CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210493Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 210493 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Akynzeo Established/Proper Name: fosnetupitant and palonosetron Dosage Form: injection		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: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is April 20, 2018	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

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

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 4/19/18
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	7/19/17 letter, 7/14/17 review
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 1/18/18, 12/7/17, 9/14/17 DMPP/PLT (DRISK): ☐ None 12/6/17 OPDP: ☐ None 12/8/17 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None See OPQ reviews 3/28/18, 12/19/17 Other: ☐ None DPMH maternal: 12/11/17, DPMH pediatrics: 12/13/17
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	6/19/17 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC November 29, 2017 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	N/A
❖ 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)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA or BPD Type 4 meeting *(indicate date of mtg)*	☐ No mtg 11/30/16
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2/4/15, 12/9/14
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 10/3/17
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 2/6/18
• Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None See Clinical Review
Division Director Summary Review *(indicate date for each review)*	☐ None See Clinical Review
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None See Clinical Review
PMR/PMC Development Templates *(indicate total number)*	☐ None 4 templates, 4/19/18

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	4/19/18
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 172 of 4/19/18 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None QT IRT 8/28/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A 12/18/17
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☐ None 1/2/18
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 11/28