA request.

Follow-up NETU-08-18 Specific Question #1A: Study Design. Protocol NETU-08-18 is proposed to be a multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified, parallel design involving 2 arms: the netupitant 300 mg plus palonosetron 0.5 mg fixed combination capsule (hereafter designated as the Combination) versus oral Aloxi (palonosetron HCl) 0.50 mg. NETU-08-18 is planned to be the sole MEC

efficacy trial in the Combination NDA program (in conjunction with the HEC efficacy trials described in sections 1.7.1 and 1.7.2.

- *Please confirm the acceptability of the proposed NETU-08-18 design as described in section 3.1 of the protocol and section 5.1 of the SAP for purposes of demonstrating efficacy in support of the MEC target indication (Section 1.3). Please comment as needed.*

FDA Response:

This question about trial design, as written, is too broad to address in a single response. The reason is that the term ‘design’ can also refer to aspects of the trial other than the general features of randomization, blinding, stratification, and group identification. Other implications of the term ‘design’ can include specific plans for data collection, blinding, data monitoring, study procedures, visits, and other trial characteristics.

Sponsor’s 7/15/10 Reply for Discussion: *Thank you for your feedback, this issue will be addressed in the next SPA. No discussion needed.*

Follow-up NETU-08-18 Specific Question #1B: Study Objectives. *The primary objective of NETU-08-18 as stated in section 2 of the protocol (located in section 3.0 of this submission) and section 4.1 of the Statistical Analysis Plan (SAP; located in section 4.0 of this submission) is to compare the efficacy of the Combination given with oral dexamethasone versus oral Aloxi (palonosetron HCl) 0.5 mg given with oral dexamethasone in terms of complete response in the delayed phase (25-120 hours) in Cycle-1. Section 12.1 of the SAP states that the primary efficacy objective is to demonstrate the superiority of the Combination to oral Aloxi 0.5 mg in terms of CR in the 25-120 hour interval (the delayed phase).*

- *Please confirm the acceptability of the proposed NETU-08-18 study objectives as described in the above cited sections of the protocol and SAP for purposes of demonstrating efficacy in support of the MEC target indication (Section 1.3). Please comment as needed.*

FDA Response:

The primary objective is acceptable.

Sponsor’s 7/15/10 Reply for Discussion: *Thank you for your feedback. No discussion needed.*

Follow-up NETU-08-18 Specific Question #1C: Primary Efficacy Endpoint. *The primary efficacy endpoint as stated in section 6.1.1 of the protocol is the proportion of patients with complete response (CR, defined as no emesis and no rescue medication) in the delayed phase (25-120 hours after MEC administration) in Cycle 1. This primary endpoint, as per FDA/OMP feedback, will be able to isolate the netupitant effect within the*

combination, since the NK1 receptor antagonist is expected to be effective in the delayed phase of emesis, while the 5HT3 receptor antagonist oral palonosetron has been proven to be effective in the acute phase (Aloxi® softgel capsules 0.5 mg are approved for “Moderately emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses”).

- Please confirm the acceptability of the proposed NETU-08-18 primary efficacy endpoint as described in the above cited sections of the protocol and SAP for purposes of demonstrating efficacy in support of the MEC target indication (Section 1.3). Please comment as needed.

FDA Response:

The primary efficacy endpoint (Complete Response, delayed phase) is acceptable.

Sponsor’s 7/15/10 Reply for Discussion: Thank you for your feedback. No discussion needed.

Follow-up NETU-08-18 Specific Question #1D: Key Secondary Efficacy Endpoints.

Key secondary efficacy endpoints are CR in the acute (0-24 hours) and overall (0-120 hours) phases in Cycle-1 as described in section 6.1.2 of the protocol and in section 12.2 of the SAP.

- Please confirm the acceptability of the proposed NETU-08-18 key secondary efficacy endpoints as described in the above cited sections of the protocol and SAP for purposes of demonstrating efficacy in support of the MEC target indication (Section 1.3). Please comment as needed.

FDA Response:

The key secondary efficacy endpoints are acceptable.

Sponsor’s 7/15/10 Reply for Discussion: Thank you for your feedback. No discussion needed.

Follow-up NETU-08-18 Specific Question #1E: Multiple-Cycle Extension. After completion of Cycle-1, patients will have the option to participate in a Multiple-Cycle Extension within NETU-08-18 if they fulfill enrolment criteria cited on pages 13 and 15 of the protocol. Regarding repeat cycle safety data beyond 4 cycles, please see Sponsor’s Follow-up Specific Question #12 below in section 2.3 for protocol PALO-10-01.

Considered in conjunction with the newly proposed approach to obtain repeat cycle safety data beyond 4 cycles as discussed in Sponsor’s Follow-up Specific Question #4 below, in section 1.7.2 above for PALO-10-01, and section 2.3 below (Specific Question #12 for PALO-10-01), please confirm the acceptability of the proposed NETU-08-18 multi-cycle extension as described in section 3.2 of the protocol for purposes of supporting inclusion

of “repeat courses” wording in the MEC target indication (Section 1.3). Please comment as needed.

FDA Response:

Please confirm whether the randomized treatment assignments and maintenance of the blind will continue beyond Cycle 1 in the NETU-08-18 (MEC) multi-cycle extension. Inclusion of a control arm for identification of a potential safety signal from netupitant is particularly important in this population, where adverse events are common even in the absence of study drug. In addition, it is important that eligibility criteria permit patients who are switched to an alternative chemotherapy regimen (MEC or HEC) to continue enrollment in multi-cycle extension study of your protocols to examine the safety of the fixed combination that includes netupitant, a new molecular entity. We remind you that the wording of indications in the label is a review issue. See our responses to the HEC questions below.

***Sponsor’s 7/15/10 Reply for Discussion:** The Sponsor confirms the initial randomization and blind will be continued throughout all cycles in NETU-08-18. To address FDA’s concerns as described in FDA comments that repeated cycle safety data be obtained from an expanded cancer patient MEC and HEC population, the Sponsor proposes the following revised repeat cycle clinical safety study program:*

- NETU-08-18 (MEC); allows unlimited repeat cycles. Though the number of repeat cycles is not limited in this trial, the Sponsor expects most safety data will be obtained in the first 4 cycles.*
- PALO-10-01 – revised to be a single cycle HEC efficacy trial as originally discussed with FDA.*
- Newly proposed repeat cycle HEC and non AC/EC MEC study NETU-10-XX allowing unlimited consecutive repeat cycles. The Sponsor expects most safety data will be obtained in the first 6 cycles.*
- Newly added supportive study NETU-08-03 providing safety data from daily doses through 8 weeks in overactive bladder patients (a non-IND study). Please advise us of the adequacy of the above proposed plan to address the safety requirement regarding repeat cycles. Please comment as needed.*

Meeting Discussion:

Helsinn referred to their slide handout proposing a revised development program to address multiple cycle extensions in HEC and MEC. Helsinn confirmed that NETU-08-18 will be blinded throughout the safety extension period and noted that the trial will not change with their revised program. Helsinn acknowledged FDA’s concern that NETU-08-18 will mostly enroll patients that will receive up to 4 cycles of chemotherapy.

Helsinn further explained that PALO-10-01 will only be conducted for 1 chemotherapy cycle. As part of their development program, Helsinn proposed a new double-blind safety study, NETU-10-XX, in which patients will be eligible to

participate in an unlimited number of chemotherapy cycles. Most safety data for NETU-10-XX will be collected through 6 cycles. Additionally, Helsinn will include safety data from completed study NETU-08-03 which evaluated netupitant in overactive bladder patients. NETU-08-03 provides information on exposure to netupitant levels that are greater than in the proposed CINV trials.

Helsinn noted that in their previous proposals for NETU-08-18 and PALO-10-01, patients could remain in the safety extension cycles as long as they continued to receive the same type of chemotherapy. In the new proposed safety study NETU-10-XX, patients will be allowed to switch chemotherapy regimens as long as they receive HEC or MEC. The patient population will include non-AC/EC chemotherapies which would encompass colorectal cancer patients. The utilization of a 3% AE incidence is per ICH guidelines which recommend an incidence between 0.5% and 5%.

FDA stated that the strength of study NETU-08-03 is that data is available from patients that received a large cumulative dose. Helsinn believes that FDA is concerned with accumulation over multiple cycles. In study NETU-08-03 approximately 60% of patients were female. The median age of patients is unknown at this time as study results are still being evaluated. FDA requested Helsinn to provide details on this trial.

FDA supported inclusion of a randomized controlled safety study. FDA questioned why a large number of patients were expected to drop out by cycle 6. Helsinn noted that they provided conservative estimates. FDA would prefer to see more than 100 patients at cycle 6. FDA commented that Helsinn's development program appears acceptable, but recommended that the program, study centers, and regimens be optimized to retain as many patients as possible by cycle 6.

Helsinn asked if an aprepitant comparator in trial NETU-10-XX was acceptable. FDA could not recommend an alternative comparator at the time.

FDA agreed that it was acceptable for Helsinn to include a few questions and outline for trial NETU-10-XX with their SPA resubmission.

Original NETU-08-18 Specific Question #2: Multiplicity of Primary and Key Secondary Efficacy Endpoints. Protocol NETU-08-18 sections 7.3.1.2 and 7.3.3.2 and Statistical Analysis Plan (SAP) sections 9.5 and 12.2 describe the proposed approach to address multiplicity for the primary (CR 25-120 hours, Cycle-1) and key secondary efficacy endpoints (CR 0-24 hours and CR 0-120 hours after chemotherapy administration at Cycle-1). In these protocol and SAP sections a hierarchical procedure is proposed as FDA recommended.

- Please advise us of the acceptability of the proposed approach for handling multiplicity as described in the above cited protocol and SAP sections. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see questions #1C, #2 and 3 (CINV MEC) and relevant FDA's answers and meeting discussion.

FDA Response to NETU-08-18 Original Question #2: The proposed approach for handling multiplicity of the primary (CR delayed) and key secondary efficacy endpoints (CR acute and CR overall) is acceptable.

Follow up NETU-08-18 Sponsor's Comment #2: Thank you for your response. No follow-up question is needed.

Original NETU-08-18 Specific Question #3: Multiplicity of Secondary Efficacy Endpoints.

In addition to key secondary efficacy endpoints, families of other secondary endpoints grouped by phase (delayed, acute, overall) will be analyzed as described in section 7.3.1.2 of the NETU-08-18 protocol and section 9.5 of the SAP. Each family will be tested only if the fixed combination demonstrates superiority vs. palonosetron on CR for that phase. The Sponsor considers that no further multiplicity adjustment is necessary within each family. Justifications are provided in section 7.3.1.2 of the protocol and in section 9.5 of SAP.

- Please advise us of the acceptability of the proposed approach as described in the above cited sections of the protocol and SAP for handling multiplicity for these secondary efficacy endpoints. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see questions #4 (CINV MEC).

FDA Response to Original NETU-08-18 Question #3: These non-key secondary endpoints are supportive only (b) (4)

Follow up NETU-08-18 Sponsor's Comment #3: Thank you for your response. No follow-up question is needed.

Original NETU-08-18 Specific Question #4: Multi-Cycle Extension. One of the study objectives is to evaluate the efficacy of the Combination in repeat cycles. As described in protocol section 3.2, after completion of Cycle 1, patients will have the option to participate in a double blind Multiple-Cycle Extension if they fulfill enrollment continuation criteria as described in sections 3.3.1 (see after item #9) and 3.3.2 (see after item #21) of the protocol. For each repeated cycle, the proportion of patients with CR and no nausea will be evaluated in the delayed, acute and overall period. As described in section 7.3.3.5 of the protocol and section 12.5 of the SAP, the results will be summarized in a frequency table by cycle, i.e. a descriptive analysis only will be presented. The Sponsor recognizes that recommendations on labeling details other than the target indication are determined during the review process.

- Please advise us if the approach described in the above cited sections of the protocol and SAP is acceptable to support the registration of the Combination in repeated cycles, i.e., to support the inclusion of the words "repeat courses" in the indication for CINV-MEC.

- Considering the number of patients and cycles proposed for this MEC trial NETU-08-18 as described in the protocol, please confirm if the approach described in the above cited sections of the NETU-08-18 protocol and SAP is acceptable to support the registration of the Combination for repeated cycles for the HEC indication, i.e., to support the inclusion of the words “repeat courses” in the labeling indication for CINV-HEC without conducting HEC trial (b) (4) (or any other further evaluation of efficacy in repeat cycles in HEC).

Reference is made to FDA’s minutes (at Appendix #3) of the SPA meeting held January 22, 2010 (please see question #5 (CINV MEC), and to FDA’s follow-up letter dated March 17, 2010, at Appendix #5.

FDA Response to Original NETU-08-18 Question #4: This study will likely enroll predominantly women who receive 4 or fewer cycles of chemotherapy. This population (exclusively female) and exposure will be inadequate to identify potential safety issues that may arise with repeat dosing. Additional safety data could be obtained in repeat dosing in HEC or MEC that extend beyond 4 cycles.

Follow up NETU-08-18 Sponsor’s Question #4: The Sponsor recognizes FDA’s concerns regarding adequacy of the safety database and proposes not to set any pre-specified number of cycles in the MEC trial NETU-08-18. Thus, patients may stay on study as long as they wish consistent with their scheduled sequence of repeat cycle chemotherapy. However, since the NETU-08-18 study will enroll predominantly women likely undergoing no more than 4 cycles of chemotherapy, it is proposed that safety in repeat cycles will be also evaluated in a continuation phase of HEC study PALO-10-01 (please see section 1.7.2 above, PALO-10-01 Specific Question #12 below, and Appendix #11 for a synopsis of the proposed revised PALO-10-01 protocol). In PALO-10-01, after an initial cycle involving HEC-only patients administered IV or oral palonosetron, HEC patients would at their option be enrolled in an open-label continuation phase of this trial where only the Combination (300/0.5 mg) would be administered as a single oral dose. This continuation phase is expected to provide open-label repeat cycle safety data for the Combination beyond 4 cycles in HEC patients. Please see PALO-10-01 repeated cycle Follow-up Sponsor’s Question #12 in section 2.3 below.

- *Please advise us if this approach is acceptable for purposes of supporting the inclusion of the words “repeat courses” in the target labeling indication for HEC and MEC stated in Section 1.3). Please comment as needed.*

FDA Response:

See our answer to Question #1E above. We encourage you to develop an extension study that could enroll patients either on HEC or MEC, and would allow within-patient changes in chemotherapy regimens. Patients could enter the study after completion of participation in other studies, but eligibility could be extended to patients who have not participated in the other trials. Ideally this extension trial should have some form of control arm for the reason discussed above in #1E.

Sponsor's 7/15/10 Reply for Discussion: Please see Sponsor's comments Question #1E above.

Original NETU-08-18 Specific Question #5: Inclusion and Exclusion Criteria. The patient inclusion and exclusion criteria are described in sections 3.3.1 and 3.3.2, respectively, of the NETU-08-18 protocol.

- Please advise us of the acceptability of the proposed patient inclusion and exclusion criteria as described in these protocol sections, and comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see question #6 (CINV MEC).

FDA Response to Original NETU-08-18 Question #5: The inclusion and exclusion criteria are acceptable. See the response to Question #4.

Follow up NETU-08-18 Sponsor's Comment #5: Thank you for your response. No follow-up question is needed.

Original NETU-08-18 Specific Question #6: Sample Size. The sample size and related assumptions are cited in section 7.1 of the NETU-08-18 protocol and section 7 of the SAP.

- Please confirm that the sample size is adequate as described in the above cited sections. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see question #7 (CINV MEC).

FDA Response to Original NETU-08-18 Question #6: The sample size and assumptions appear to be adequate. Please explain the low power proposed for the key secondary endpoints.

Follow-Up NETU-08-18 Sponsor's Comment #6. The sample size calculation is driven by the primary objective of the trial and is based on the primary efficacy endpoint, i.e., the percentage of patients with Complete Response in the delayed phase. The sample size is based on the assumption of a CR rate in the time interval 25-120 hours at Cycle 1 of 60% in the fixed combination arm and 51% in the palonosetron arm. For a two-sided test of difference using alpha equal to 0.050, a sample size of 661 evaluable patients per group (increased up to 730 patients) is needed to ensure 90% power to detect the above mentioned difference of 9%.

The power for the test on key secondary endpoints is described in the protocol for completeness (see section 7.1 of the protocol in Section 3.0 of this background package). Power is lower for only one of the two key secondary endpoints, i.e. the percentage of patients with CR in the acute phase: the study will have a power of about 60% (61%) to detect a difference of 6% in the CR rate in the acute phase (assuming 70% and 64% in the

combination and palonosetron groups respectively) while the power to detect a difference of 9% in terms of CR in the overall phase will be close to 90%.

Overall, the Sponsor considers the study sample size large enough to provide a reliable answer to its primary question (the power is 90%) and the risk associated with a lower power on CR in the acute phase is considered by the Sponsor to be acceptable.

FDA Response:

Your justification is acceptable at this time.

Sponsor's 7/15/10 Reply for Discussion: Thank you for your feedback. No discussion needed.

Original NETU-08-18 Specific Question #7: Populations of Analyses. The populations to be used for the analyses (Full Analysis Set, Per Protocol and Safety) both for Cycle 1 and Multiple-Cycle Extension are defined in section 7.2 of protocol NETU-08-18 and section 8 of the SAP.

- Please confirm that the definitions of the populations for analyses as described in these sections are adequate. Please comment as needed.

FDA Response to Original NETU-08-18 Question #7: The analysis populations are acceptable.

Follow-Up NETU-08-18 Sponsor's Comment #7: Thank you for your response. No follow-up question is needed.

FDA Response:

The analysis populations should also include the intent-to-treat population (all randomized patients).

Sponsor's 7/15/10 Reply for Discussion: Thank you for your feedback, we will also include the ITT population. No discussion needed.

Original NETU-08-18 Specific Question #8: Randomization and Stratification. As noted in section 4.9 of protocol NETU-08-18 and section 5.3 of the SAP, treatment assignment will be managed through a static central blocked randomization stratified by region and age class.

As described in protocol NETU-08-18 section 7.3.1.3 and section 9.6 of the SAP, countries with a reasonably consistent number of patients will be considered as regions themselves, countries with few patients will be grouped together based both on regional proximity and clinical practice. Applying this criterion, regions will be defined upfront on the basis of the projected enrollment rate before the study starts. Definition of "regions" will be reviewed and approved during the Data Blind Review Meeting.

Age classes are defined as less than or equal to 55 years and more than 55 years.

For the reasons outlined in protocol section 7.3.1.3 and section 9.4 of SAP, site will not be a stratification factor.

- Please advise us of the acceptability of the proposed stratification factors and criteria for region definition as described in the above cited protocol and SAP sections. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see question #8 (CINV-MEC) and relevant FDA's answers and meeting discussion.

FDA Response to Original NETU-08-18 Question #8: Please clarify your plan to stratify randomization by region. For this purpose, your definition for region needs to be prespecified and not be data dependent.

***Follow-Up NETU-08-18 Sponsor's Question #8.** Sponsor's plan to stratify by region is based on the consideration that some countries will likely enroll few patients.*

In a planned revision to protocol NETU-08-18 sections 4.9 and 7.3.1.3 and SAP sections 5.3 and 9.6, it will be clarified that the following "regions" based on geographical proximity are defined as follows: US, Latin America including Mexico, Europe, Commonwealth of Independent States (i.e. former Soviet Republics), and Asia.

Treatment assignment will be managed through a static central blocked randomization stratified by region and age class (age < 55 years and age ≥ 55 years). Two randomization lists will be prepared, one for each age class. For each region a different block of the relevant list is allocated, i.e. each time a new region starts to randomize patients or each time a block for the relevant region has been completed; the next unused block is attributed to that region.

The same factors used for stratification purpose, i.e. age class and region, will be used for the analysis (the following wording will be proposed in section 7.3.1.3 of the protocol and section 9.6 of the SAP that will be submitted in a new SPA request after the July 15, 2010, FDA meeting: "these factors will be used for randomization and for the analyses").

- Please advise us if the above-described approach is acceptable. Please comment as needed.

FDA Response:
Your approach is acceptable.

***Sponsor's 7/15/10 Reply for Discussion:** Thank you for your feedback. No discussion needed.*

Original NETU-08-18 Specific Question #9: Overall Plan for Statistical Analysis. The planned statistical analysis is described in section 7 of the NETU-08-18 protocol and further detailed in the SAP. As suggested by FDA, the Sponsor is proposing to use the stratified CMH

test instead of the logistic regression model and to impute all missing data as treatment failures for the primary analysis.

- Please comment on the overall acceptability of the proposed statistical analysis plan as described in these sections of the protocol and SAP, and add any other considerations regarding the SAP.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see question #10 (CINV-MEC).

FDA Response to Original NETU-08-18 Question #9: See the responses to the above questions. Use of the stratified CMH test and imputation of missing data as treatment failures are acceptable. Note that your region stratification variable has to be the same as defined for the randomization.

You are proposing to use a one-sided 5% significance level for your CMH test. You should use a two-sided 5% significance level.

If you pursue only a MEC indication (if your HEC development plan fails), this study may constitute the single pivotal trial and must therefore show substantial evidence of efficacy as described in the FDA *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). Consequently, this may further impact your sample size and planned significance levels.

***Follow-Up NETU-08-18 Sponsor's Question #9.** In FDA's feedback above, FDA stated that the Sponsor is proposing to perform a one-sided 5% significance level CMH test. This appears to be a misunderstanding. Please be aware that the Sponsor plans to perform a two-sided test at 5% significance level as stated in section 7.1 of the study protocol and section 7 of the SAP ("For a two-sided test of difference using alpha equal to 0.050, a sample size of 661 evaluable patients per group (increased up to 730 patients) is needed to ensure 90% power"). This is also stated in protocol section 7.3.3.1 and in SAP section 12.1 ("Odds Ratio (OR) and two-sided 95% CI for OR"). Clarification of other sentences in these same sections which may have been the source of the confusion will be accomplished in the planned revised protocol NETU-08-18 and SAP that will be submitted in a new SPA request after the July 15, 2010, FDA meeting.*

- *Please confirm that the proposed two-sided 5% significance level for the CMH test as described above is acceptable. Please comment as needed.*

FDA Response:

Thank you for the clarification. A two-sided 5% significance level for the CMH test is acceptable.

***Sponsor's 7/15/10 Reply for Discussion:** Thank you for your feedback. No discussion needed.*

Original NETU-08-18 Specific Question #10: Number of Cycles and Patients. As described in NETU-08-18 protocol section 2, one of the study objectives is to evaluate the safety and tolerability of the Combination in repeat cycles. As FDA agreed at the SPA meeting held January 22, 2010, it appears to be accepted by all oncologists that 4 cycles of cyclophosphamide/doxorubicin is a standard regimen for breast cancer (MEC) [Jones SE, et al. J Clin Oncol, 24; 34: 5381 -5387, 2006].

As described in section 3.2 of the NETU-08-18 protocol, after completion of Cycle 1, patients will have the option to participate in a Multiple-Cycle Extension if they fulfill enrollment criteria. All the patients enrolled will be given the possibility to undergo at least four cycles. The study will be closed after the last patient enrolled and still on treatment will have completed four cycles. In this situation most patients may undergo more than four cycles.

- Please advise us if the number of cycles and patients described in sections 3.2 and 7.1 of protocol NETU-08-18 are sufficient to support the planned NDA safety database and also for purposes of including “repeat courses” wording in the CINV- MEC target indication (please see section 1.3 of this submission). Please comment as needed.
- Recognizing that a repeat cycle HEC clinical safety and efficacy trial may not be performed in the NDA program if trial (b)(4) is not necessary as FDA suggested (please see FDA letter March 17, 2010, at Appendix #5), please advise us if the number of cycles and patients described in sections 3.2 and 7.1 of MEC protocol NETU-08-18 are also anticipated to be sufficient for purposes of the phase 3 clinical plan to support CINV-HEC target indication including the “repeat courses” wording in the indication (please see section 1.3 of this submission) without conducting trial (b)(4) (or any other further evaluation of safety and efficacy in repeat cycles in HEC). Please comment as needed.

Reference is made to FDA’s minutes (at Appendix #3) of the SPA meeting held January 22, 2010 (please see question #11 (CINV-MEC)), and to FDA’s March 17, 2010 letter at Appendix #5.

FDA Response to Original NETU-08-18 Question #10: See the response to Question #4.

***Follow-Up NETU-08-18 Sponsor’s Comment #10:** Please see Sponsor’s Follow up Question #4 above, section 1.7.2 above regarding the newly planned open-label repeat cycle extension to PALO-10-01, and Sponsor’s follow-up Question #12 in Section 2.3 below for protocol PALO-10-01.*

FDA Response:

Please see FDA responses to Question #4. Please confirm whether the randomized treatment assignments and maintenance of the blind will continue beyond Cycle 1 in the NETU-08-18 (MEC) multi-cycle extension. Loss of a control arm after Cycle 1 would raise concerns about the acceptability of such a plan.

***Sponsor’s 7/15/10 Reply for Discussion:** We confirm the randomized treatment assignments and maintenance of the blind will continue beyond Cycle 1 in the NETU-08-18 (MEC) multi-cycle extension. Please see reply to Question #1E.*

Original NETU-08-18 Specific Question #11: Safety Measures. NETU-08-18 protocol Sections 6.2 and 7.3.4 and SAP sections 4.2.5 and 13 describe safety measures and analyses planned for evaluation in the first and in repeat cycles in the trial. Section 8 in the protocol describes the role and function of the planned Data Safety Monitoring Board (DSMB) for the purposes of reviewing safety data in this trial. A copy of the DSMB charter is in Appendix #9 (of the original SPA request, Serial #019 dated 30Mar10, IND 73,493).

- Please advise us if the safety measures proposed as described in the above cited sections are suitable for the NETU-08-18 protocol and for purposes of the planned NDA safety database. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see questions #12(CINV-MEC).

FDA Response to Original NETU-08-18 Question #11: Although use of troponin ranges (e.g., "<0.12 ng/mL") for clinical management of patients in this trial is acceptable, troponin levels need to be reported by the lab and recorded in the trial data as ng/mL rather than as a range. Otherwise, the scheduled safety assessments and DSMB in NETU-08-18 appear acceptable.

***Follow-Up NETU-08-18 Sponsor's Question #11.** The Sponsor agrees that troponin levels should be reported by the lab and recorded as exact values. This matter will be addressed in a planned revision of the NETU-08-18 protocol and SAP that will be submitted with the next SPA request after the July 15, 2010, FDA meeting. Proposed revised wording to clarify this matter in the protocol is provided below:*

- *Section 6.2.6 of the Study Protocol: "To assure consistency a central laboratory will be used and details on specimens handling, storage, shipment, and processing will be described in a separate document. Cardiac troponin levels will be reported by the central laboratory and recorded as exact values (i.e. as ng/mL rather than as a range)"*
- *Section 13.5.2 of the Statistical Analysis Plan: "As far as cardiac safety is concerned, troponin levels will be evaluated. They will be summarized by treatment for Cycle 1 and Multiple-Cycle Extension by visit (and by cycle for Multiple-Cycle Extension) using descriptive statistics including median and quartiles. In addition, troponin levels above or equal to 0.12 ng/mL and above or equal to 0.50 ng/mL will be listed. Listings of all troponin levels will be provided."*
- *Please advise us if the above- proposed revised wording in the protocol and SAP for reporting troponin levels is acceptable. Please comment as needed.*

FDA Response:

This is acceptable wording for the protocol and SAP.

***Sponsor's 7/15/10 Reply for Discussion:** Thank you for your feedback. No discussion needed.*

Original NETU-08-18 Specific Question #12: Cardiac Safety. Protocol NETU-08-18 sections 6.2.3, 6.2.4, 6.2.5 and 6.2.6 and SAP sections 13.5.1, 13.5.2, 13.6 and 13.8 describe provisions to assess cardiac safety in the first cycle and throughout repeat cycles of chemotherapy and incorporate FDA's recommendations. In addition a Data Safety Monitoring Board (DSMB), including a cardiologist, will review safety data during the course of the trial with special focus on cardiac safety; please see the DSMB charter at Appendix #9 (of the original SPA request, Serial #019 dated 30Mar10, IND 73,493).

- Please advise us if the cardiac safety measures and evaluations as described in the above cited protocol and SAP sections, specifically 12-lead ECG recordings, laboratory tests (CK, CK-MB, myoglobin), LVEF and troponin measurements, are adequate to evaluate the cardiac safety of the netupitant and palonosetron fixed-dose combination, in particular given concomitantly with anthracycline-based chemotherapeutic regimens. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see Question #13 (CINV-MEC) and relevant FDA replies and meeting discussion.

FDA Response to Original NETU-08-18 Question #12: See the response to Question #11.

Follow-Up NETU-08-18 Sponsor's Comment #12: Thank you for your response. No follow-up question is needed.

Original NETU-08-18 Specific Question #13: DSMB Charter. Section 8 in the NETU-08-18 protocol describes the composition and function of the DSMB with regard to this trial; specific details are provided in the DSMB Charter at Appendix #9 (of the original SPA request, Serial #019 dated 30Mar10, IND 73,493).

- Please advise us of the adequacy of the overall DSMB composition and planned function as described in section 8 of the protocol and in the DSMB charter in Appendix #9 (of the original SPA request, Serial #019 dated 30Mar10, IND 73,493). Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see Action Item #2 and relevant meeting discussion.

FDA Response to Original NETU-08-18 Question #13: The DSMB composition, function, and charter appear acceptable. See the response to Question #11.

Follow-Up NETU-08-18 Sponsor's Comment #13: Thank you for your response. No follow-up question is needed.

Original NETU-08-18 Specific Question #14: Population PK/PD Assessment. As addressed at the FDA SPA meeting held January 22, 2010 (please see Question #16 of FDA minutes, page 14, at Appendix #3), Population PK/PD Plan NETU-10-02, which includes up to 500 patients

from NETU-08-18, has been submitted to IND 73,493 (Serial #018 dated 29Mar10). Population PK Plan NETU-10-02 is addressed in NETU-08-18 protocol sections 4.9 (allocation and number of patients to participate in the PK/PD assessment), 6.3 (PK blood sampling) and 7.3.5 (brief description of the PK/PD analysis). Since Population PK/PD Plan NETU-10-02 is brief (17 pages), for ease of review a full copy of the proposed PK/PD Plan submitted in Serial #018 is attached at Appendix #10 (of the original SPA request, Serial #019 dated 30Mar10, IND 73,493).

- Please advise us of the adequacy of the overall NETU-10-02 phase 3 population PK/PD plan (at Appendix #10 of this SPA submission [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493], and in Serial #018, Appendix #2). In particular, recognizing Cycle-1 of planned phase 3 protocol NETU-08-18 will contain the largest sample size of patients, please address the acceptability of the proposed Population PK/PD Plan to obtain PK blood samples only from Cycle-1 of NETU-08-18 and not subsequent cycles. Please comment as needed.

Reference is made to FDA's minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see Question #14 (on page 20), FDA's replies and meeting discussion.

FDA Response to Original NETU-08-18 Question #14: It is acceptable to limit the population PK assessment to Cycle 1. We recommend you also analyze blood samples for palonosetron as the drug product is a fixed-dose combination of netupitant and palonosetron. It would be important to know if the exposures to either component change when administered in combination to patients. The meeting package indicated that a drug interaction study between netupitant and palonosetron was conducted but did not specify if oral or IV palonosetron was used.

The proposed PK/PD evaluation for efficacy might have limited value because you are only using exposures for one component (i.e., netupitant) of the fixed-dose combination product at one dose level. Efficacy responses might be due to both netupitant (and metabolites) and palonosetron. You should consider combining data from the Phase 3 and the Phase 2 dose ranging studies (if PK samples were collected in Phase 2) for evaluating PK/PD or exposure/response relationships.

Follow-Up NETU-08-18 Sponsor's Question #14. In addition to the planned netupitant (and metabolites) plasma concentrations analyses, the Sponsor agrees to determine and describe palonosetron plasma concentrations in the population PK/PD assessment in patients in NETU-08-18. PK/PD plan NETU-10-02 will be revised accordingly and will be re-submitted to the IND and attached to the next SPA process after the July 15, 2010, FDA meeting.

A drug-drug interaction clinical study between netupitant and palonosetron was conducted (study NETU-06-27) using an oral form for both drugs; a synopsis of the NETU-06-27 study report is in Appendix #9.

Please note that PK samples were not collected in phase 2 HEC study NETU-07-07 which is the sole phase 2 clinical trial in this program.

- *Please advise us of the adequacy of the proposed approach for the population PK/PD phase 3 plan NETU-10-02. Please comment as needed.*

FDA Response:

The proposed PK/PD plan is acceptable.

***Sponsor's 7/15/10 Reply for Discussion:** Thank you for your feedback. No discussion needed.*

Original NETU-08-18 Specific Question #15: Overall Protocol. Please confirm that, overall, if the results of the trial substantiate the hypothesis of the protocol, phase 3 protocol NETU-08-18 is acceptable in design, sample size, outlined execution and analyses for purposes of supporting the planned future MEC labeling claim in Section 1.3 of this submission. Please comment as needed and add any other considerations regarding protocol NETU-08-18.

FDA Response to Original NETU-08-18 Question #15: See the responses to Questions #1-14.

***Follow-Up NETU-08-18 Sponsor's Question #15:** The Sponsor is planning to prepare a revised NETU-08-18 protocol incorporating all of FDA's recommendations. In order to provide the requested additional safety data in repeat cycles in a broader cancer population and beyond cycle 4 of chemotherapy, it is proposed that repeat cycle safety data on the Combination will be collected in a newly proposed open-label repeat cycle safety extension of revised HEC protocol PALO-10-01 as described in section 1.7.2 above, section 2.3 above and in Appendix #11. Please confirm that, overall, if the results of this trial substantiate the hypothesis of the protocol, phase 3 protocol NETU-08-18 as revised is acceptable in design, sample size, outlined execution and analyses for purposes of supporting the planned future MEC labeling claim in Section 1.3 of this submission.*

- *Please comment as needed and add any other considerations regarding protocol NETU-08-18.*

FDA Response:

See the previous responses. Additionally, for addressing the issue of missing data, you should propose several sensitivity analyses. Details for handling missing data and the sensitivity analyses should be pre-specified in the protocol.

Sensitivity analyses should include:

- **Observed case:** exclude subjects from the analysis at a specific time point if the patient has insufficient data at that time point.
- **Complete case:** exclude subjects from the analysis at all time points if they had insufficient data at any of the time points of analysis.
- **Worst case:** subjects with missing observations at any of the time points of analysis are assumed to be "failed."
- **Last observation carried forward (LOCF)**

- **Per Protocol**

Sponsor's 7/15/10 Reply for Discussion: Thank you for your feedback. We will implement your suggestions. No discussion needed.

2.2 SPECIFIC QUESTIONS FOR PROTOCOL PALO-10-01 (HEC)

Original PALO-10-01 Specific Question #1: Study Design, Objectives and Endpoints.

Protocol PALO-10-01 is proposed to be a multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified, parallel design study comparing palonosetron 0.5 mg oral formulation (Aloxi® softgel capsules) with palonosetron 0.25 mg IV formulation (Aloxi® IV), both given with dexamethasone, in patients receiving highly emetogenic chemotherapy (HEC). It will be a single-cycle trial [Post Note: please note that based on FDA SPA feedback that a newly proposed open label repeat cycle extension involving the Combination is planned to be added to PALO-10-01].

As described in sections 1.1 and 1.7.2, the intended role of study PALO-10-01 in the Combination (netupitant plus palonosetron 300/0.5 mg) NDA program is to demonstrate that oral palonosetron 0.5 mg is efficacious for the prevention of HEC-CINV and therefore contributes to the fixed dose combination, and that completed study NETU-07-07 (a dose-ranging, single-cycle safety and efficacy trial conducted in Russia and Ukraine), where oral palonosetron 0.5 mg alone was used as the active comparator, can serve as the sole adequate and well-controlled pivotal efficacy trial for purposes of supporting the HEC-CINV target indication cited in section 1.3.

The primary objective of PALO-10-01 as stated in section 2 of the protocol (located in section 5.0 of this submission) and section 4.1 of the Statistical Analysis Plan (SAP; located in section 6.0 of this submission) is to demonstrate the non-inferiority of a single oral dose of palonosetron 0.5 mg versus palonosetron I.V. 0.25 mg in terms of percentage of patients with complete response (CR; no emetic episodes and no rescue medication) during the acute phase (0-24 hours). As previously agreed with FDA 22Jan10 (please see the 22Jan10 FDA meeting background package follow-up Question #1C item #2, on page 16 in IND 73493 Serial #016 dated 7Jan10; FDA minutes, Question #1D on page 4 at Appendix #3, and the FDA Division/OMP letter dated 8Mar10 at Appendix #4), a superiority comparison on CR in 25-120 hour and overall 0-120 hour intervals between oral and IV palonosetron will not be performed, since the Sponsor is not aiming to claim in the target indication that the palonosetron component of the combination is efficacious for the 25-120 hour and 0-120 hour intervals.

Aloxi® softgel capsules 0.5 mg are FDA-approved for “*Moderately emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses*” but are not FDA approved for the prevention of acute nausea and vomiting induced by highly emetogenic chemotherapy (HEC). I.V. palonosetron 0.25 mg (Aloxi® I.V.) is approved for “*Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses*”.

As described in Section 1.3 of this submission, the proposed target HEC indication for the fixed dose combination is “*prevention of acute and delayed nausea and vomiting associated with*

initial and repeat courses of highly emetogenic cancer chemotherapy. The palonosetron component is effective in the acute phase and the netupitant component is effective in the acute, delayed and overall phases of nausea and vomiting” (a contribution for the netupitant component in the acute, delayed and overall phases will be claimed in the label since these endpoints are considered successful by the Sponsor in completed study NETU-07-07, provided that FDA will not raise major concerns regarding NETU-07-07 validity during FDA’s presently ongoing review of the NETU-07-07 study report).

- Please confirm the acceptability of the proposed PALO-10-01 study design, objectives, patient population, efficacy endpoints, analyses and planned execution, all as described in the PALO-10-01 protocol and SAP in sections 5.0 and 6.0, respectively, for purposes of demonstrating that the oral palonosetron 0.5 mg active comparator used in completed trial NETU-07-07 is efficacious for the prevention of HEC and therefore contributes to the fixed dose combination, and for purposes of rendering the oral Aloxi 0.5 mg active comparator used in NETU-07-07 to be effective for prevention of HEC-CINV thereby allowing single-cycle study NETU-07-07, performed exclusively in Russia and the Ukraine, to serve as the sole adequate and well-controlled HEC efficacy trial for purposes of NDA submission to obtain FDA approval of the Combination for the target CINV-HEC indication described in section 1.3. Please comment as needed.

Reference is made to FDA’s minutes (at Appendix #3) of the SPA meeting held January 22, 2010; please see question #1D (CINV HEC) and relevant FDA’s answers and meeting discussion. Reference is also made to FDA’s letter dated March 8, 2010 (at Appendix #4), containing FDA Office of Medical Policy (OMP) feedback.

FDA Response to Original PALO-10-01 Question #1: We cannot provide agreement for such a general question. Per the FDA *Guidance for Industry – Special Protocol Assessment*, you should include “focused questions concerning specific issues regarding the protocol, protocol design (including proposed size), study conduct, study goals, and/or data analysis for the proposed investigation.” Please see the responses to the specific questions below.

Follow-up PALO-10-01 Sponsor’s Questions #1: *Consistent with the above FDA feedback, the Sponsor’s Original Question #1 is now divided into Follow-up Specific Questions #1A and #1B provided below.*

Please confirm that Sponsor’s Follow-up Specific Questions #1A and #1B below are sufficiently focused for FDA to provide a reply in the planned follow-up SPA request submission for protocol PALO-10-01, and if appropriate for you at this time, please provide replies to help us address any outstanding matters in the next SPA request.

Follow-up PALO-10-01 Sponsor’s Question #1A: Study Design. *Protocol PALO-10-01 is proposed to be a multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified noninferiority study design involving 2 arms: oral palonosetron (Aloxi) 0.5 mg versus I.V. palonosetron HCl (Aloxi) 0.25 mg. The combination will not be evaluated in the PALO-10-01 trial. The role of PALO-10-01 in the Combination Phase 3 program is as described in section 1.7.2 of this background package.*

- *Please confirm the acceptability of the proposed PALO-10-01 design as described in section 3.1 of the protocol (in Section 5.0 of this background package) and section 5.1 of the SAP (in Section 6.0 of this background package) for purposes of fulfilling the role of PALO-10-01 as described in section 1.7.2 of the background package. Please comment as needed.*

FDA Response:

See FDA response to MEC Question #1A.

Sponsor's 7/15/10 Reply for Discussion: *Thank you for your feedback. This issue will be addressed in the next SPA. No discussion needed.*

Follow-up PALO-10-01 Sponsor's Question #1B: Study Objective. *The primary objective of PALO-10-01 as stated in section 2 of the protocol (located in section 5.0 of this submission) and section 4.1 of the Statistical Analysis Plan (SAP; located in section 6.0 of this submission) is "To demonstrate the non-inferiority of a single oral dose of palonosetron 0.50 mg versus palonosetron I.V. in terms of percentage of patients with complete response during the acute phase (0-24 hours)."*

- *Please confirm the acceptability of the proposed PALO-10-01 study objective as described in the above cited sections of the protocol and SAP for purposes of fulfilling the role of the PALO-10-01 study as described in section 1.7.2 of this background package. Please comment as needed.*

FDA Response:

The primary study objective is acceptable.

Sponsor's 7/15/10 Reply for Discussion: *Thank you for your feedback. No discussion needed.*

Original PALO-10-01 Specific Question #2a: Primary Efficacy Endpoint. The primary efficacy endpoint is described in Section 6.1.1 of the PALO-10-01 protocol and in Statistical Analysis Plan –SAP- section 4.2.1. The primary endpoint is proposed to be the proportion of patients with Complete Response (CR) defined as no emesis, no rescue medication within 24 hours after the start of the HEC administration on Day 1.

- Please advise us of the acceptability of the proposed PALO-10-01 primary efficacy endpoint as described in Section 6.1.1 of the protocol, considering the proposed role of study PALO-10-01 in the Combination NDA clinical efficacy program as described in sections 1.1 and 1.7.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493]. Please comment as needed.

FDA Response to Original PALO-10-01 Question #2a: **This primary efficacy endpoint is acceptable.**

Follow-Up PALO-10-01 Sponsor's Comment #2a: *Thank you for your response. No follow-up question is needed.*

Original PALO-10-01 Specific Question #2b: Secondary Efficacy Endpoints. The secondary endpoints of protocol PALO-10-01 are described in Section 6.1.2 of the protocol (Statistical Analysis Plan –SAP- section 4.2.2) [both in the original SPA request, Serial #019 dated 30Mar10, IND 73,493].

- Please advise us of the acceptability of the secondary efficacy endpoints as described in Section 6.1.2 of the PALO-10-01 protocol, considering the proposed role of study PALO-10-01 in the Combination NDA clinical efficacy program as described in sections 1.1 and 1.7.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493]. Please comment as needed.

FDA Response to Original PALO-10-01 Question #2b: **The secondary efficacy endpoints are acceptable. These secondary endpoints are supportive only** (b) (4)

Follow-Up PALO-10-01 Sponsor's Comment #2b: *Thank you for your response. No follow-up question is needed.*

Original PALO-10-01 Specific Question #3: Non-inferiority Margin. The non-inferiority margin is proposed to be 15% as described in protocol PALO-10-01 section 7.3.1.1 and Statistical Analysis Plan (SAP) section 9.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493]. This proposed non-inferiority margin is based on regulatory precedents, statistical and clinical evaluation and takes into account ICH E10 and FDA guidances on non-inferiority clinical trials (Draft March 2010). The efficacy of palonosetron I.V. 0.25 mg, the active comparator for PALO-10-01, has been clearly established and quantified in HEC study PALO-99-05 which served as the pivotal efficacy trial to support FDA-approval of IV Aloxi 0.25 for HEC-CINV. The percentage of patients with CR in the acute phase was 59.2% (95% CI: 52.4% to 65.6%).

Since, for many years, the use of placebo in antiemetic efficacy trials has not been considered ethical in patients undergoing HEC, study PALO-99-05 did not include a placebo arm and for this same reason there are no CINV studies directly comparing palonosetron IV to placebo. Given the absence of any CINV clinical efficacy trials directly comparing palonosetron versus placebo, the Sponsor used a meta-analysis involving controlled trials of other 5-HT₃ antagonists (or other antiemetics) versus placebo- or active comparators (78 treatment arms and n=7274 patients) to predict the outcome of interest for placebo for HEC-CINV. This meta-analysis, PALO-01-23, was submitted to FDA (original NDA 21-372, volumes 368-371) to support approval of IV palonosetron 0.25 mg for both MEC and HEC. Based on this meta-analysis, the modeled historical placebo indicated a percentage of HEC patients with CR in the acute phase of 11.8% (95% CI: 8.7% to 15.8%). The difference between palonosetron IV 0.25 mg and modeled historical placebo in terms of CR in the acute phase is 47.4% (99% CI: 37.5% to 57.3%) as stated in section 7.3.1.1 of the protocol. Considering the lower bound of this 99% CI, the non-

inferiority margin for this study should not exceed 37.5%. Based on clinical judgment, it is considered that a substantial portion (at least 50%) of the treatment effect should be preserved, leading to a value of 18.5%. To be conservative, a small additional adjustment is applied to reflect uncertainties and the non-inferiority margin is reduced to 15%.

The proposed 15% non-inferiority margin for PALO-10-01 is consistent with that used in earlier palonosetron (PALO-99-03, PALO-99-04 and PALO-99-05) and dolasetron non-inferiority pivotal efficacy trials to support NDA approvals, and more recently in the sole pivotal efficacy trial supporting the Sancuso granisetron transdermal NDA approval. During the FDA SPA meeting held 22Jan10, FDA noted for the PALO-10-01 trial that “...a 15% delta has been used in the past and hence is likely to be accepted, but will need to be reviewed further during the Special Protocol Assessment (SPA) review”, that “...no additional information will need to be submitted at this point to support the proposed margin.” (please see FDA minutes of the 22Jan10 FDA meeting, Question #1A, page 5, at Appendix #3).

- Please confirm that the proposed non-inferiority margin of 15% for PALO-10-01 is acceptable to demonstrate the non inferiority of oral palonosetron 0.5 mg when compared to IV palonosetron 0.25 mg in the HEC setting, and considering the proposed role of PALO-10-01 in the Combination NDA clinical efficacy program as described in sections 1.1 and 1.7.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493]. Please comment as needed.

Reference is made to FDA minutes (at Appendix #3) of the FDA SPA meeting held 22Jan10; please see question #1D on page 7 of FDA’s minutes and item 3.0(1.) on page 21.

FDA Response to Original PALO-10-01 Question #3: Your proposed single study must provide substantial evidence that oral palonosetron is in fact non-inferior to I.V. palonosetron. We recommend your type I error be controlled at a 1% level (two-sided). A 15% non-inferiority margin is acceptable based on past usage; however, we would expect your results to demonstrate consistent and robust findings. The acceptability of your study results for establishing clear non-inferiority of oral palonosetron will ultimately be a review issue.

Follow-Up PALO-10-01 Sponsor’s Comment #3: The Sponsor agrees to control the Type I error at the 1% level (two-sided). This change will increase the sample size to 740, equally distributed in two treatment groups (i.e., 370 patients in each group). Please see Follow-Up Sponsor’s Question #5 below.

**FDA Response:
This is acceptable.**

Sponsor’s 7/15/10 Reply for Discussion: Thank you for your feedback. No discussion needed.

Original PALO-10-01 Specific Question #4: Analyses of Primary and Secondary Efficacy Endpoints. The statistical analyses planned for primary and secondary efficacy endpoints are described in section 7.3.3 of the protocol and section 12 of the SAP.

- Please confirm that the proposed analyses of efficacy endpoints as described in the above cited sections are acceptable for purpose of demonstrating the non-inferiority of oral palonosetron 0.5 mg vs. I.V. palonosetron 0.25 mg for prevention of HEC-CINV, and considering the proposed role of PALO-10-01 in the Combination NDA clinical efficacy program as described in sections 1.1 and 1.7.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493]. Please comment as needed.

Reference is made to FDA's 22Jan10 SPA meeting minutes at Appendix #3; please see question #1D (page 7 of the minutes) and relevant FDA's answers and meeting discussion.

FDA Response to Original PALO-10-01 Question #4: The use of confidence interval formulas based on stratum-adjusted CMH proportions may be acceptable for non-inferiority testing. However, confidence limits so derived should be consistent with those based on normal approximation and/or the use of exact methods. You should explore the sensitivity of your results to different calculation methods.

Follow-Up PALO-10-01 Sponsor's Question #4: The Sponsor's proposal is to keep the confidence interval formulas based on stratum-adjusted CMH proportions as the primary analysis for non-inferiority testing and to use the unadjusted Wilson-Newcombe method as secondary/sensitivity analysis.

- *Please clarify whether this approach is in line with your expectation and comment as needed.*

FDA Response:

In addition to Wilson-Newcombe, the sensitivity analyses should also include the exact method. The non-inferiority analysis of the primary efficacy endpoint should be conducted on the Intent-to-Treat population. The comparison of the difference in the primary efficacy endpoint should be made using the confidence interval approach, which should be pre-specified. The two-sided 95% confidence interval should be used. Similar analysis should be conducted on the Per-Protocol population.

The non-inferiority criteria should be satisfied for both the ITT and PP populations for the study to be considered successful.

Sponsor's 7/15/10 Reply for Discussion: Thank you for your feedback. No discussion needed.

Original PALO-10-01 Specific Question #5: Sample Size. The sample size and related assumptions (including the choice of the type I error) are cited in section 7.1 of the PALO-10-01 protocol and section 7 of the SAP.

- Please confirm that the sample size as described in the above cited sections of the PALO-10-01 protocol and SAP is adequate, and comment as needed.

FDA Response to Original PALO-10-01 Question #5: The sample size assumptions appear reasonable. However, we recommend you change your two-sided alpha level to .01. (See our response to Question #3.)

Follow-Up PALO-10-01 Sponsor's Question #5: *Type I error has been changed according to FDA's request; assumptions on percentage of patients with CR in oral palonosetron group has been changed in the light of FDA request on handling missing data (which favors the palonosetron IV group). Therefore it is proposed that the sample size and relative assumptions change as follows:*

For the sample size estimation, it is assumed that (1) 69% of patients will have CR in the acute phase in the oral palonosetron group, (2) 70% of patients will have CR in the acute phase in the I.V. palonosetron group, (3) the non-inferiority margin will be set at -15%, (4) two-sided type I error will be set at 0.01, (5) power will be 90%. These assumptions lead to a total sample size estimation of 322 evaluable patients/group which is rounded up to 370. The number of patients to be randomized in the study is estimated to be 740.

- *Please confirm if this approach is acceptable and comment as needed.*

FDA Response:
Your approach is acceptable.

Sponsor's 7/15/10 Reply for Discussion: *Thank you for your feedback. No discussion needed.*

Original PALO-10-01 Specific Question #6: Randomization and Stratification. As stated in section 4.9 of PALO-10-01 protocol and section 5.3 of the SAP, treatment assignment will be managed through a static central blocked randomization stratified by region and gender.

As described in section 9.7 of the SAP and in section 7.3.1.4 of protocol PALO-10-01, countries with a reasonably consistent number of patients will be considered as regions themselves, countries with few patients will be grouped together based both on regional proximity and clinical practice. Applying this criterion, regions will be defined upfront on the basis of the projected enrollment rate before the study starts. Definition of "regions" will be reviewed and approved during the Data Blind Review Meeting. For the reasons outlined in protocol section 7.3.1.4 and section 9.5 of SAP, site will not be a stratification factor.

- Please advise us of the acceptability of the proposed stratification factors and criteria for region definition as described in the above cited PALO-10-01 protocol and SAP sections. Please comment as needed.

FDA Response to Original PALO-10-01 Question #6: Please clarify your plan to stratify randomization by region. For this purpose, your definition for region should be pre-specified and not be data dependent. Also, provide details for any post-stratification planned for your primary analyses.

Follow-Up PALO-10-01 Sponsor's Question #6: *Sponsor's plan to stratify by region is based on the consideration that some countries will likely enroll few patients.*

In a planned revision to protocol PALO-10-01 sections 4.9 and 7.3.1.3 and SAP sections 5.3 and 9.6, it will be clarified that the following "regions" based on geographical proximity are defined: US, Latin America including Mexico, Europe, Commonwealth of Independent States (i.e. former Soviet Republics), and Asia.

Treatment assignment will be managed through a static central blocked randomization stratified by region and gender. Two randomization lists will be prepared, one for each gender. For each region a different block of the relevant list is allocated, i.e., each time a new region starts to randomize patients or each time a block for the relevant region has been completed; the next unused block is attributed to that region.

The same factors used for stratification purpose, i.e., gender and region, will be the sole ones that will be used for the analysis (the following wording is proposed in section 7.3.1.3 of the coming newly revised protocol and section 9.6 of the coming newly revised SAP "these factors will be used for randomization and for the analyses"). Therefore there is no plan for post-stratification in the primary analysis.

- *Please advise us if the above-described approach is acceptable. Please comment as needed.*

FDA Response:
Your approach is acceptable.

Sponsor's 7/15/10 Reply for Discussion: *Thank you for your feedback. No discussion needed.*

Original PALO-10-01 Specific Question #7: Populations of Analyses. The populations to be used for the analyses (Full Analysis Set, Per Protocol and Safety) and their role are defined in section 7.2 of PALO-10-01 protocol and section 8 of the SAP.

- Please confirm that in protocol PALO-10-01 the definitions of the populations for analyses and their role as described in these sections are adequate. Please comment as needed.

FDA Response to Original PALO-10-01 Question #7: **The analysis populations are acceptable.**

Follow-Up PALO-10-01 Sponsor's Comment #7: *Thank you for your response. No follow-up question is needed.*

FDA Response:
The analysis populations should also include the intent-to-treat population (all randomized patients).

Sponsor's 7/15/10 Reply for Discussion: Thank you for your feedback, we will also include the ITT population. No discussion needed.

Original PALO-10-01 Specific Question #8: Assay Sensitivity. The Sponsor is aware of the importance of the presence of assay sensitivity in the context of a non-inferiority trial. As described in section 7.3.1.5 of the PALO-10-01 protocol and section 9.8 of the SAP, some important features have been considered during the study design (e.g., historical evidence of sensitivity to comparator effects, important study attributes, and choice of non-inferiority margin). Other factors providing reassurance about assay sensitivity (e.g. good compliance, few drop-outs and missing data, similar effect of the comparator as in the historical trials) can be evaluated only at study completion. The Sponsor plans to discuss all these points in the study report but does not plan to perform a formal statistical test versus historical data.

- Please confirm that the proposed approach to address assay sensitivity as described in these section 7.3.1.5 of the PALO-10-01 protocol and section 9.8 of the SAP is acceptable recognizing the proposed role of PALO-10-01 in the Combination NDA clinical efficacy program as described in sections 1.1 and 1.7.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493; see section 1.7.2 of this present background package]. Please comment as needed.

FDA Response to Original PALO-10-01 Question #8: This approach is acceptable.

Follow-Up PALO-10-01 Sponsor's Comment #8: Thank you for your response. No follow-up question is needed.

Original PALO-10-01 Specific Question #9: Overall Plan for Statistical Analysis. The overall statistical analysis plan is described in PALO-10-01 protocol Section 7 and further detailed in the SAP.

- Please comment on the overall acceptability of the proposed statistical analysis plan as described in these sections of the protocol and SAP, and add any other considerations regarding the SAP.

FDA Response to Original PALO-10-01 Question #9: See the responses to the above questions. For a non-inferiority design, imputing all missing data as treatment failures may favor establishing non-inferiority. We recommend you impute missing data in oral group as treatment failures and those in the I.V. group as treatment successes. Other sensitivity analyses should be pre-specified.

Follow-Up PALO-10-01 Sponsor's Question #9: Please be aware that, due to the short follow-up period (the endpoint is measured at 24 hours), the amount of missing data is anticipated to be negligible and it is not expected to be a source of concern in this trial.

ICH E9 recommendation is to use a “sensible” method to deal with missing data. Actually, it appears that the FDA-requested method favors the reference treatment. The Sponsor acknowledges the need for a conservative approach but also believes that the true treatment effect should be characterized and that the use of a method which deliberately penalizes one treatment is inconsistent with this aim.

The European CPMP guidance “points to consider on missing data”, the only specific regulatory guidance currently available, mentions an approach similar to the FDA-requested method but as sensitivity analyses investigating both directions: “Some simple ways of performing a sensitivity analysis are: ...

- *to compare the results of two analyses, one assigning the best possible outcome to all missing values in both groups, and the other assigning the worst possible outcome to all missing values in both groups*
- *to compare the results of two analyses, one assigning the best possible outcome to missing values in the control group and the worst possible to those of the experimental group and vice-versa”.*

Given this background, the primary analysis is proposed to be the one which imputes all missing data as failures, as accepted by FDA so far for pivotal palonosetron non-inferiority trials; the Sponsor proposes to use the analysis recommended by FDA as a sensitivity analysis as previously suggested by FDA for non-inferiority protocol PALO-99-05 (please see FDA SPA letter dated January 27, 2000 at Appendix #12, Question #10, item #4 on page 4).

Please confirm if the proposed approach is acceptable and comment as needed.

FDA Response:
Your approach is acceptable.

***Sponsor’s 7/15/10 Reply for Discussion:** Thank you for your feedback. No discussion needed.*

Original PALO-10-01 Specific Question #10: Inclusion and Exclusion Criteria. The patient inclusion and exclusion criteria are described in sections 3.3.1 and 3.3.2 of the PALO-10-01 protocol. They are similar to the inclusion and exclusion criteria used in HEC efficacy trial NETU-07-07. Also, the inclusion and exclusion criteria used in PALO-10-01 are as similar as feasible to the those applied in study PALO-99-05 (the pivotal efficacy study which supported FDA approval of IV Aloxi 0.25 mg for the HEC indication, NDA 21-397), taking into account changes in the clinical practice since 2000.

- Please advise us of the acceptability of the proposed patient inclusion and exclusion criteria as described in PALO-10-01 protocol sections 3.3.1 and 3.3.2, and comment as needed.

FDA Response to Original PALO-10-01 Question #10: The inclusion and exclusion criteria are acceptable.

Follow-Up PALO-10-01 Sponsor's Comment #10: *Thank you for your response. No follow-up question is needed.*

Original PALO-10-01 Specific Question #11: Safety Measures. Protocol PALO-10-01 sections 6.2 and 7.3.4 and SAP sections 4.2.3 and 13 describe provisions to evaluate safety in the study.

- Please advise us if the safety measures proposed as described in the above cited sections are suitable for PALO-10-01. Please comment as needed.

FDA Response to Original PALO-10-01 Question #11: **The proposed safety assessments are acceptable.**

Follow-Up PALO-10-01 Sponsor's Comment #11: *Thank you for your response. No follow-up question is needed.*

Original PALO-10-01 Specific Question #12: Safety Database for HEC Patients. In protocol PALO-10-01 patients will not receive the Combination, only IV Aloxi or oral Aloxi, so study PALO-10-01 will not contribute to the Combination NDA safety database. Single-cycle study NETU-07-07, conducted entirely in Russia and the Ukraine, will be the only study in the NDA clinical program to contribute HEC patients to the NDA safety database. Specifically, in NETU-07-07 n=135 patients received the proposed phase 3 and NDA netupitant/palonosetron 300/0.5 mg dose, and an additional n=137 and n=135 patients were treated with 200/0.5 mg and 100/ 0.5 mg, respectively, for one cycle, which collectively will comprise the HEC NDA safety database. The NDA safety database will also include approximately 730 MEC patients (first cycle) enrolled in MEC study NETU-08-18 who are planned to be treated with the phase 3/NDA proposed 300/ 0.5 mg dose. It is projected that approximately 80% of patients enrolled in MEC study NETU-08-18 will be on study through at least the fourth cycle.

- Considering that study PALO-10-01 will not contribute to the Combination NDA safety database, and recognizing that single-cycle study NETU-07-07 is planned to be the sole HEC safety and efficacy clinical trial in the Combination NDA, please confirm if the above-described number of HEC patients from NETU-07-07, in conjunction with safety data from the above-described number of MEC patients anticipated to receive the Combination 300/0.5 mg dose in MEC repeat cycle study NETU-08-18, is considered collectively adequate for the overall planned NDA safety database. Please comment as needed.

Reference is made to FDA's letter dated March 8, 2010 (at Appendix #4), containing FDA Office of Medical Policy (OMP) feedback. Reference is also made to FDA's March 17, 2010 letter at Appendix #5 and to Questions #4 and #10 of the Sponsor's request for protocol NETU-08-18 (MEC) SPA, submitted on March 30, 2010.

FDA Response to Original PALO-10-01 Question #12: **It appears that you expect that there will be 850 patients in the combined safety database for netupitant. This falls short of**

the ICH guidelines of a total of 1500 patients with at least short term exposure. The total number might be considered acceptable if a substantial proportion of the patients have been treated for greater than or equal to 6 cycles of treatment, i.e., 300-600 patients. Your current proposed clinical data base will fall short of that. We recommend that you develop a plan for extension studies to evaluate safety over multiple cycles of chemotherapy, which could include changes to the chemotherapy regimens within patients. Your plan should be designed to assure that the safety dataset will meet the ICH recommendations of 100 patients treated for a minimum of 1 year.

Although the patients in PALO-10-01 will not be counted toward the total number needed for the combination safety database, the safety data from PALO-10-01 must be submitted with the NDA.

Follow-Up PALO-10-01 Sponsor's Question #12: Please be aware that the planned Combination NDA clinical safety database will include about 2000 individuals exposed to netupitant alone or in combination with palonosetron, as described below:

- *Approximately 1450 patients are anticipated to collectively derive from (1) completed phase 2 study NETU-07-07 (407 patients), (2) planned phase 3 NETU-08-18 (approximately 730 patients planned in the Combination arm) and (3) the safety extension of planned trial PALO-10-01 (approximately 350 patients planned assuming a 50% retention rate between the first and second cycle of chemotherapy). Of these approximately n=1450 cancer patients, about 1150 are planned to be treated with the proposed commercial Combination product dose (300/0.5 mg), and about 1000 patients are anticipated to be treated in repeated cycles.*
- *362 healthy volunteers given netupitant alone (up to 450 mg) or in combination (up to 600 mg) with palonosetron (up to 1.50 mg) are already available from completed phase 1 studies. In some such studies, subjects received more than one administration of netupitant; the total number of exposures is 570.*
- *160 subjects to be enrolled in planned phase 1 studies to be administered the netupitant/palonosetron Combination; the total number of planned exposures is 216.*

Regarding the intended duration of use, please consider that netupitant/palonosetron Combination administration is driven by the chemotherapy regimen(s) and therefore is not intended for the long-term treatment (of CINV), i.e. neither for chronic nor repeated intermittent use for longer than 6 months. As you know, according to ICH guidelines the safety profile of a drug should be characterized and quantified "over a reasonable duration of time consistent with the intended long-term use of the drug". The Combination will be administered according to the HEC schedule and the current status of clinical practice does not foresee the administration of chemotherapy beyond 4-6 cycles of first-line platinum-based chemotherapy (Azzoli, JCO, 2009). Since cycle frequency is usually of 21 days, the duration of exposure will not exceed 6 months. Moreover, the collection of safety data in this type of chemotherapy setting, i.e. HEC cisplatin-based, is severely limited by disease progression and chemotherapy toxicity to such an extent that it would be impossible to provide data on patients treated for 1 year with HEC. Furthermore, the few chemotherapy regimens that could continue up to 1 year, e.g. pemetrexed, are

classified as low emetogenic and hence the administration of an anti-emetic therapy should be limited to dexamethasone only according to current MASCC guidelines; NK₁/5-HT₃ RAs are not recommended for the prevention of CINV in this setting. The option to include changes to the chemotherapy regimens within patients, as suggested by FDA, has been explored but seems unproductive since second and following lines of chemotherapy are less emetogenic and therefore do not require the use of NK₁/5-HT₃ RAs.

For the above-mentioned reasons, the maximum duration of exposure reasonably feasible given current clinical practice is the maximum duration of the HEC and MEC chemotherapy regimens requiring NK₁/5-HT₃ RAs, which are almost always significantly less than 1 year (please see clinical oncology expert opinion at Appendix #13) The Sponsor understands FDA's safety concerns and will not limit the number of cycles of chemotherapy in either setting; however it is recognized that repeat cycle safety data for anywhere close to one year are unlikely to be obtained for purposes of the planned NDA safety database, based on feedback from clinical oncology experts. Such patients apparently are not clinically available, i.e., do not appear to exist (please see written clinical oncology CINV expert opinion at Appendix #13).

The Sponsor believes the longest term repeat cycle clinical safety data presently feasible given current medical oncology practice will be obtained from the Sponsor's newly proposed open-label repeat cycle safety extension of PALO-10-01 (please see section 1.7.2, Appendix #11, and Follow up NETU-08-18 Sponsor's Question #4) where patients will stay on study according to their scheduled chemotherapy scheme; this is the proposed approach to obtain long-term repeat cycle safety data for the planned NDA clinical safety database.

- *Please advise us of the acceptability of this proposed approach and comment as needed.*

FDA Response:

We agree with your plan to conduct multi-cycle extensions for evaluation of safety. However, we remain concerned about retention of patients beyond Cycle 4 in trial NETU-08-18 (MEC) and about the lack of a concurrent control group in the multi-cycle extension of PALO-10-01 (HEC). To address these concerns, we encourage you to:

- **permit enrollment of new patients into the multi-cycle extension, who were not already enrolled in the first part of these studies; and**
- **permit changing of chemotherapy regimens (regarding of emetogenic potential) between the first part of the trial and the multi-cycle extension, in both NETU-08-18 (MEC) and PALO-10-01 (HEC)**

We also expect the extension protocol(s) to address the importance of a comparator group for detection of a safety signal for netupitant.

Sponsor's 7/15/10 Reply for Discussion: *Please see Sponsor's reply to NETU-08-18 follow-up Question #1E.*

Original PALO-10-01 Specific Question #13: Number of Cycles in HEC/MEC Patients to Support Efficacy and Safety to Obtain “repeat courses” Wording in the Target HEC

Indication. In proposed protocol PALO-10-01 patients will not receive the Combination, only oral Aloxi or IV Aloxi. As suggested by FDA (please see FDA Division/OMP letter dated 8Mar10 at Appendix #4), the only HEC efficacy trial in the planned Combination NDA program will be completed single-cycle trial NETU-07-07. FDA also commented that “*The inclusion of repeat cycles and an adequate numbers of patients in the MEC trial NETU-08-18 might be sufficient to support the safety database and inclusion of the words “repeat (b) (4) in the indication for CINV-HEC (...).”* It is projected that approximately 730 MEC patients (first cycle) will be enrolled in the Combination arm of the MEC study NETU-08-18 and about 80% of them will be on study through at least the fourth cycle.

- Please confirm that the number of cycles and patients described in sections 3.2 and 7.1 of MEC protocol NETU-08-18 (submitted for FDA SPA 30Mar10 in IND 73493 Serial #019) are anticipated to provide sufficient efficacy and safety data for purposes of supporting the CINV-HEC target indication, specifically the “repeat courses” wording in the HEC indication (please see section 1.3 of this submission). Please comment as needed.

Reference is made to FDA’s letter dated 8Mar10 (at Appendix #4), containing FDA Division and Office of Medical Policy (OMP) feedback. Reference is also made to FDA’s 17Mar10 letter at Appendix #5 and to Questions #4 and #10 of the protocol NETU-08-18 (MEC) SPA, submitted 30Mar10.

FDA Response to Original PALO-10-01 Question #13: To obtain the “repeat courses” wording for HEC and MEC, there needs to be additional safety data for cycles beyond cycle 4 in either HEC and/or MEC.

Follow-Up PALO-10-01 Sponsor’s Comment #13: *Please see the Sponsor’s Follow-up Question #12 above.*

FDA Response:

See FDA response to Question #12.

Sponsor’s 7/15/10 Reply for Discussion: *Please see Sponsor’s reply to NETU-08-18 follow-up Question #1E.*

Original PALO-10-01 Specific Question #14: Overall Adequacy of NETU-07-07

Considered with PALO 10-01 for the Planned NDA HEC Indication. As described in Section 1.3 of this submission, the proposed target indication for the fixed dose combination is “*prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. The palonosetron component is effective in the acute phase and the netupitant component is effective in the acute, delayed and overall phases of nausea and vomiting*” (a contribution for the netupitant component in the acute, delayed and overall phases will be claimed in the label since these endpoints are considered successful by the Sponsor in completed trial NETU-07-07, provided that FDA does not raise major concerns

regarding NETU-07-07 validity during FDA's present ongoing review of the NETU-07-07 study report).

Completed single cycle study NETU-07-07 was entirely conducted in Russia and the Ukraine and therefore there will be no US patients treated with the Combination in the HEC setting in the planned NDA. If PALO-10-01 is successful and if FDA finds the efficacy analyses in FDA's ongoing review of the NETU-07-07 study report to be acceptable, study NETU-07-07 is planned to serve as the sole pivotal trial for purposes of supporting HEC efficacy and safety for the Combination (in conjunction with MEC study NETU-08-18 in the planned NDA). NETU-07-07 demonstrated statistical superiority of the combination 300/0.5 mg dose group versus oral palonosetron 0.5 mg alone in the overall ($p=0.004$), acute ($p=0.007$) and delayed ($p=0.018$) phases (please see the NETU-07-07 study report synopsis at Appendix #8).

As described in sections 1.1 and 1.7.2 [in the original SPA request, Serial #019 dated 30Mar10, IND 73,493; see section 1.7.2 of this present background package], the intended role of study PALO-10-01 in the Combination NDA program is to demonstrate that oral palonosetron 0.5 mg is efficacious for HEC and therefore contributes to the fixed dose Combination, and that the oral palonosetron 0.5 mg active comparator used is NETU-07-07 is effective for HEC thereby permitting completed trial NETU-07-07 to serve as the sole adequate and well-controlled pivotal trial to support FDA-approval of the HEC target indication cited in section 1.3.

- Please confirm that proposed HEC protocol PALO-10-01 as described in section 3.0 herein is acceptable in design, objectives, patient population, efficacy endpoints, sample size, outlined execution and analyses to support HEC efficacy study NETU-07-07 as described in sections 1.1 and 1.7.2 of this submission.
- Consistent with FDA Division and OMP feedback that "*Trials PALO-10-XX [i.e., PALO-10-01] and NETU-07-07 will be acceptable to support the proposed fixed-dose combination capsule for the prevention of acute and delayed CINV-HEC, provided that we [FDA] are able, after our [FDA] review of the trial data, to confirm the outcome you [the Sponsor] have reported for NETU-07-07, and if the outcome of PALO-10-XX [PALO-10-01] is also positive*", if FDA's review of the NETU-07-07 study report confirms the outcome the Sponsor reported for NETU-07-07, and if the outcome of PALO-10-01 is also positive, please confirm that completed single-cycle study NETU-07-07 will be acceptable as the sole adequate and well controlled efficacy trial to support the proposed fixed-dose combination capsule for the prevention of acute and delayed CINV-HEC, including repeated cycles, as described in the target HEC indication cited in section 1.3. Please comment as needed.
- Please comment as needed regarding the Sponsor-proposed HEC NDA clinical efficacy plan.

FDA Response to Original PALO-10-01 Question #14: NETU-07-07 will be acceptable as the sole efficacy trial for the fixed dose combination capsule in acute and delayed CINV-HEC prevention, provided the reviews of NETU-07-07 and PALO-10-01 conclude the data support efficacy, and there are sufficient data beyond cycle 4. With regards to repeat (b) (4) from an efficacy standpoint, this labeling in HEC will rely on the observations in the

MEC study. From a safety standpoint, the repeat (b) (4) labeling claim will need to be obtained from HEC and/or MEC.

Follow-Up PALO-10-01 Sponsor's Question #14: *FDA previously requested that the NETU-07-07 clinical study report be submitted by the Sponsor to the IND for preliminary FDA review (not the detailed review planned during the combination NDA submission) to help the Division get an idea if the statistical efficacy analyses in the NETU-07-07 clinical study report is suitable to serve as the sole HEC efficacy trial in support of the target HEC indication (see Section 1.3). The NETU-07-07 clinical study report was submitted to the IND on March 22, 2010 (IND 73493, Serial #017) as FDA requested. From an efficacy perspective, and because study NETU-07-07 is the sole HEC pivotal efficacy trial and is therefore critically important to the overall program to support efficacy for the target HEC indication, please advise the Sponsor, based on the Division's recent preliminary review, whether the NETU-07-07 efficacy analysis in the submitted clinical study report appears suitable for this purpose. Please comment.*

FDA Response:

The phase 2 study NETU-07-07 has the potential for consideration as the sole pivotal efficacy trial to support HEC indication. However, the acceptability of the data submitted with respect of demonstrating efficacy of the Combination in HEC-CINV treatment will be a review issue. We currently have the following concerns about NETU-07-07:

- **This study was designed as a Phase 2 dose-ranging study, not as a Phase 3 confirmatory study.**

Sponsor's 7/15/10 Reply for Discussion: *The Sponsor acknowledges that NETU-07-07 is a phase 2 dose ranging study and that FDA has suggested that NETU-07-07 serve as the sole pivotal efficacy trial for HEC.*

- **The primary endpoint was CR Overall (0-120 hours), however, from our prior discussions, CR Delayed (>24-120 hours) is the primary analysis of interest for establishing the contribution of netupitant to efficacy of the combination product.**

Sponsor's 7/15/10 Reply for Discussion: *The Sponsor acknowledges that the primary efficacy endpoint was CR overall (0-120 hrs). However, the analysis was repeated per FDA's suggestion with CR delayed as the primary endpoint with statistical significance maintained. Please advise us if this approach is acceptable and comment as needed.*

- **The primary analysis was based on a logistic regression model, and a model-based approach is not generally acceptable for the primary analysis. Based on the study design, a CMH test would have been more appropriate.**

Sponsor's 7/15/10 Reply for Discussion: *Please note that a CMH test was performed as per FDA suggestion with results very close to the original and*

statistical significance maintained. Please advise us if this approach is acceptable and comment as needed.

- **Although you did prespecify a plan to adjust for multiplicity of the three netupitant dose levels in NETU-07-07, you did not pre-specify a plan to adjust multiplicity for the secondary endpoints CR acute (0-24 hours) and Delayed (>24-120 hours). However, the delayed phase is the endpoint of interest for establishing the efficacy of netupitant. Therefore, in light of our concerns about the use of CR Overall (0-120 hours), further multiplicity adjustment would be needed.**

Sponsor's 7/15/10 Reply for Discussion: *As per FDA suggestion we applied a hierarchical procedure to control Type I error for the 3 phases (delayed, acute and overall) and at each step we adjusted for the 3 doses using Holm-Bonferroni method. Statistical significance was maintained for all comparisons. Please advise us if this approach is acceptable and comment as needed.*

Meeting Discussion:

Helsinn acknowledged FDA's first 2 bulleted responses. Helsinn noted that they repeated the study analysis using CR delayed as the primary endpoint and statistical significance was maintained. FDA stated that in looking at the ITT analysis, several randomized patients from some of the study dose groups were not included in the analysis. FDA further stated that the ITT analysis results in a two-sided p-value greater than 0.05. FDA's analysis is looking only at the dose response. If statistical significance is not seen in dose response testing, then additional analysis versus a control group should not be conducted. Additionally, NETU-07-07 is a phase 2 study which is not confirmatory.

FDA stated that true ITT principle refers to all randomized subjects. The results do not appear robust based on the preliminary analysis. FDA acknowledged that this was not the final test because all data were not available. FDA indicated that Helsinn is responsible for conducting the analysis, which should be a stratified analysis.

Helsinn replied that some patients did not receive chemotherapy, and therefore, did not receive the study drug. FDA requested the sponsor to provide details on these patients to include why they did not receive chemotherapy. Given these issues, FDA cautioned that NETU-07-07 may not be strong enough to serve as a confirmatory trial. Helsinn will further evaluate NETU-07-07 based on FDA's feedback and provide the information with their next SPA submission. Helsinn stated that a dose-response test was not the main pre-planned test and not part of their testing strategy. FDA noted that multiplicity adjustment and order of endpoints was also not pre-specified.

Helsinn stated that the analysis was repeated per FDA's previous comments and results were still robust. This is a new issue that the sponsor will need to review

further. Helsinn asked if they should consider ITT populations for analyses in their pivotal trials rather than FAS population. FDA replied that ITT analyses should be conducted. Helsinn argued that in previous trials, they utilized FAS for the primary analysis. The FAS population excluded patients that did not receive chemotherapy. The sponsor explained that with the FAS population, patients are not at emetogenic risk if they do not receive chemotherapy. FDA agreed, and proposed that the FAS analysis serve as the primary analysis. The ITT analysis should be conducted as sensitivity analysis. Helsinn agreed.

Helsinn stated that a CMH test was performed, per FDA's third bulleted response, and statistical significance was maintained. FDA requested Helsinn to submit their CMH analysis as a separate amendment to the IND.

Helsinn noted that they applied a hierarchical procedure per FDA's fourth bulleted response. FDA requested Helsinn to submit the information with their IND amendment containing the CMH analysis results. FDA noted that the multiplicity adjustment was applied post hoc. Therefore, a more conservative method should be used to determine the p-values. Helsinn replied that their re-analysis was conducted according to FDA's comments. Per pre-specified levels, the results are statistically significant. Helsinn argued that additional adjustments cannot be made other than what has already been pre-specified. FDA emphasized that extra caution must be used when conducting post hoc analyses, and that the concerns expressed so far remain potential issues for Study NETU-07-07.

Based upon FDA's comments, Helsinn expressed concern that NETU-07-07 may not be considered an adequate study to support the proposed fixed-dose combination for HEC. Helsinn asked how they can ensure that NETU-07-07 would be acceptable. FDA replied that the study design indicates that NETU-07-07 can be acceptable for the development program. FDA expressed concern that this study has already been completed and not all data are available at this SPA stage. FDA informed the sponsor that the acceptability of study NETU-07-07 as a single confirmatory study will be decided after a detailed review at the NDA stage. FDA stated that the above comments and discussion are to provide Helsinn with issues that will be considered during review of the NDA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

1. Helsinn should submit the details of completed study NETU-08-03.
2. Helsinn may submit the protocol outline for trial NETU-10-XX and a few questions on the protocol with their SPA resubmission.
3. FDA prefers to have more than 100 patients at cycle 6 of trial NETU-10-XX. Helsinn should optimize the development program to include the maximum number of patients.

4. Regarding NETU-07-07, Helsinn should submit the details of patients that were not included in the sponsor's study analysis.
5. For NETU-07-07, the sponsor's FAS analysis can serve as the primary analysis. An ITT analysis should be performed as sensitivity analysis.
6. Helsinn will submit their CMH analysis of NETU-07-07 as an amendment to the IND.

5.0 ATTACHMENTS AND HANDOUTS

1. Helsinn Slides – Sponsor's considerations on FDA preliminary comments

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73493	GI-1	HELSINN HEALTHCARE SA	PALONOSETRON HCL / NETUPITANT

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

/s/

JAGJIT S GREWAL
09/07/2010



IND 073493

MEETING MINUTES

Helsinn Healthcare SA
C/O August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for netupitant and palonosetron HCl fixed-dose combination capsule.

We also refer to the meeting between representatives of your firm and the FDA on January 22, 2010. The purpose of the meeting was to discuss the FDA responses, dated November 27, 2009, to your requests for special protocol assessment of clinical protocols [REDACTED] ^{(b) (4)} and NETU-08-18.

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

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 22, 2010
TIME: 11:30AM EST
LOCATION: FDA – White Oak Campus
10903 New Hampshire Avenue, Building #22
Silver Spring, MD 20993
APPLICATION: IND 073493
DRUG NAME: netupitant and palonosetron HCl fixed-dose combination capsule
TYPE OF MEETING: Type A meeting
MEETING CHAIR: Nancy Snow, D.O., M.P.A
MEETING RECORDER: Jagjit Grewal, M.P.H.

FDA ATTENDEES:

Division of Gastroenterology Products

Donna Griebel, M.D.	Director
Joyce Korvick, M.D., M.P.H	Deputy Director for Safety
Nancy Snow, D.O., M.P.A.	Acting Medical Team Leader
John Troiani, M.D., Ph.D.	Medical Reviewer
Jagjit Grewal, M.P.H.	Regulatory Project Manager

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Reviewer
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Division of Biometrics III

Mike Welch, Ph.D.	Deputy Director
Freda Cooner, Ph.D.	Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Helsinn Healthcare SA

Dr. Angioletta Navini	Manager, Regulatory Affairs
Dr. Fabio Trento	Senior Manager, Project and Operation Controller
Dr. Giada Rizzi	Manager, Statistics and Data Management
Dr. Giorgia Rossi	Manager, Corporate Clinical Development
Dr. Marco Palmas	Head of Corporate Clinical Development
Dr. Sergio Cantoreggi	Senior Director, Head of Corporate R&D
Dr. Dario Ceriani	Director, Regulatory Affairs

(b) (4)

Dr. Craig Lehmann	Authorized Representative/Consultant
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1.0 BACKGROUND:

Reference is made to the end of phase 2 meeting with Helsinn Healthcare on July 20, 2009. Further reference is made to the sponsor's submissions dated October 12, 2009 requesting special protocol assessment (SPA) of their proposed phase 3 clinical trials for netupitant and oral palonosetron fixed-dose combination capsule. The sponsor's SPA submissions proposed the following phase 3 trials:

[REDACTED] (b) (4)

2. NETU-08-18 (CINV-MEC): Superiority trial comparing oral palonosetron HCl + netupitant (0.5mg/300mg) combination capsule versus FDA-approved Aloxi (palonosetron HCl) [REDACTED] (b) (4) in patients receiving moderately emetogenic cancer chemotherapy

FDA SPA responses were sent to the sponsor on November 27, 2009 which included recommendations to [REDACTED] (b) (4) and to change the active comparator in trial NETU-08-18 to 0.5 mg oral palonosetron HCl.

Helsinn submitted Type A meeting requests dated December 4, 2009 to discuss the FDA responses to the sponsor's requests for special protocol assessment. FDA granted Helsinn's meeting requests in the letter dated December 10, 2009.

Helsinn's meeting background package dated January 7, 2010 contained a revised clinical development program as follows:

[REDACTED] (b) (4)

2. NETU-10-XX (CINV-HEC) – Non-inferiority trial comparing 0.5 mg oral palonosetron HCl to 0.25 mg I.V. palonosetron in patients receiving highly emetogenic cancer chemotherapy. Complete Response in the acute phase (0-24 hours) is proposed as the primary endpoint. This trial is incorporated to establish the contribution of the oral palonosetron component in the combination product for CINV-HEC.
3. NETU-08-18 (CINV-MEC): Superiority trial comparing oral palonosetron HCl + netupitant (0.5mg/300mg) combination capsule versus FDA-approved Aloxi (palonosetron HCl) [REDACTED] (b) (4) in patients receiving moderately emetogenic cancer chemotherapy. Complete Response in the overall phase (0-120 hours) is proposed as the primary endpoint.

Additionally, Helsinn proposes to utilize the completed phase 2 study NETU-07-07 to demonstrate the contribution of the netupitant component to the treatment effect of the combination product. NETU-07-07 is a superiority study comparing three single oral doses of

netupitant (100 mg, 200 mg, 300 mg) each combined with 0.5 mg oral palonosetron HCl versus 0.5 mg oral palonosetron HCl in patients receiving highly emetogenic cancer chemotherapy. The FDA-approved oral EMEND (aprepitant) regimen was also included as an active comparator for exploratory purposes.

FDA preliminary comments were sent to the sponsor on January 20, 2010. On January 21, 2010, Helsinn provided their replies to the FDA preliminary responses to facilitate discussion at the meeting.

2.0 DISCUSSION POINTS:

The format of these minutes provides for Helsinn's questions in regular typeface, followed by the Agency's responses in **bolded** print (sections 2.0 – 2.3). Helsinn's January 21, 2010 replies to the FDA responses are presented in *italic* print. The January 22, 2010 meeting discussion is presented in *italic and bolded* print.

Introductory Meeting Discussion:

FDA began the meeting by noting that the sponsor's proposed clinical development program is complex from a regulatory standpoint. The comments and recommendations conveyed to the sponsor to date are what the division believes to be the best path forward at this time. Given the complexity of the development program, the division will meet with the FDA Office of Medical Policy (OMP) to further discuss the sponsor's proposed clinical program. FDA stated that the purpose of the meeting with OMP is to confirm the division's recommendations and to ensure that the necessary regulatory requirements are met. Helsinn indicated that their development program is time sensitive and they would like to begin the program as soon as possible.

2.1 CINV-HEC PROTOCOL (b) (4) QUESTIONS

(b) (4)

(b) (4)

Sponsor's 1/21/10 Reply for Discussion: *As you are aware, the background package included data to support the proposed noninferiority margin for NETU-10-XX (i.e., PALO-10-XX) which was determined to be 15%. To help the Sponsor prepare for submission of this revised protocol for SPA, please clarify the nature of evidence you wish the Sponsor to provide in the SPA submission to support the proposed noninferiority margin.*

Meeting Discussion:

Helsinn asked what additional information should be submitted with the revised SPA to support the proposed 15% non-inferiority margin. FDA replied that no additional information will need to be submitted at this point to support the proposed margin.

FDA noted that a 15% delta has been used in the past and hence is likely to be accepted, but will need to be reviewed further during Special Protocol Assessment (SPA) review.

Question #1B: Netupitant contribution to the combination. Please confirm that NETU-07-07 demonstrated the netupitant contribution to the combination and therefore meets requirements in 21 CFR 300.50 for fixed-dose combinations for the HEC target indication. Please comment as needed.

FDA Response:

We agree that the NETU-07-07 study design isolates the effect of netupitant. However, we will need to review the final study results and statistical analysis plan for NETU-07-07 before we can provide comment on whether 300 mg of netupitant was superior in the overall, acute, and delayed phases of CINV-HEC.

Sponsor's 1/21/10 Reply for Discussion: *The Sponsor plans to submit the phase 2 NETU-07-07 SAP and study efficacy results in conjunction with (at the same time as) the planned (b)(4) SPA. In this (b)(4) the Sponsor plans to include a specific question regarding the acceptability of both the NETU-07-07 SAP and efficacy results for purposes of demonstrating the netupitant contribution to the Combination. Please comment regarding the acceptability of this proposed approach, and please advise us if there is specific information that FDA wishes the Sponsor to include in this planned submission for NETU-07-07. Please comment as needed.*

Meeting Discussion:

FDA stated that the acceptability of the phase 2 study NETU-07-07 to demonstrate the efficacy of the netupitant component to the combination product is a review issue.

FDA noted that the sponsor should submit their NETU-07-07 full study report to the IND, including the statistical analysis plan, in a separate submission from the revised SPA request. The SPA may contain an appendix with a synopsis of the NETU-07-07 study report and reference to the IND submission that contains the full study report and statistical analysis plan. The cover letter of the SPA request will contain a reference to the questions regarding the NETU-07-07 study report from the IND submission.

Question #1C(1): Proposed role of studies PALO-10-XX and (b) (4). Please clarify if (1) a non inferiority evaluation of 0.5 mg oral palonosetron versus the approved IV palonosetron 0.25 formulation performed in a separate trial (PALO-10-XX) (b) (4) all as described above, is adequate to establish the contribution of the oral palonosetron component to the combination to fulfill fixed dose combination regulation 21 CFR 300.50, and (2) if the (b) (4) study design described in #1 above considered in conjunction with NETU-07-07 and PALO-10-XX, all as described above, are acceptable for purposes of demonstrating efficacy for the combination. Please comment as needed.

FDA Response:

See the responses to CINV-HEC questions #1A and #1B. If the concerns mentioned in questions #1A and #1B are adequately addressed, trial NETU-10-XX may be an acceptable alternative to a (b) (4) in order to establish the contribution of oral palonosetron to the combination, if these trials are similar in populations and outcomes. For example, you propose that NETU-10-XX will be conducted in countries where 5-HT3 therapy (with dexamethasone) is still standard of care in HEC. However, such countries may differ in important ways from countries where (b) (4) is conducted. Significant differences in severity/extent of disease at diagnosis, demographics (age at first diagnosis), concomitant therapy, use of rescue medication, and other factors can affect safety and efficacy outcomes in the two trials.

Sponsor's 1/21/10 Reply for Discussion: Thank you for your reply. Sponsor is evaluating the feasibility of performing NETU-10-XX (i.e., PALO-10-XX) across the same countries as (b) (4)

Meeting Discussion:

Helsinn explained that they are evaluating the feasibility of conducting both studies across the same countries. FDA asked what the expected US component in terms of the number of patients. Helsinn replied that it is difficult to answer at this time as they are still investigating the issue. They feel that a fair amount of patients will be from the US.

Helsinn noted that a study center may be unlikely to take on both trials. If a center was involved in both trials, certain patients may be enrolled in trial (b) (4) while other patients may be enrolled in trial NETU-10-XX. This may lead to some difference between the trials.

Helsinn asked if patients from Western Europe were considered to be the same as US patients. FDA replied that differences have been seen between these patient populations and it varies per application. There have been different results noted for different regions. As a cautionary note, FDA stated that the sponsor should diversify the study population to the best extent possible.

FDA indicated that NETU-10-XX is being studied for CINV-HEC but no NK-1 antagonist will be used and there may be only certain places in the world in which the trial can be conducted. Helsinn replied that palonosetron plus a NK-1 antagonist is not the standard

of care at all US sites. Therefore, the sponsor can select US sites for the trials, but noted that the sites may not be the same for both trials.

Question #1C(2): Single components contribution to the combination to be cited in labeling.

Please confirm if the labeling indication would include the indication for the combination, i.e., will the indication reflect results of the efficacy endpoints proposed for the combination, with an added statement in labeling regarding the contribution of the single components, all as described above. Please comment as needed. Please also refer to Sponsor's Follow-Up HEC Comment, Question #2.

FDA Response:

It is premature to comment on the details of labeling at this time. Labeling will be a review issue. As we have stated previously, it will be key to clearly state in the labeling the contribution of each component to the combination.

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your feedback.*

Meeting Discussion:

No meeting discussion.

Question #1D: Non-inferiority evaluation of 0.5 mg oral palonosetron and IV palonosetron

0.25. Please advise us if the proposed PALO-10-XX study design and noninferiority margin are acceptable as described above, and comment as needed. Also, please advise us if it is acceptable to submit both noninferiority protocol PALO-10-XX, (b) (4)

(b) (4) as described above, separately at the same time for FDA Special Protocol Assessment. Please comment as needed.

FDA Response:

The study design and non-inferiority margin for Study PALO-10-XX may be acceptable, depending upon the full protocol and statistical analysis plan submission. Please note that prior Aloxi approvals based on non-inferiority assessment utilized an adjusted confidence interval when there was a single supportive study.

It is acceptable to submit protocol PALO-10-XX and your revised protocol (b) (4) separately at the same time for Special Protocol Assessment review.

Sponsor's 1/21/10 Reply for Discussion: *Thank you. Please note that the adjusted CIs in the pivotal efficacy trials for prior Aloxi approvals were applied because of multiple comparisons due to multiple palonosetron doses involved in the trials.*

Meeting Discussion:

Helsinn commented that the adjusted confidence intervals utilized in the approval of the oral Aloxi application was due to testing against multiple doses of palonosetron. FDA acknowledged the sponsor's comment, but noted that the FDA itself will adjust the

confidence interval during the review evaluation, especially in the case of a single trial. This adjustment may not be reflected in comments back to the sponsor.

Helsinn asked if the adjustment is done even if the hierarchical order is clearly stated. FDA replied that the adjustment is also done in this case because there is only a single trial.

Question #2: Adequacy of endpoints for the combination and labeling implication. The Sponsor will accept to report information on the efficacy of each single component in the labeling. However, it is Sponsors understanding that the indication of the drug (i.e., the fixed combination product) will reflect results of (b) (4) Please also see Sponsor's questions on labeling implications and proposed evaluation of the oral palonosetron component in Sponsor's Follow-up Questions #1C(1) and #1C(2) above.

Please clarify if the proposed endpoints are acceptable to register the fixed dose combination product for the proposed indication, i.e., prevention of acute and delayed nausea and vomiting, provided that information on the efficacy of each single component will be reported in the labeling.

FDA Response:

Complete Response in the overall phase was an acceptable endpoint in the approval of the NK-1 antagonist EMEND. However, given that the NK-1 antagonist netupitant is expected to have its major effect in the delayed phase, we prefer that (b) (4)

or labeling of all three phases, this trial should show superiority on all three endpoints. Please also see the responses to CINV-HEC questions #1A through #1D regarding labeling.

Sponsor's 1/21/10 Reply for Discussion: *The Sponsor understands that for the target indication as currently proposed (please see Section 1.3 of the background package; "prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy"), this trial should show superiority on all three endpoints. However, recognizing that this single dose combination product is intended to address the clinical problem of nausea and vomiting during the overall 0-120 hour period which includes the delayed and acute phases, the Sponsor would like to test the following hierarchical order: primary endpoint as the overall phase followed by the delayed and acute phases, respectively. The Sponsor recognizes that ultimately the indication will be driven by the study outcomes on these three endpoints. Please address the acceptability of this approach and comment as needed.*

Meeting Discussion:

Helsinn noted that a single capsule of the combination capsule will be given on day 1 to address CINV during the overall period, which includes acute and delayed phases. Due to the clinical orientation, the sponsor prefers testing the overall phase followed by the delayed and acute phases. Helsinn recognized that the results on all three phases will be

reflected in the product label. From a clinical perspective, Helsinn argued that patients do not care if their vomiting episode occurs on day 1 or day 3. Therefore, it would be better to use the overall phase as the primary endpoint.

FDA stated that their recommendations are based upon legal and regulatory requirements. This issue will be discussed further with OMP before making a final decision on acceptable hierarchy of endpoints.

Helsinn indicated that their ultimate goal is an indication with both acute and delayed phases, but depending on the data results, it may be acceptable to get a less specific indication. The sponsor proposed possibly obtaining a more generic indication or an indication similar to that of EMEND. Helsinn acknowledged that results for each phase needs to be positive to obtain labeling for all three phases. Yet, there may be options in between depending upon the outcome of the data. Thus, it would be better to test the overall phase first. Additionally, if acute and delayed phases were tested first and found to be positive, then you would also expect to win on the overall phase. Therefore, it would be redundant to test the overall phase after the acute and delayed phases. Helsinn agreed that the indication would be data driven.

FDA commented that with the prevention indication and over time, patients may not be as ill on later days than on the first few days of illness. If there is a difference between acute and delayed phases, are we seeing a meaningful effect or are patients just getting better. Helsinn noted that in looking at earlier trials, 25% of patients had delayed vomiting in the absence of acute vomiting.

Helsinn asked if FDA would prefer that the revised SPA be submitted with a generic endpoint which may possibly be changed later if the trial had positive data results. FDA did not recommend a change to the indication at this time. FDA explained that addressing this issue now lends to a better understanding of the development program. Additionally, it can be determined what level of evidence is needed to support the product labeling and how the indication may be written in the label.

FDA questioned if a testing hierarchy is needed. FDA asked if testing could be done simultaneously with adjustment of the p-value. Therefore, having co-primary endpoints may be feasible. FDA also noted that the point of changing the hierarchical order as FDA recommended is to show that the overall phase has a meaningful value.

Helsinn asked if netupitant were developed as a single agent, rather than a combination product, would the overall phase be acceptable as the primary endpoint as in the case of EMEND. FDA could not comment on this question at the time. FDA would need to look back at what was done in the approval of EMEND.

In conclusion, the division still believes that the delayed phase should be tested first in the hierarchy but will discuss this further with the Office of Medical Policy (OMP). Feedback from the meeting with OMP will be provided to the sponsor after that discussion. FDA will also explore the possibility of simultaneously testing co-primary endpoints for acute and delayed phases.

Question #3: Multiplicity, key secondary endpoints. Thank you for your reply. Regarding appropriateness of proposed endpoints for the combination and labeling constraints in relation to the single components, please see request of clarification above.

FDA Response:
No response needed.

Question #4: Multiplicity, non-key secondary endpoints. Thank you for your reply.

FDA Response:
No response needed.

Question #5: Multi-cycle extension. Please see Sponsor's reply in Follow-up Question #13 below.

FDA Response:
No response needed.

Question #6: Inclusion/exclusion criteria. Thank you for your reply.

FDA Response:
No response needed.

Question #7: Sample Size. Thank you for your reply.

FDA Response:
No response needed.

Question #8: Interim analysis. The following Sponsor's comments are in regard to the (b) (4) not the PALO-10-XX noninferiority trial described above.

(b) (4)

(b) (4)

Please comment as needed.

FDA Response:

(b) (4)

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your feedback. The Sponsor no longer plans to perform (b) (4). However for the (b) (4) (as well as for the NETU-08-18 MEC trial), the DSMB will be in place for reviewing safety data and a Charter is planned to be prepared for this purpose. Given this information, please advise us if FDA still wishes the Sponsor to submit the DSMB Charter in the (b) (4) (b) (4) SPA. Please comment.*

Meeting Discussion:

Helsinn asked if a DSMB Charter is needed for submission with the (b) (4)

(b) (4)

(b) (4)

Question #9: Early study termination and safety data. Please refer to Sponsors Follow-up Question #13.

FDA Response:
No response needed.

Question #10: Randomization.

(b) (4)

FDA Response:
Thank you for your clarification. Your plan is acceptable.

Question #11: Forced randomization. Sponsor agrees to avoid "forced randomization".

FDA Response:
No response needed.

Question #12: Overall statistical analysis. Sponsor agrees to use the stratified CMH test appropriately, and impute all missing data as treatment failures for the primary efficacy analysis.

FDA Response:
No response needed.

Question #13: Number of cycles.

(b) (4)

(b) (4)

FDA Response:

Your approach is acceptable. Please add this clarification to your protocol.

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your reply.*

Meeting Discussion:

No meeting discussion.

Question #14: Safety measures. The Sponsor agrees.

FDA Response:

No response needed.

Question #15: Cardiac safety. The Sponsor acknowledges the importance of obtaining the FDA-requested standardized troponin assay using a central laboratory and agrees to implement this assay in (b) (4)

Concerning the 12-hour additional sampling, the Sponsor wishes to note that cTnl levels increase in the first 72 hours after cardiac injury [Cardinale d, Sandri M, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004; 109: 2749-2754) and remain elevated longer than CK isoforms (beyond 8 days) [Jafe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease. The present and the future. *J Am Coll Cardiol*. 2006; 48; 1-11]. Therefore sampling at intermediate timepoints does not appear to provide conclusive information. In addition, obtaining the 12 hour sample would be logistically extremely challenging based on the need to hospitalize the patient. For these reasons, the Sponsor proposes that no sample will be collected at 12 hours after dosing but the Sponsor agrees to collect the 24-hour sample since the patient will undergo hospital visit on Day 2 (Visit 3).

The Sponsor plans not to perform echocardiography in the (b) (4) on a routine basis since cisplatin based chemotherapy will be used and evaluation of cardiac safety will be based to a large extent on the troponin assessment. Only patients with high troponin values are proposed to undergo LVEF evaluation. Please advise us of the acceptability of this approach and comment as needed.

FDA Response:

Thank you for apprising us of the operational constraints in obtaining a 12-hour troponin sample. Your proposal to eliminate the 12-hour troponin sample is acceptable.

However, performing LVEF only in subjects with a high troponin level does not allow for assessment of change in LVEF. Therefore, unless a baseline LVEF is obtained for all patients the change in LVEF cannot be assessed when an elevated troponin level is detected. Therefore, a baseline LVEF is needed in all subjects who enter the study. In addition, an end-of-study LVEF should be obtained in all patients on cardiotoxic drugs.

Sponsor's 1/21/10 Reply for Discussion: *The Sponsor agrees to perform LVEF in all patients at baseline and at the end of each cycle for each patient.*

Meeting Discussion:

FDA asked if LVEF will be performed at each cycle or at each course of treatment. The sponsor clarified that LVEF will be performed on each patient at baseline and at the end of study.

FDA asked if patients will be withdrawn from the study if their troponins are elevated. Helsinn replied that if the patients' troponin rises, then they will be enrolled in a sub-study where their LVEF will be taken. If this measurement is above a specified threshold, the patient will be withdrawn from the study but will be followed.

Question #16: PK assessment. The PK plan is proposed to be submitted for FDA review with the revised (b) (4) when the (b) (4) protocol is re-submitted for FDA SPA.

FDA Response:

Your PK plan should be submitted separately from your SPA request.

Sponsor's 1/21/10 Reply for Discussion: *The PK Plan (which is for both (b) (4) and NETU-08-18) is planned to be submitted as a separate document in conjunction with the (b) (4) protocol for SPA; the SPA is planned to include a Sponsor's specific question regarding the acceptability of the overall PK Plan as described in the (b) (4) protocol and PK Plan. Please comment as needed.*

Meeting Discussion:

Helsinn indicated that they planned to include a question in their revised SPA regarding their PK plan, which will be submitted in a separate submission.

FDA replied that the sponsor may submit their PK plan and PK plan questions in a separate IND submission from the SPA request. The SPA request may contain an appendix with a synopsis of the PK plan and reference to the IND submission that contains the PK plan. The cover letter of the SPA request will contain a reference to the questions regarding the PK plan from the IND submission.

Question #17: Re-submission of the revised (b) (4) and the proposed PALO-10-XX protocol for FDA SPA review. The Sponsor plans to submit a revised (b) (4) protocol along with the proposed PALO-10-XX noninferiority protocol described above both (separately) for FDA SPA review.

FDA Response:

It is acceptable to submit protocol PALO-10-XX and your revised protocol separately at the same time for Special Protocol Assessment review. (b) (4)

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your reply.*

Meeting Discussion:

No meeting discussion.

2.2 CINV-MEC PROTOCOL (NETU-08-18) QUESTIONS

Question #1A: NETU-07-07 demonstration of the netupitant contribution to the combination.

Based on the above information, please advise us if you agree, as discussed during the EoP2 meeting, that NETU-07-07(HEC) was sufficient to also demonstrate the netupitant contribution to the combination for MEC as described above, and comment as needed.

FDA Response:

You must show the contribution of netupitant to the combination in MEC. The outcome of the HEC study, NETU-07-07, is inadequate on its own to establish the contribution of netupitant to the combination in MEC. The role of favorable outcomes in HEC trials for MEC development plans is the reduction in the number of trials that must be submitted to support the MEC indication.

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your comment. Please see Sponsor's Reply to Question 1B below.*

Meeting Discussion:

See meeting discussion section under CINV-MEC Question #1B.

Question #1B: NETU-08-18 active comparator. Based on the above considerations, the Sponsor requests that FDA please reconsider the acceptability of using (b) (4) palonosetron (b) (4) as the active comparator in NETU-08-18 to demonstrate the efficacy of the combination. Please comment as needed.

FDA Response:

Although (b) (4) palonosetron (b) (4) is technically acceptable as the active comparator in NETU-08-18 (MEC), it is not ideal. Non-inferiority between I.V. and oral palonosetron in MEC was based on a single study, where oral Aloxi had a numerically higher Complete Response (and the lower bound of two-sided 98.3% confidence interval was -6.5%). The cleanest path is to utilize the approved oral Aloxi as a comparator, since it is the 5-HT3 antagonist in the combination arm.

Sponsor's 1/21/10 Reply for Discussion: Thank you for your feedback that (b) (4) palonosetron (b) (4) is technically acceptable to use as the active comparator in NETU-08-18 (MEC). The Sponsor believes that NETU-08-18 comparing the Combination versus FDA-approved (b) (4) Aloxi (b) (4) provides a clinically relevant comparison to a very commonly used regimen. To help the Sponsor better understand FDA's feedback above, please clarify whether use of this comparator will be adequate in this study for purposes of demonstrating the contribution of netupitant in the Combination and for demonstrating the efficacy of the Combination. Please comment.

Meeting Discussion:

Helsinn believes that comparing the proposed combination product to the FDA approved (b) (4) palonosetron is a more relevant clinical comparison for a well recognized treatment. Helsinn noted that the approved oral palonosetron product is not currently used anywhere, whereas (b) (4) palonosetron is available in the US, making it a meaningful and more practical active comparator choice.

In conclusion, the sponsor pointed out the clinical relevance of using the palonosetron (b) (4) comparator, and that the approved palonosetron I.V. product has the acute and delayed phase indication for CINV-MEC. FDA will take the sponsor's points into consideration when during discussions with OMP.

Question #1C: Single components contribution to the combination to be cited in labeling.

Please confirm if the labeling indication will include the indication for the combination, i.e., will the indication reflect the results of the efficacy endpoint proposed for the combination, with an added statement in labeling regarding the contribution of the single component(s), all as described above. Please comment as needed. Please also refer to Sponsor's Follow-Up MEC Comment, Question #2 below.

FDA Response:

It is premature to comment on the details of labeling at this time. Labeling will be a review issue. As we have stated previously, it will be key to clearly state in the labeling the contribution of each component to the combination.

Sponsor's 1/21/10 Reply for Discussion: Thank you.

Meeting Discussion:

No meeting discussion.

Question #2: Adequacy of endpoints for the combination and labeling implication.

The Sponsor will accept to report information on the efficacy of each single component in the labeling. However, it is Sponsors understanding that the indication of the drug (i.e., the fixed combination product) will reflect the results of the efficacy endpoints proposed to register the combination in the pivotal trial. Please also see Sponsors question on labeling implications and proposed evaluation of the oral palonosetron component above - Sponsor's Follow-up Question #1C.

Please clarify if the proposed endpoints are acceptable to register the fixed dose combination product in the proposed indication, i.e. prevention of acute and delayed nausea and vomiting, provided that information on the efficacy of each single component will be reported in the labeling.

FDA Response:

Given that netupitant is expected to have its major effect in the delayed phase (oral palonosetron in the acute phase), we prefer that the primary endpoint for study

(b) (4)

(b) (4)

See the response to CINV-MEC question #1C.

Sponsor's 1/21/10 Reply for Discussion: *The Sponsor understands that for the target indication as currently proposed (please see Section 1.3 of the background package; "prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy"), this trial should show superiority on all three endpoints. However, recognizing that this single dose combination product is intended to address the clinical problem of nausea and vomiting during the overall 0-120 hour period which includes the delayed and acute phases, the Sponsor would like to test the following hierarchical order: primary endpoint as the overall phase followed by the delayed and acute phases, respectively. The Sponsor recognizes that ultimately the indication will be driven by the study outcomes on these three endpoints. Please address the acceptability of this approach and comment as needed.*

Meeting Discussion:

See the meeting discussion for CINV-HEC Question #2.

The division still believes that delayed phase should be tested first in the hierarchy but will discuss this further with the Office of Medical Policy (OMP). Feedback from the meeting with OMP will be provided to the sponsor after that discussion. We will also explore the possibility of simultaneously testing co-primary endpoints for acute and delayed phases.

Question #3: Multiplicity, key secondary endpoints. Thank you for your reply. The Sponsor agrees to change and use the gate-keeping sequential testing procedure or multiplicity adjustment (Hochberg). Regarding appropriateness of proposed endpoints and labeling constraints in relation to the single oral palonosetron component, please see Sponsor's request of clarification in Sponsor's Follow-up MEC Question #1C above.

FDA Response:

No response needed.

Question #4: Multiplicity, non-key secondary endpoints. Thank you for your reply.

FDA Response:
No response needed.

Question #5: Multi-cycle extension. Please see Sponsor's reply in Follow-up Question #11 below.

FDA Response:
No response needed.

Question #6: Inclusion/exclusion criteria. Thank you for your reply.

FDA Response:
No response needed.

Question #7: Sample Size. Thank you for your reply.

FDA Response:
No response needed.

Question #8: Randomization. Though it is difficult to predict, since breast cancer patients are likely to comprise the majority of participants in NETU-08-18 (MEC), the proportion of females and males is projected to be approximately 95% and 5%, respectively. This is why stratification by gender is not proposed, and instead stratification by age is planned since age is another important prognostic factor for CINV. Please comment as needed.

FDA Response:
Thank you for your clarification. We agree with your plan not to stratify by gender in MEC.

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your reply.*

Meeting Discussion:
No meeting discussion.

Question #9: Forced randomization. Sponsor agrees to avoid "forced randomization".

FDA Response:
No response needed.

Question #10: Overall statistical analysis. Sponsor agrees to use the stratified CMH test appropriately, and impute all missing data as treatment failures for the primary efficacy analysis.

FDA Response:

No response needed.

Question #11: Repeat cycles. The Sponsor acknowledges the need to collect significant safety data in repeat cycles in NETU-08-18. However, it appears to be accepted by all oncologists that 4 cycles of cyclophosphamide/doxorubicin is a standard regimen for breast cancer (MEC) [Jones SE, et al. J Clin Oncol, 24; 34: 5381 -5387, 2006]. Therefore all the patients enrolled will be given the possibility to undergo at least four cycles. The study will be closed after the last patient enrolled and still on treatment will have completed four cycles. In this situation some patients may undergo more than four cycles. This is a more conservative approach than the regulatory precedent Emend (which stopped the study after the fourth cycle for all patients).

This proposal is anticipated to meet FDA's request for safety data beyond the 5th cycle and will allow the NDA to be submitted in a reasonable timeframe for the Sponsor. Please advise us of the acceptability of this approach and comment as needed.

FDA Response:

Thank you for this information. Your approach is acceptable.

Sponsor's 1/21/10 Reply for Discussion: *Thank you for your reply.*

Meeting Discussion:

No meeting discussion.

Question #12: Safety measures. The Sponsor agrees.

FDA Response:

No response needed.

Question #13: Cardiac safety. The Sponsor acknowledges the importance of obtaining the FDA-requested standardized troponin assay using a central laboratory and agrees to implement this assay in NETU-08-18 (MEC).

Concerning the 12-hour additional sampling, the Sponsor wishes to note that cTnl levels increase in the first 72 hours after cardiac injury [Cardinale d, Sandri M, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004; 109: 2749-2754] and remain elevated longer than CK isoforms (beyond 8 days) [Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease. The present and the future. J Am Coll Cardiol. 2006; 48; 1-11]. Therefore sampling at intermediate timepoints does not appear to provide conclusive information. In addition, obtaining the 12 hour sample would be logistically extremely challenging based on the need to hospitalize the patient. For these reasons, the Sponsor proposes that no sample will be collected at 12 hours after dosing but the

Sponsor agrees to collect the 24-hour sample since the patient will undergo hospital visit on Day 2 (Visit 3).

The Sponsor plans to use the same echocardiography for both baseline and end-of study assessments in the same patient.

Please advise us of the acceptability of this approach and comment as needed.

FDA Response:

Please see the response to CINV-HEC question #15.

***Sponsor's 1/21/10 Reply for Discussion:** The Sponsor agrees to perform LVEF in all patients at baseline and at the end of each cycle for each patient.*

Meeting Discussion:

See the meeting discussion for CINV-HEC Question #15.

The sponsor clarified that LVEF will be performed on each patient at baseline and at the end of study.

Question #14: PK assessment. The PK plan is proposed to be submitted for FDA review with the revised NETU-08-18 protocol when the NETU-08-18 protocol is re-submitted for FDA SPA.

FDA Response:

Your PK plan should be submitted separately from your SPA request.

***Sponsor's 1/21/10 Reply for Discussion:** The PK Plan is planned to be submitted as a separate document in conjunction with the MEC clinical efficacy protocol SPA; the SPA is planned to include a Sponsor's specific question regarding the acceptability of the overall PK plan as described in the MEC clinical efficacy and safety protocol and PK Plan. Please comment as needed.*

Meeting Discussion:

See the meeting discussion for CINV-HEC Question #16.

The sponsor may submit their PK plan in a separate submission from the SPA request. The SPA request may contain an appendix with a synopsis of the PK plan and reference to the IND submission that contains the PK plan. The cover letter of the SPA request will contain a reference to the questions regarding the PK plan IND submission.

Question #15A: Mass balance study. As described in the EoP2 meeting background package (IND 73493, Serial #008 dated June 18, 2009, page 67), a clinical mass balance PK study on netupitant is planned.

FDA Response:
Your plan is acceptable.

Question #15B: Re-submission of the revised NETU-08-18 (MEC) protocol for FDA SPA review. The Sponsor plans to submit a revised NETU-08-18 (MEC) protocol for FDA SPA, incorporating all of the FDA-itemized issues.

FDA Response:
It is acceptable to submit your revised protocol NETU-08-18 for Special Protocol Assessment review.

Sponsor's 1/21/10 Reply for Discussion: *Thank you.*

Meeting Discussion:
No meeting discussion.

2.3 ADDITIONAL MEETING DISCUSSION

Helsinn asked if would be suitable to submit the revised SPAs for the CINV-HEC and CINV-MEC trials separated by a few weeks, rather than at the same time. FDA found this to be acceptable.

3.0 UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. FDA will review Helsinn's proposal of a 15% non-inferiority margin for trial NETU-10-XX with the sponsor's SPA submission. The sponsor is not required to submit additional information to support the proposed non-inferiority margin.
2. The division will discuss the recommended clinical endpoint testing hierarchy (delayed phase followed by acute phase, then overall phase) with the FDA Office of Medical Policy (OMP) and provide the sponsor with comments as needed.
3. The division will discuss with OMP the issue of using oral palonosetron 0.5 mg versus (b) (4) palonosetron (b) (4) as the active comparator in the proposed CINV-MEC trial. The sponsor will be provided with comments as needed.

4.0 ACTION ITEMS:

1. Helsinn will submit their NETU-07-07 full study report, including the statistical analysis plan and questions regarding the study, in a separate submission from the SPA request to the IND for FDA review. The sponsor's SPA submission may contain an appendix with a synopsis of the NETU-07-07 study report and a reference to IND submission containing the NETU-07-07 study report.
2. Helsinn will submit the DSMB Charter with their requests for special protocol assessment.

3. Helsinn will submit their PK plan, including questions regarding the plan, in a separate submission from the SPA request to the IND for FDA review. The sponsor's SPA submission may contain an appendix with a synopsis of the PK plan and a reference to IND submission containing the PK plan study report.
4. The review division will meet with OMP to discuss the proposed phase 3 clinical program. The review division will provide Helsinn with comments and recommendations per discussion at the meeting.

5.0 ATTACHMENTS/HANDOUTS:

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73493	GI-1	HELSINN HEALTHCARE SA	PALONOSETRON HCL / NETUPITANT

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/s/

JAGJIT S GREWAL
03/05/2010



IND 073493

MEETING MINUTES

Helsinn Healthcare SA
US Representative: August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 Capital of Texas Hwy, Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for netupitant plus palonosetron HCl fixed-dose combination capsule.

We also refer to the meeting between representatives of your firm and the FDA on July 20, 2009. The purpose of the meeting was to discuss your proposed phase 3 development program.

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

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 20, 2009
TIME: 10:30AM EST
LOCATION: FDA – White Oak Campus
10903 New Hampshire Avenue, Building #22
Silver Spring, MD 20993
APPLICATION: IND 73,493
DRUG NAME: Netupitant + Palonosetron HCl fixed-dose combination capsule
TYPE OF MEETING: Type B (End of Phase 2 meeting)
MEETING CHAIR: Nancy Snow, D.O., M.P.A
MEETING RECORDER: Jagjit Grewal, M.P.H.

FDA ATTENDEES:

Division of Gastroenterology Products

Donna Griebel, M.D.	Director
Anne Pariser, M.D.	Acting Deputy Director
Nancy Snow, D.O., M.P.A.	Acting Medical Team Leader
John Troiani, M.D., Ph.D.	Medical Reviewer
Tamara Johnson, M.D.	Medical Reviewer
David Joseph, Ph.D.	Acting Pharmacology Team Leader
Ke Zhang, Ph.D.	Pharmacology Reviewer
Jagjit Grewal, M.P.H.	Regulatory Project Manager

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Reviewer
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Office of New Drug Quality Assessment

Rajiv Agarwal, Ph.D.	Chemistry Reviewer
Tien Mien Chen, Ph.D.	Biopharm Reviewer

Division of Biometrics III

Michael Welch, Ph.D.	Team Leader
Freda Cooner, Ph.D.	Reviewer

Controlled Substances Staff

Katherine Bonson, Ph.D.	Pharmacologist
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EXTERNAL CONSTITUENT ATTENDEES:

Helsinn Healthcare SA

Dr. Annamaria Muraro	Manager, Statistics and Data Management
Dr. Angioletta Navini	Manager, Regulatory Affairs
Dr. Emanuela Lovati	Manager, Research and Preclinical Development

Dr. Gionata Frasca	Manager Technical Affairs
Dr. Fabio Trento	Senior Manager, Project and Operation Controller
Dr. Giada Rizzi	Manager, Statistics and Data Management
Dr. Giorgia Rossi	Manager, Corporate Clinical Development
Dr. Marco Palmas	Head of Corporate Clinical Development Unit 2
Dr. Roberta Cannella	Senior Manager, Technical Affairs
Dr. Sergio Cantoreggi	Senior Director, Head of Corporate R&D
Dr. Claudio Pietra	Senior Manager, Head of Research and Preclinical Development

(b) (4)

Dr. Craig Lehmann Authorized Representative/Consultant

BACKGROUND:

Helsinn Healthcare SA submitted a Type B, end of phase 2 meeting request dated April 20, 2009 to discuss their proposed phase 3 development plan for netupitant + palonosetron HCl fixed dose combination capsule. The proposed fixed dose combination capsule is being proposed for the following indications:

1. prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC)
2. prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC)

FDA granted Helsinn's meeting request in the letter dated May 12, 2009. Helsinn's meeting background package was received on June 19, 2009. FDA preliminary comments were sent to the sponsor on July 16, 2009.

As described in the meeting background package, Helsinn has completed a phase 2 dose-response study (NETU-07-07). This was a superiority study to compare the efficacy and safety of three single oral doses of netupitant (100 mg, 200 mg, 300 mg) combined with oral palonosetron (0.5 mg) and given with dexamethasone, versus oral palonosetron (0.5 mg) alone given with dexamethasone for the prevention of HEC induced nausea and vomiting. An additional study arm consisting of the FDA-approved regimen for oral aprepitant was included as an active comparator for exploratory purposes.

Additionally, Helsinn proposed the following phase 3 trials:

(b) (4)

2. NETU-08-18 (MEC): Superiority trial comparing oral palonosetron HCl + netupitant (0.5mg/300mg) combination capsule versus FDA-approved (b) (4) palonosetron HCl

(b) (4)

Helsinn proposed to use the completed phase 2 study NETU-07-07 [REDACTED] (b) (4) [REDACTED] to support efficacy for the HEC indication. If successful, the single planned phase 3 study NETU-08-18 was proposed to support the indication for MEC.

IND 73,493 is currently on inactive status per the sponsor's request pending the submission of additional pre-clinical data and/or clinical safety data for the netupitant + palonosetron HCl combination. Helsinn intends to request reactivation of the IND.

MEETING OBJECTIVE:

1. Discuss and reach agreement on Helsinn's proposed phase 3 development program.
2. Discuss requirements for reactivation of IND 73,493.

DISCUSSION POINTS:

Clinical/Statistical Program

Specific Question #1: Phase 3 efficacy program for the highly emetogenic CINV (HEC) indication. The proposed palonosetron + netupitant fixed-dose Combination capsule phase 2/3 clinical efficacy program for the HEC indication is described in Section 6.3. This HEC efficacy program is comprised of completed phase 2 HEC trial NETU-07-07 [REDACTED] (b) (4) [REDACTED]. Please advise us if this proposed efficacy program, if successful, is suitable to support the HEC target indication (please see Section 1.3) and for purposes of the planned fixed-dose combination capsule NDA. Please comment as needed.

FDA Response:

You propose to use the completed phase 2 HEC trial (NETU-07-07) as a confirmatory trial [REDACTED] (b) (4)

Although oral ondansetron and aprepitant are approved in the U.S. for CINV-HEC and CINV-MEC, oral palonosetron is approved only for CINV-MEC. You must show that oral palonosetron and netupitant individually contribute to the treatment effect. Currently, you do not have information to support that oral palonosetron is effective for CINV-HEC (and hence contributes to the treatment effect of the combination for this indication). For these reasons, the proposed study design is inadequate to support an application for your combination product for CINV-HEC.

Meeting Discussion:

FDA clarified that for phase 2 HEC trial NETU-07-07, the oral palonosetron active comparator is not sufficient to support efficacy for the proposed combination product because oral palonosetron is not approved for the HEC indication. Helsinn explained that although oral palonosetron is not approved for HEC, the oral palonosetron alone arm had an overall complete response rate greater than 70%, implying that that there is more activity than placebo or dexamethasone.

FDA stated that palonosetron (b) (4), has an established treatment effect for HEC and it may be advantageous to use the (b) (4) formulation for the combination product. Additionally, it is difficult to do a non-inferiority analysis with a comparator that has not been established. Helsinn explained that oral palonosetron was used per discussion at the pre-IND meeting.

Helsinn asked if there was another possible pathway to show efficacy for the HEC indication for the combination product. FDA suggested that an oral palonosetron effectiveness argument could be made per literature for placebo controlled studies. However this will be difficult as there may not be a lot of available literature. FDA clarified that the active comparator does not need to be approved for the proposed indication, but evidence must be provided that the active comparator is effective for the indication.

Helsinn asked if netupitant and oral palonosetron are shown to be effective for MEC individually, could this provide evidence of effectiveness for HEC, since the indications are closely related. FDA replied that this is not acceptable because the HEC population is more difficult to treat than the MEC population.

Helsinn stated that the phase 2 study results for palonosetron alone arm were close to the results for the aprepitant arm. Helsinn asked if additional subgroup analysis for female patients could be presented to show that palonosetron alone is equal to aprepitant, and therefore, support efficacy for palonosetron alone for HEC. DGP explained that the sponsor would need to show that the observed Complete Response (CR) rate is superior to what would be expected from placebo. The sponsor would need to compare the observed CR rates to that for placebo controlled studies found from the literature. FDA recommended that the sponsor look at previous antiemetic approvals to see what has been done in the past.

Helsinn inquired if phase 2 study NETU-07-07 was sufficient to fulfill the combination requirement for both HEC and MEC indications. FDA reiterated that more work will be needed for the HEC indication since oral palonosetron is not approved for this indication.

Helsinn asked FDA to confirm that an individual netupitant monotherapy study is not needed to support the effectiveness of netupitant to fulfill the combination rule requirement. FDA confirmed that the sponsor's phase 2 study confirmed that netupitant was effective for the proposed indication.

Helsinn proposed using (b) (4) palonosetron as the active comparator and changing the trial to superiority design similar to the MEC trial design. This was discussed later in Question #2.

Helsinn requested that FDA clarify the last sentence from the preliminary comment indicating that proposed study design is inadequate to support a CINV-HEC indication. FDA explained that this statement specifically refers to the proposed combination product arm because the treatment effect of oral palonosetron for HEC has not been established.

Specific Question #2: Phase 3 efficacy program for the moderately emetogenic CINV (MEC) indication. The proposed fixed-dose combination Capsule phase 3 clinical efficacy program for the MEC indication is described in Section 6.4. This MEC efficacy program is comprised of one planned phase 3 MEC efficacy trial, NETU-08-18, considered in conjunction with the phase 2/3 HEC trials described in Specific Question #1 above. Please advise us if this proposed efficacy program, if successful, is suitable to support the MEC target indication (please see Section 1.3) for the planned NDA. Please comment as needed.

FDA Response:

The phase 3 MEC trial is a superiority trial with a control group receiving (b) (4) palonosetron alone compared to a netupitant and palonosetron combination capsule. It will enroll approximately 1500 women (750 per group). Why are you using an (b) (4) comparator in this add-on design? We recommend that you should use oral palonosetron as the comparator.

Because you have not identified an appropriate HEC study design, you will need to conduct at least two adequate, well-controlled MEC studies.

Meeting Discussion:

Helsinn asked if either formulation of palonosetron could be used as the active comparator. FDA's preliminary response to Question #2 recommends using oral palonosetron while the preliminary response to Question #5a refers to (b) (4) palonosetron. FDA clarified that the preliminary response to question #5a focuses on the endpoints, and that (b) (4) palonosetron should be used as the active comparator since it is approved for both the acute and delayed phases.

Helsinn inquired if two adequate, well-controlled MEC studies would still be needed if an (b) (4) palonosetron arm was implemented in the proposed HEC studies. FDA stated that HEC studies have been accepted to support proposed MEC indications. FDA clarified that if a path forward cannot be found for the HEC indication, then two MEC studies will be needed.

Helsinn revised their phase 3 trials as follows:

- **CINV-HEC:** combination oral palonosetron + netupitant versus I.V. palonosetron
- **CINV-MEC:** combination oral palonosetron + netupitant versus (b) (4) palonosetron

Helsinn proposed both studies to be superiority trials demonstrating the efficacy of the combination product and to fulfill the combination drug rule requirements recognizing that oral palonosetron is not approved for CINV-HEC. Helsinn also acknowledged that the standard of care for CINV-HEC is use of a NK-1 receptor antagonist. FDA noted that the sponsor's proposal may be possible if it is ethical to use (b) (4) palonosetron alone for CINV-HEC. Helsinn stated that per the MD Anderson Cancer Center, (b) (4) palonosetron may be used as a community standard for HEC. FDA reiterated that superiority trials are preferred.

Specific Question #3: Fixed-dose Combination Capsule dose selection for phase 3 clinical trials. Rationale and supporting data for selecting the netupitant dose and the palonosetron dose for the single-strength, fixed-dose Combination Capsule planned for evaluation in HEC and MEC phase 3 trials are described in Section 5.3. Please advise us of the suitability of the proposed netupitant dose and palonosetron dose for the Fixed-dose combination Capsule planned for use in both HEC and MEC phase 3 trials. Please comment as needed.

FDA Response:

The proposed netupitant dose for the fixed-dose combination capsule planned for use in both HEC and MEC phase 3 trials is acceptable. It is unclear if 300 mg netupitant confers any additional benefit over 100 mg netupitant, as there is no clear dose-response relationship among the three dose levels. Although 300 mg showed statistically significant superiority to palonosetron in most endpoints, the combination at 100 mg was superior to palonosetron alone for the overall and delayed phases. Additionally, the response rate of the exploratory aprepitant group was numerically similar to that of the other netupitant doses.

See responses to Questions #1 and #2 for our comments regarding palonosetron.

Specific Question #4: Planned phase 3 HEC pivotal efficacy trial

(b) (4) (b) (4)

FDA Response:

See response to Question #1.

Specific Question #4a:

(b) (4)

(b) (4)

FDA Response:

(b) (4)

Specific Question #4b:

(b) (4)

(b) (4)

Specific Question #5: Planned MEC phase 3 efficacy trial NETU-08-18. NETU-08-18 is the sole phase 3 efficacy study planned to demonstrate efficacy for the moderately emetogenic CINV (MEC) indication cited in Section 1.3. The proposed NETU-08-18 protocol design, objectives, study hypothesis, patient population, active comparator, endpoints, sample size and analyses are described in Section 6.4.1 and the full draft NETU-08-18 protocol is at Appendix #5. This protocol is planned for FDA SPA, however, the Sponsor wishes to be sure the basic proposed protocol characteristics are reasonably close the FDA expectations before the SPA submission. Please advise us of the suitability of the NETU-08-18 MEC protocol as described in Section 6.4.1 and Appendix #5 for purposes of demonstrating fixed-dose Combination Capsule efficacy, supporting the proposed indication (please see Section 1.3) and the planned NDA. Please comment as needed.

FDA Response:

See response to Question #2. Based on your current proposal, you will need two MEC studies to support your efficacy claims. We recommend that at least one of your two studies include a substantial number of male patients.

Specific Question #5a: NETU-08-18 (MEC) potential efficacy outcomes. NETU-08-18 is planned to evaluate the superiority of the palonosetron + netupitant fixed-dose Combination Capsule over FDA-approved IV palonosetron (Aloxi™) for the proposed MEC target indication

(please see Section 1.3), i.e., for the prevention of acute and delayed nausea and vomiting associated with MEC. IV Aloxi™ is FDA-approved for the prevention of both acute phase (0-24h) and delayed phase (24-120h) MEC CINV.

Please advise us if study NETU-08-18 demonstrates superiority of the fixed-dose Combination Capsule over IV Aloxi™ for the primary efficacy endpoint (CR 0-120 hours), will this be sufficient to support proposed target labeling for MEC (please see Section 1.3).

FDA Response:

Your planned efficacy evaluation is acceptable. The current label for I.V. palonosetron CINV-MEC provides efficacy results for acute (0-24hr), delayed (24-120hr), and overall (0-120hr) phases. In addition the division has accepted 0-120 hrs as a primary endpoint for a prior submission for a drug of this class, with 0-24 and 24-120 studied as secondary endpoints. Finally, at a 14 June 2006 teleconference between the division and Helsinn, it was agreed that “the 0 to 120 hours complete response would be acceptable as the primary endpoint of efficacy.”

Specific Question #5b: NETU-08-18 (MEC) repeat cycles and efficacy evaluation. As described in Section 6.4.1.10, patients will have the option to participate in a multiple-cycle extension phase of the study which will include up to 2 additional chemotherapy cycles (total maximum of up to 3 cycles). In each repeated cycle, the proportion of patients with CR and the proportion of patients with no significant nausea will be evaluated in the overall 0-120 hour period. These data are proposed to be summarized in a frequency table by cycle, i.e., a descriptive analysis only will be presented. Please advise us if this proposed number of repeat cycles and proposed evaluation is adequate, if the data are favorable, to support inclusion of the “repeat courses” wording in the proposed MEC indication in Section 1.3. Please comment as needed.

FDA Response:

Given the nonclinical findings (i.e., accumulation of drug and metabolites in dog myocardium), you would need safety data after repeat cycles of therapy (i.e., ≥ 4 cycles).

Meeting Discussion:

See meeting discussion for Question #4b.

Specific Question #6: Fixed-dose combination prescription drug regulatory requirements.

21CFR300.50 for fixed-dose combination prescription drug indicates that each component should make a contribution to the claimed effects, i.e., in this case, that palonosetron and netupitant in the fixed-dose Combination Capsule should each make a contribution to efficacy. Phase 2 clinical trial NETU-07-07 described in Section 5.2 demonstrated improved efficacy of the fixed-dose Combination (with dexamethasone) versus palonosetron (with dexamethasone) using the same palonosetron plus netupitant fixed-dose combination dose planned for phase 3 trials. Clinical trials comparing the fixed-dose Combination Capsule versus netupitant alone are not ethically feasible since NK-1 receptor antagonists (as a class) by themselves generally do not provide adequate acute phase (0-24 hour) protection against CINV. Recognizing that the proposed

(b) (4)

and the proposed phase 3 NETU-08-18 (MEC) efficacy trial

plans to use FDA-approved (b) (4) palonosetron (Aloxi™) as the active comparator, (i.e., these comparators are other than the components/routes in the oral fixed-dose combination Capsule), the Sponsor proposes that phase 2 trial NETU-07-07 serve to meet the requirements of 21 CFR 300.50 for purposes of the planned NDA program, and that no further clinical efficacy studies of the fixed-dose Combination Capsule versus its separate active constituents are required. Please advise us if FDA agrees with this approach and comment as needed.

FDA Response:

An add-on trial design with a superiority analysis is appropriate for a MEC indication. However, see the response to Question #2.

See the response to Question #1 regarding the HEC indication. The phase 2 study does not establish the efficacy of oral palonosetron for the prevention of CINV-HEC.

Meeting Discussion:

See meeting discussion for Questions #1 and #2.

Specific Question #7: Safety measures in phase 3 trials. As described in proposed MEC phase 3 protocol NETU-08-18 (please see Appendix #5) (b) (4) each include provisions to assess safety in the first cycle through up to 3 cycles of chemotherapy, all in a double-blind fashion. Please advise us if the safety measures proposed for these phase 3 protocols are suitable for purposes of the planned NDA safety database. Please comment as needed.

FDA Response:

We are concerned about the findings of accumulation of netupitant and its metabolites in heart tissue taken from female dogs at the end of a 4-week toxicology study. Although you note that tQT study 07-20 did not show evidence of significant QT prolongation and that “the relevance of these data (preclinical) should be considered in relation to the proposed single administration,” we strongly urge you to incorporate additional cardiovascular safety monitoring such as measurement of troponin in your protocol. Although CK-MB, CK, and myoglobin will be obtained, troponin (TN) is a more sensitive indicator of myocardial injury.

It may be important to evaluate the safety of netupitant with chemotherapeutic agents representing a range of cardiotoxicity.

See responses to the above questions regarding duration of exposure.

Meeting Discussion:

Helsinn agreed to add troponin monitoring to their phase 3 trials. Helsinn asked if the MEC trial to include anthracyclines and the HEC trial without anthracyclines would be sufficient to address a range of cardiotoxic chemotherapeutic agents. FDA replied that the sponsor’s proposal was acceptable.

Specific Question #8: Proposed NDA clinical safety database. As described in Section 6.6, please advise us of the acceptability of the proposed NDA clinical safety database, including the total number of subjects planned by dose/exposure for this single-dose treatment. Please comment as needed.

FDA Response:

See responses to previous questions.

Specific Question #9: Proposed pediatric study plan. As described in Section 6.7, for the purposes of selecting pediatric study doses for the fixed-dose combination for the NDA pediatric assessment, the safety and efficacy of the palonosetron + netupitant oral fixed-dose combination in adults will not be sufficiently known until after adult phase 3 clinical trials are completed. For this reason, the NDA for adult use of the fixed-dose Combination Capsule is planned to include a request for (b) (4) and deferral, based on age groups, of the planned pediatric assessment (see Section 6.7). Please advise us of the acceptability of this overall approach and comment as needed.

FDA Response:

You should attempt to develop an age appropriate formulation. We cannot agree to a (b) (4) or deferral at this time.

Biopharm Program

Specific Question #10: Biopharm/PK data to support initiating phase 3 clinical trials.

Completed phase 1 biopharm/PK trials are described in Section 4.3, 4.4. Please advise us if these phase 1 studies and data are adequate to start the planned phase 3 trials outlined in Section 6.0. Please comment as needed.

FDA Response:

Completed phase 1 studies are acceptable to initiate the planned phase 3 trials.

Specific Question #11: Biopharm/PK study program for the NDA. The overall planned biopharm/PK program to support the planned NDA, including planned drug-drug interaction studies, bridging, and other studies are described in Biopharm Sections 4.0 and 4.5. Please advise us of the acceptability of this overall Biopharm/PK program for purposes of the planned NDA and comment as needed.

FDA Response:

We note that you plan on conducting in vivo drug interaction studies with chemotherapeutics which are CYP3A4 substrates based on in vitro interaction studies. It is unclear if you actually obtain Ki from in vitro study. We recommend that you try to obtain Ki value and also justify why representative substrate from a class of chemotherapeutics was considered most sensitive. We suggest that you prioritize in vivo drug interaction potential based on Cmax/Ki and conduct an in vivo study(ies) with chemotherapeutics with the greatest Cmax/Ki. Depending on the results, additional in vivo drug interaction studies may be necessary.

We recommend that pharmacokinetics of major active metabolites be adequately characterized, as apparently there is a metabolite(s) which is equipotent e.g. M3 to netupitant and present at ~ 30% of AUC of netupitant.

We note that you conducted PK study using intravenous formulation of netupitant although it was not discussed in this background package. We request that the results of intravenous PK study be submitted to NDA.

We recommend that potential induction of CYP enzymes by netupitant be addressed.

Specific Question #12: Bridging phase 2 study NETU-07-07 Combination test articles to the phase 3 fixed-dose Combination Capsule (to be used in phase 3 trials (b) (4) and NETU-08-18), and bridging the phase 3 fixed-dose Combination Capsule to the proposed NDA to-be-marketed Fixed-dose combination Capsule. The plan to bridge (using an in-vivo comparative bioavailability study) the palonosetron + netupitant Combination test articles used in phase 2 trial NETU-07-07 to the fixed-dose Combination Capsule formulation planned for use in the two proposed phase 3 trials ((b) (4) and NETU-08-18) is described in Biopharm Section 4.5.1 (see Planned Bridging Program). In addition, the plan to bridge (using SUPAC-based dissolution data) the phase 3 fixed-dose Combination Capsule drug product manufactured at (b) (4) and the proposed NDA to-be-marketed fixed-dose Combination Capsule drug product manufactured at Helsinn Birex, Ireland (same formulation), is described in CMC/Quality Section 8.8; BCS information for palonosetron and netupitant are in Biopharm Section 4.5.1.2. Fixed-dose Combination Capsule batches at the site planned to be cited in the NDA for commercial manufacture of fixed-dose Combination Capsule drug product are not planned for use in phase 3 clinical studies. Please advise us of the acceptability of this overall bridging plan and comment as needed (This Specific Question is essentially the same as CMC/Quality Specific Questions #27 and #28)

FDA Response:

Your proposed relative BA study between products for phase 2 and phase 3 trials is acceptable. We however note that you plan to (b) (4) the BE criteria for Cmax based on (b) (4). Our standard BE criteria will remain as 80-125% and the acceptability of your relative BA results will be a review issue.

It is acceptable to bridge (using SUPAC-based in vitro dissolution data) the phase 3 fixed-dose combination capsule drug product (b) (4), and the proposed NDA to-be-marketed fixed-dose combination capsule drug product (to be manufactured at Helsinn Birex, Ireland; same formulation).

According to SUPAC guidance for an immediate release solid oral dosage form, you need to:

- 1. First develop an acceptable dissolution methodology.
Please refer to the Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms:**

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm>

2. For a Level (b) change (for manufacturing site) and a Level (b) change (for equipment), conduct multiple-point dissolution profiles in (b) (4).
(b) (4)
Adequate sampling should be performed at (b) (4) and (b) (4) until either (b) (4) of drug from the drug product is dissolved or an asymptote is reached. A (b) (4) may be used with appropriate justification (under 2.b.ii, (b) (4) for equipment).
3. Show the dissolution profiles of the drug product at the current (Phase 3 trial batch) and the proposed sites (to-be-marketed; stability batches) are similar in terms of f2 value calculation (values between 50-100).
4. Propose dissolution specifications for the product.
5. Submit the above dissolution information with a biowaiver request to the NDA for review.

Meeting Discussion:

Helsinn stated that they believe the manufacturing site change to be a Level (b) and the equipment equivalency to be a Level (b) (4). FDA replied that this determination is made on a case by case basis. The FDA preliminary response is a conservative approach based upon currently available information. The sponsor can provide their justification with the NDA submission for review.

Helsinn noted that they will continue to evaluate the equipment. If they proceed with (b) (4) then they may request a follow-up discussion regarding the dissolution media. Helsinn is still developing the dissolution methods. FDA reiterated that the preliminary response is a conservative, general statement based upon the available information. The Agency, however, agreed that the sponsor may submit their justification and concept for review prior to the pre-NDA meeting and submission of the NDA.

FDA reminded the sponsor that in order to link to the approved Aloxi labeling information in the Clinical Pharmacology section, the issue of changing the formulation of palonosetron (Table 8.7:1, page 194 of meeting package) needs to be addressed under the biowaiver request and appropriate rationale and justification should be provided in writing.

Specific Question #13: Plan to rely on FDA-approved Aloxi™ labeling for oral palonosetron monotherapy clinical pharmacology, drug interaction and special population biopharm/PK data. In the planned fixed-dose Combination Capsule 505(b)(1) NDA, the Sponsor plans to rely on and reference current FDA-approved IV and oral palonosetron (Aloxi™) labeling (a copies are in Appendix #2) from NDA 21-372 and NDA 22-233, both sponsored by Helsinn, to convey applicable oral palonosetron monotherapy clinical pharmacology (PK/PD information), drug interaction information, and specific population information to Fixed-dose combination Capsule labeling. Separately, similar types of data from de novo biopharm/PK/PD

studies on netupitant monotherapy and on the fixed-dose Combination all as described in Biopharm Section 4.0 are planned to be included in the fixed-dose Combination Capsule NDA to support proposed labeling. Please advise us if this plan to convey palonosetron monotherapy information from IV and Oral Aloxi labeling to fixed-dose Combination Capsule labeling is acceptable for the planned 505b1 NDA. Please comment as needed.

FDA Response:

Your plan is acceptable, as long as the drug-drug interaction study between palonosetron and netupitant was deemed to be adequate.

Specific Question #14: Special patient population PK program. The proposed overall special patient population PK program for the NDA is described in Section 4.5.1. Please advise us if this proposed program is acceptable for purposes of the planned NDA, and comment as needed.

FDA Response:

Your plan is generally acceptable. As a general comment, we recommend including a sufficient number of elderly patients (≥ 65 years old) in your clinical trials, so that a meaningful conclusion on safety and efficacy for this important subgroup population can be drawn.

We suggest that you include subjects with severe hepatic impairment in the hepatic impairment study.

Based on your summary of phase 1 studies and the intended single dose use, it appears that a full renal impairment study may not be necessary. However, we recommend that you consider evaluating the effect of severe renal impairment and dialysis on PK of netupitant and major active metabolites (Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling).

Specific Question #15: Fixed-dose combination capsule netupitant and palonosetron PK in CINV patients. The study plan to describe the PK of the fixed-dose Combination Capsule in CINV patients is described in Section 4.5.1. Please advise us if this approach is acceptable for purposes of the planned NDA and for purposes of including CINV patient PK data in proposed labeling. Please comment as needed.

FDA Response:

It is acceptable. Nonetheless, we recommend that you collect sparse PK samples for netupitant and major active metabolites in your phase 3 trials to evaluate the effects of various covariates, including but not limited to renal function, on PK of netupitant and major active metabolites.

Meeting Discussion:

Helsinn noted that they will address the population PK for HEC and MEC with their request for phase 3 special protocol assessment. FDA agreed that it was acceptable to address this with the request for special protocol assessment.

Specific Question #16: Food effect evaluation. A food effect bioavailability study has been completed on netupitant given alone; please see a summary of Study NP16600 in Section 4.4.2. Oral palonosetron absorption is not affected by a high fat meal as described in Oral Aloxi® labeling (a copy of IV and Oral Aloxi labeling is in Appendix #2). Given this information, the Sponsor proposes that a food-effect bioavailability study on the planned to-be-marketed netupitant plus palonosetron fixed-dose Combination Capsule formulation is not required for the NDA program. Please advise us if this approach is acceptable and comment as needed.

FDA Response:

We do not agree because Study NP16600 was conducted with an early capsule formulation of netupitant and the to-be-marketed combination capsule will contain a tablet of netupitant. We note that you plan to conduct a food effect with the to-be-marketed combination capsule in section 4.5.1. and agree with your plan.

Specific Question #17: Phase 1 clinical study reports to be submitted to the IND. At the FDA pre-IND meeting April 5, 2006 (FDA minutes are in Appendix #1), FDA asked that the Sponsor submit full reports of completed phase 1 (and pharm/tox) studies to the IND instead of summarizing them in the IND (the IND is a traditional paper, non-eIND). Collectively, these studies are voluminous. Please confirm if you wish to have all completed phase 1 study reports, as described in the background package, to be submitted to the IND. Please comment as needed.

FDA Response:

Full reports of all completed studies should be submitted to the IND.

Pharm/Tox Program

Specific Question #18: Adequacy of the proposed pharm/tox program to support starting planned phase 3 clinical trials. Completed pharm/tox studies for netupitant-alone and the netupitant + palonosetron combination are described in Section 7.0. Please advise us if these pharm/tox studies are sufficient to support initiating the phase 3 clinical trials described in Section 6.0. Please comment as needed.

FDA Response:

The completed nonclinical studies are appropriate for supporting the proposed clinical studies. However, we need to review the study reports to determine whether the nonclinical studies provide a reasonable assurance of safety.

Specific Question #19: Plan to rely on FDA-approved Aloxi™ labeling for palonosetron monotherapy toxicology data. In the planned 505b1 NDA, the Sponsor plans to rely on and reference current FDA-approved IV and oral palonosetron (Aloxi™) labeling (copies are in Appendix #2) from NDA 21-372 and NDA 22-233, both sponsored by Helsinn, to convey

applicable palonosetron monotherapy mutagenicity, reprotox and carcinogenicity data and information to fixed-dose Combination Capsule labeling. Separately, pharm/tox data for netupitant monotherapy and for the Combination all as described in Section 7.0 are planned for inclusion in the NDA to support labeling. Please advise us if this plan to convey palonosetron monotherapy information from IV and Oral Aloxi labeling to fixed-dose Combination Capsule labeling is acceptable for the planned 505b1 NDA. Please comment as needed.

FDA Response:

Yes, your plan is acceptable.

Specific Question #20: Overall pharm/tox program to support the planned NDA. The overall pharm/tox program planned for the netupitant + palonosetron fixed-dose Combination Capsule NDA is described in Section 7.0. Please also see FDA feedback regarding carcinogenicity studies in previous FDA correspondence dated July 2, 2008 and July 22, 2008, in Appendix #1. Please advise us of the adequacy of the overall proposed pharm/tox NDA program and comment as needed.

FDA Response:

The proposed nonclinical NDA program appears adequate. However, a Segment III reproductive/developmental toxicity study is also needed (see response to question #22).

Netupitant is a new molecular entity with a novel mechanism of action within the central nervous system. In order to determine whether netupitant has abuse potential, the following information should be submitted to the Controlled Substances Staff for review:

- 1. A full receptor binding profile for netupitant and all metabolites that are present at greater than 10% of parent drug systemic exposure at steady state (e.g., M1 and M3)**
- 2. Safety pharmacology in animals, especially with regard to behavioral studies**
- 3. A summary of adverse events reported during clinical studies with netupitant, with an emphasis on neurological and psychiatric AEs**

Based on a review of the above information, additional studies may be required to further assess netupitant if there is evidence of CNS stimulation or depression, or if receptor binding suggests similarity to known drugs of abuse.

Specific Question #21: Pharm/Tox study reports to be submitted to the IND. At the pre-IND meeting April 5, 2006 (FDA minutes are included in Appendix #1), FDA asked that the Sponsor submit full reports of pharm/tox (and clinical phase1) studies to the IND instead of summarizing them in the IND (as in the original IND submission). As evident from the summary of pharm/tox studies in Section 7.0 and in Appendix #3 herein, there are many pharm/tox study reports (collectively voluminous) that remain to be submitted to the IND (this is a traditional paper IND; not an eIND). Please confirm if you wish to have all of these pharm/tox study reports submitted to the IND, or alternatively, please clarify which pharm/tox study reports, if any, you wish the Sponsor to submit. Please comment as needed.

FDA Response:

The full reports of all completed nonclinical studies should be submitted.

Specific Question #22: Segment III Reprotox Data. Please see Section 7.3.3.4 (and Appendix #3) of the background package which describes reprotox studies completed in support of the netupitant Combination pharm/tox program. The netupitant reprotox program plan does not include a Segment III reprotox study. Please advise us of the acceptability of this plan to support phase 3 and the planned NDA submission. Please comment as needed.

FDA Response:

The Segment III reproductive toxicity study should be conducted with netupitant and the report of this study should be submitted with the NDA.

CMC/Quality Program

Specific Question #23: Adequacy of proposed overall CMC/Quality program in support of phase 3 and the planned NDA. Please advise us of the acceptability of the proposed overall CMC program as described in Section 8.1 through Section 8.8 for purposes of supporting the proposed phase 3 clinical program and the planned NDA. An overview of the drug product is presented in Section 8.1. Specific questions pertaining to the drug substance synthesis and specifications and drug product manufacturing strategy and specifications are presented below in Questions 24 - 28. Background information supporting the questions is presented in Sections 8.2 - 8.8. Please comment as needed.

FDA Response:

At this time your proposal appears to be adequate. However, the data and information provided in each section will be reviewed in detail during the NDA review cycle. Please refer to “Guidance for Industry: M4Q: The CTD-Quality, August 2001”.

Specific Question #24: Starting materials for netupitant synthesis. Please advise us if FDA agrees with the designation of [REDACTED] (b) (4) as starting materials in the netupitant synthesis process as described in Section 8.2. Please comment as needed.

FDA Response:

The two intermediates, [REDACTED] (b) (4) may be designated as the ‘starting material’ provided that:

- **Full information on the synthetic process for each ‘starting material’ is provided either in the NDA or in a DMF with the appropriate Letter of Authorization.**
- **A commitment is made that the listed manufacturer(s) of each ‘starting material’ are the only manufacturers of the starting materials and that if there is any change in the manufacturing process at these sites or a new manufacturer is introduced after the NDA is approved, applicant will notify the FDA via a prior approval supplement.**

Meeting Discussion:

Helsinn stated that they will provide information on the synthetic process of the starting materials in the NDA. Additionally, Helsinn may submit the comparability protocol related to the second bullet point with the NDA. FDA agreed that it would be acceptable to submit the comparability protocol with the NDA submission.

Specific Question #25: Approach to establish drug substance specifications. Please advise us if FDA agrees with the approach for establishing drug substance specifications for netupitant (described in Section 8.2) and palonosetron HCl (described in Section 8.3). Please also advise us if FDA agrees to the specific approach described for establishing specifications of impurities, including evaluation of potential genotoxic impurities as described in Section 8.2, (also see Annex 1, and Annex 2 both in Section 8.2) for netupitant and Section 8.3 for palonosetron HCl. Please comment as needed.

FDA Response:

At this time your proposal appears to be adequate. However, the final specification will be established based on the review of the data submitted in the NDA.

Additionally, based on the synthetic pathway, including (b) (4) steps of netupitant and palonosetron HCl, please address the formation of potential genotoxic impurities with a validated analytical method to detect and quantitate the potential genotoxic impurities. Analytical methods must be able to assure that the potential genotoxic impurities are not at a level that is associated with a maximum daily intake of (b) (4) per person per day by taking 300 mg of netupitant tablets and 0.5 mg of palonosetron oral capsules. Please refer to “Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008”.

Meeting Discussion:

Helsinn requested FDA to confirm their evaluation of genotoxic impurities and the conclusion that additional genotoxic studies are not needed. FDA replied that it is too early to confirm the sponsor’s position. Helsinn should submit their information and justification with the NDA per the available guidance. FDA will review the data and make a determination if the limits and impurities are acceptable.

Helsinn asked if FDA could provide advice on how the structural identity is evaluated. FDA referred the sponsor to the available guidance. Additionally, the chemistry reviewer noted that the modeling group and the pharmacology/toxicology team are consulted for their recommendations.

Helsinn inquired if they could provide information prior to the pre-NDA meeting to determine if any impurities need to be included in genotox studies. FDA stated that the amount of impurities are also important, which the sponsor will not have available prior to the NDA submission. Helsinn replied that they will have data on the API prior to submission of the NDA. FDA agreed that the sponsor may submit the information prior to submission of the NDA, but the information may not be reviewed until the NDA has been received.

Helsinn asked if the available information on palonosetron as currently approved is acceptable. FDA agreed that the currently marketed information on palonosetron is acceptable. FDA cautioned the sponsor on the potential interaction between netupitant and palonosetron and that the same impurities should be present from batch to batch.

Specific Question #26: Adequacy of proposed drug product specifications for phase 3 clinical trials and the planned NDA. Please advise us if FDA agrees with the approach for establishing specifications, and the proposed specifications for the final fixed-dose Combination netupitant/palonosetron Capsule drug product, described in Section 8.5), Netupitant 100 mg Tablets (a component of the fixed-dose Combination Capsule) (described in Section 8.6) and Palonosetron 0.5 mg Oral Capsules (also a component of the fixed-dose Combination Capsule) (described in Section 8.7). Please comment as needed.

FDA Response:

At this time your proposal appears to be adequate. However, the final specification of netupitant 100 mg tablets, palonosetron 0.5 mg oral capsules, and the final fixed-dose combination netupitant+palonosetron capsule drug product will be established based on the review of the data submitted in the NDA.

Specific Question #27: Bridging phase 2 study NETU-07-07 Combination test articles to the phase 3 fixed-dose Combination Capsule (to be used in phase 3 trials (b)(4) and NETU-08-18). The plan to bridge (using an in-vivo comparative bioavailability study) the palonosetron + netupitant Combination test articles used in phase 2 trial NETU-07-07 to the fixed-dose Combination Capsule formulation planned for use in the two proposed phase 3 trials (b)(4) and NETU-08-18) is described in Biopharm Section 4.5.1 (see Planned Bridging Program). (This Specific Question is also presented in the Biopharm Specific Question #12)

FDA Response:

See response to Question #12.

Specific Question #28: Commercial drug product manufacturing site. As described in Section 8.8, the fixed-dose Combination Capsule drug product planned to be used in phase 3 studies will be produced at (b)(4). For commercial drug product, production of the Netupitant Tablets (which are inserted as a component in the fixed-dose Combination Capsule) and the final fixed-dose Combination Capsule drug product manufacturing processes are planned to be transferred to Helsinn Birex, Ireland, for commercialization and inclusion in the original NDA. Fixed-dose Combination Capsule batches manufactured at Helsinn Birex are not planned for use in phase 3 clinical studies and no bioequivalence study is planned to bridge phase 3 material with the proposed commercial. Dissolution comparisons will be performed in accordance with SUPAC-IR Case B requirements. Please advise us if FDA agrees to the development and regulatory strategy described in Section 8.8 for inclusion of Helsinn Birex, Ireland, as a site of commercial manufacture of Netupitant Tablets and the netupitant/palonosetron Fixed-dose combination Capsule drug product, in the original NDA submission. Please comment as needed.

FDA Response:

See response to Question #12.

Meeting Discussion:

See meeting discussion for Question #12.

Regulatory Program

Specific Question #29: Planned reactivation of the IND to start phase 3 clinical trials. The IND was temporarily inactivated by the Sponsor in October 2006, pending submission of additional safety data for the netupitant plus palonosetron combination. Presently, as described in Sections 7.0, 4.0 and 5.0, a broad array of preclinical and clinical safety data, including E14 Thorough QT clinical study data, on the netupitant plus palonosetron combination are available. Please advise us if these data are suitable for purposes of reactivating the IND and starting the phase 3 trials outlined in the background package. Please comment as needed.

FDA Response:

Per 21 CFR312.45(d), clinical investigations under your inactive IND may only be initiated:

1. 30 days after FDA receives your request to resume clinical studies, unless FDA notifies you that the investigations described are subject to clinical hold, or
2. on earlier notification that the clinical investigations described in the request may begin.

Your request should include a protocol amendment containing the proposed general investigational plan for the coming year and appropriate protocols.

The data may be suitable for reactivating your IND, but a thorough review of these data is beyond the scope of this meeting. We encourage you to submit completed study reports, particularly the thorough QT study report, as soon as possible.

Meeting Discussion:

Helsinn asked if all non-clinical study data are needed. FDA clarified that toxicity studies for the proposed combination product are needed for reactivating the IND. FDA agreed that the sponsor does not need to submit their clinical protocol for review with the request for IND reactivation.

Specific Question #30: Planned 505b1 NDA submission. Since oral palonosetron NDA 22-233 and IV palonosetron NDA 21-372 are FDA-approved for the prevention of CINV, both sponsored by Helsinn, the planned market application for the netupitant plus palonosetron fixed-dose Combination Capsule is proposed to be a 505b1 NDA. This NDA is planned to contain data for netupitant and for the netupitant plus oral palonosetron combination as described herein, and reference IV palonosetron NDA 22-233 and oral palonosetron NDA 22-372 to convey applicable data such as palonosetron toxicology (mutagenicity, reprotox and carcinogenicity) and biopharm/PK data to fixed-dose Combination Capsule labeling. Please advise us if this plan for

referencing such data and submission via the 505b1 NDA route is acceptable. Please comment as needed.

FDA Response: It is acceptable to submit your application via the 505(b)(1) NDA pathway and reference your data for palonosetron I.V. (NDA 21-372) and oral palonosetron (NDA 22-233).

Overall Proposed Fixed-dose Combination Capsule NDA Program

Specific Question #31: Overall fixed-dose Combination Capsule development plan. Please advise of the acceptability of the overall fixed-dose Combination Capsule development program for purposes of initiating phase 3, and for supporting the planned NDA. We do not wish to miss anything not covered above. Please comment as needed.

FDA Response:

See responses to above questions.

DECISIONS (AGREEMENTS) REACHED:

1. A separate netupitant monotherapy study is not needed to support the effectiveness of netupitant for CINV.
2. Two adequate, well controlled MEC studies will be needed if a path forward cannot be developed for the HEC indication.
3. In general, a phase 3 superiority HEC trial comparing the proposed fixed-dose combination product (netupitant + oral palonosetron) versus the currently approved I.V. palonosetron regimen (0.25 mg) is acceptable.
4. In general, a phase 3 superiority MEC trial comparing the proposed fixed-dose combination product (netupitant + oral palonosetron) versus the currently approved (b) (4) palonosetron regimen (b) (4) is acceptable.
5. Helsinn will not limit their phase 3 trials to 4 cycles.
6. Helsinn will include troponin monitoring in their phase 3 trials.
7. Helsinn can submit their justification for a Level (b) manufacturing site change and Level (b) equipment change with the NDA for review.
8. If Helsinn's equipment evaluation is a (b) (4) they may request a follow up meeting to discuss the dissolution media. Helsinn may submit their justification prior to the pre-NDA meeting and NDA submission for review.
9. Helsinn may submit their information on genotoxic impurities and justification that no additional genotoxicity studies are needed prior to the submission of the NDA. FDA is not obligated to review this information until submission of the NDA.
10. Helsinn's request for IND reactivation must include toxicity studies on the proposed drug combination, but does not have to include detailed clinical protocols.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. Helsinn will submit their phase 3 trial protocols for special protocol assessment. FDA will review the trial designs for acceptability.

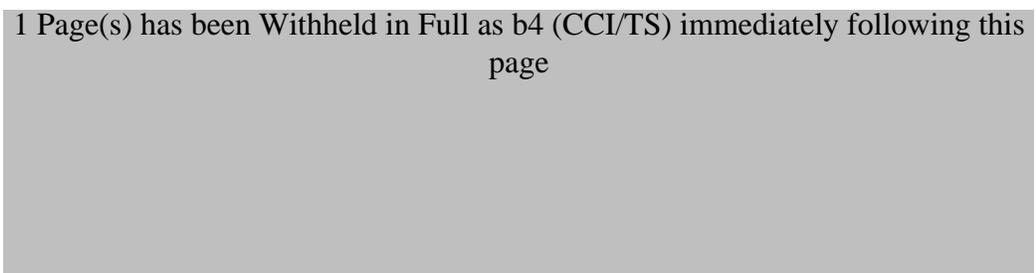
ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

1. At the conclusion of the meeting, Helsinn provided a slide summarizing their revised phase 3 efficacy program. The slide is attached.

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 73493	GI 1		PALONOSETRON HCL / NETUPITANT
IND 73493	GI 1		PALONOSETRON HCL / NETUPITANT

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

/s/

JAGJIT S GREWAL
08/19/2009

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205718

LATE-CYCLE MEETING MINUTES

Helsinn Healthcare SA
C/O August Consulting, Inc.
Attention: Craig Lehmann, Pharm.D.
Authorized Representative
515 S. Capital of Texas Hwy., Suite #150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Akynzeo (netupitant and palonosetron hydrochloride fixed-dose combination capsule).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 11, 2014.

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

If you have any questions, call Mary Chung, Regulatory Project Manager at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Ruyi He, M.D.
Cross-Discipline Team Leader
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 11, 2014 11:00 AM to 12:30 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: NDA 205718
Product Name: Akynzeo (netupitant/palonosetron)
Applicant Name: Helsinn Healthcare, SA

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Office of Drug Evaluation III

Amy Egan, M.D. Deputy Director (Acting)
Maria Walsh, M.S., R.N. Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products

Ruyi He, M.D. Medical Team Lead
Nancy Snow, D.O. Medical Reviewer
David Joseph, Ph.D. Pharmacology Team Lead
Ke Zhang, Ph.D. Pharmacology Reviewer
Mary Chung, PharmD. Regulatory Project Manager

Office of Clinical Pharmacology

Sue-Chih Lee, Ph.D. Team Lead
Insook Kim, Ph.D. Clinical Pharmacology Reviewer
Dilara Jappar, Ph.D. Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment/ Division of New Drug Quality Assessment II

Raymond Frankewich, Ph.D. CMC Reviewer
Assadollah Noory, Ph.D. Biopharmaceutics Reviewer

Division of Biometrics III

Freda Cooner, Ph.D. Statistics Team Lead
Yeh-Fong Chen, Ph.D. Statistics Reviewer

Office of Compliance/ Office of Scientific Investigations

Susan Leibenhaut, M.D. Scientific Investigator

Office of Compliance/Office of Manufacturing and Product Quality/ New Drug Manufacturing
Assessment Branch

Christina Capacci-Daniel Reviewer

Pediatric and Maternal Health Staff

Erica Radden, M.D. Medical Officer
Denise Pica-Branco Senior Regulatory Project Manager

Office of Strategic Programs

Kimberly Taylor Research Analyst

Office of Surveillance and Epidemiology

LingYu (Eileen) Wu Team Lead, Division of Pharmacovigilance
Christian Cao Reviewer, Division of Pharmacovigilance
Matthew Barlow Reviewer, Division of Medication Error Prevention &
Analysis

EASTERN RESEARCH GROUP ATTENDEES

SoHyun Kim, Independent Assessor

APPLICANT ATTENDEES

Sergio Cantoreggi, Chief Scientific Officer, Helsinn
Dario Ceriani, Director, Corporate Regulatory Affairs, Helsinn
Giada Rizzi, Manager, Statistics and Data Management, Helsinn

(b) (4)

(b) (4)

Angioletta Navini, Senior Manager Regulatory Affairs
Ruben Giorgino, Director, Drug Development
Roberta Cannella, Director, Corporate Pharmaceutical Technology
Fabiola Bambini, Manager, Product Quality Compliance
Emanuela Lovati, Manager, Research and Preclinical Development
Claudio Pietra, Director, Research and Preclinical Development
Marco Palmas, Head, Corporate Clinical Development
Fabio Trento, Senior Manager, Project Management and Operations Controller
Alberto Bernareggi, Director, Drug Development

(b) (4)

Florence Colantonio attended as the U.S. Agent for the NDA

1.0 BACKGROUND

NDA 205718 was submitted on September 27, 2013 for Akynzeo (netupitant and palonosetron hydrochloride fixed-dose combination capsule).

Proposed indication: Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy including highly emetogenic chemotherapy.

PDUFA goal date: September 26, 2014

FDA issued a Background Package in preparation for this meeting on May 30, 2014.

2.0 DISCUSSION

1. Introductory Comments 5 minutes
Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues 15 minutes
Each issue will be introduced by FDA and followed by a discussion.
- Biostatistics review issue. Please see “2. Substantive Review Issues” of the Late Cycle Meeting Background Package

Discussion:

FDA indicated the assessment of the additional analyses submitted by the sponsor on June 5, 2014 to address the biostatistics substantive review issue identified in the LCM background package will be completed the end of June 2014.

3. Discussion of Upcoming Advisory Committee Meeting – NONE
4. REMS or Other Risk Management Actions – NONE
5. Postmarketing Requirements/Postmarketing Commitments 30 minutes

A. PREA Post Marketing Requirement

The proposed pediatric plan was presented to the Pediatric Review Committee (PeRC). PeRC and the division do not agree with the timelines for submitting the protocols for the PK/PD

study and the clinical study, or with the date for submission of the final study reports (see listed below). We will discuss more expeditious timelines. In addition, please provide timelines for submission of the juvenile animal study.

Applicant Proposed Timelines for Submission



FDA Comments on Pediatric Development Program

We understand the proposed plan to develop an I.V.  (b) (4) formulation if an oral formulation of netupitant+palonosetron cannot be developed for all or some of the pediatric population. However, our comments are restricted to the potential development of netupitant+palonosetron pediatric formulations. If you are unable to develop an oral or I.V. formulation of netupitant+palonosetron that is suitable for all ages, you may qualify for a waiver of pediatric studies for the populations for which an age-appropriate formulation of netupitant+ palonosetron cannot be developed. However, you will need to submit data that demonstrates your failure to create either an oral or I.V. formulation of netupitant+palonosetron.

We also note safety concerns with I.V. administration of netupitant+palonosetron, based on nonclinical safety studies (e.g. the local adverse effects due to I.V. administration of netupitant alone in rats and rabbits, demonstration of hemolytic potential of netupitant in human blood). Therefore, you may qualify for a waiver of pediatric studies for the populations for which an oral formulation of netupitant+palonosetron cannot be developed. You should provide a detailed rationale to support your safety concern based on the completed nonclinical studies. Additional nonclinical studies may be submitted to further support your rationale. If a waiver is granted because the product would be unsafe in one or more pediatric group(s), this information must be included in the pediatric use section of labeling.

If you are able to develop an oral formulation of netupitant+palonosetron that is suitable for all ages, then the only definitive (GLP) juvenile animal toxicity study that is needed is an oral toxicity study with netupitant alone in juvenile rats, of at least 8 weeks duration. This study should include evaluation of developmental parameters, neurobehavioral effects, and fertility. You should submit a protocol for the definitive juvenile rat toxicity study for review and evaluation, with allowance of sufficient time (about 60 days) for the Agency to provide recommendations and comments prior to initiation of the study. The proposed pediatric single-dose PK study (Study #1) using an oral liquid netupitant formulation in combination with Aloxi Injection given orally may be conducted before completion of the juvenile animal studies. However, the definitive juvenile rat toxicity study report must be submitted to the

Agency for review and evaluation to support the pediatric clinical efficacy study in patients age 0 to < 17 years (Study #2). If you cannot develop an oral liquid formulation of netupitant+palonosetron that is suitable for use in patients ≤ 6 years old as you proposed, and you cannot develop an I.V. formulation of netupitant+palonosetron, the definitive juvenile rat oral toxicity study will still be needed to support an efficacy study in older pediatric patients (ages > 6 to 11 years) using a solid oral dosage form. Your proposed timeline for the pediatric study plan should be revised according to these recommendations.

In the event that pediatric studies for a specific age group (e.g. ≤ 6 years old) can only be conducted with an I.V. formulation of netupitant+palonosetron, you will need to provide a convincing rationale that assures the safety of intravenous administration of the drug combination, with the major focus on the safety of netupitant. This rationale should include a discussion of the toxicity and local tolerance studies with I.V. netupitant alone in rats and rabbits, and the hemolysis study in human blood (e.g. provide an explanation as to why the safety signals seen in these studies do not preclude the conduct of pediatric studies with I.V. netupitant+ palonosetron). Additional nonclinical studies may be submitted to further support your rationale. Your safety assessment must be submitted prior to initiation of pediatric study #1. The definitive oral toxicity study in juvenile rats, as requested above, may be acceptable to support the use of I.V. netupitant+palonosetron in pediatric study #2, but you will need to provide a convincing rationale to justify this approach (e.g. comparison of PK parameters from oral dosing in rat pups and I.V. dosing in children). This issue will be addressed by the Agency when you submit the protocol for the definitive juvenile rat toxicity study.

Discussion:

Sponsor indicated a revised pediatric development program with expedited study timelines will be submitted the end of June 2014.

B. ClinPharm Post Marketing Commitment (PMC)

- We are considering a PMC for an in-vivo drug interaction study to evaluate the duration of inhibitory effects of AKYNZEO on CYP3A4 enzyme activity beyond 4 days after AKYNZEO administration. (PMC #1)
- We are considering a PMC for an in-vitro study to evaluate the potential of netupitant being a substrate for P-gp transporter in a bi-directional transport assay system. (PMC #2)

Discussion:

Sponsor agreed to submit by the end of June 2014, proposed timelines and additional comments they may have on the PMCs being considered for this NDA.

FDA inquired about the status of the sponsor's ongoing study to evaluate the potential of netupitant being a substrate for P-gp transporter in a bi-directional transport assay system, because the completion and submission of this study may address information which will

be requested through PMC # 2. Sponsor indicated they will submit the study by the end of July 2014.

6. Major labeling issues – 10 minutes

Sponsor may raise high level questions or issues identified from the draft labeling.

Discussion:

Sponsor requested clarification on why FDA proposed to amend the indication with the additional statement "... including highly emetogenic chemotherapy." FDA stated this is to clearly indicate that the product is indicated for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.

Sponsor requested clarification on why FDA

(b) (4)

FDA clarified that per CDER Study Endpoints and Labeling Development (SEALD) review non-key endpoints not included in the multiplicity adjustment in the statistical analysis plan are generally not included in product labeling because they do not provide conclusive evidence on treatment benefit. Additionally, the Sponsor's instrument measured (b) (4), not worst nausea severity in the past 24 hours.

FDA stated that additional comments on FDA's proposed labeling can be provided when submitting the sponsor's revised proposed labeling to FDA. Sponsor requested a due date extension to June 17, 2014 and FDA agreed.

Sponsor inquired if their proposed Burgopack Label and Carton Labeling submitted on April 25, 2014 (sequence #0025) could be considered the final version. FDA disagreed and indicated the Final burgopack label and carton labeling are to be provided with the final action letter for this application.

7. Review Plans

PDUFA date: September 26, 2014

8. Wrap-up and Action Items – 10 minutes

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

RUYI HE
06/25/2014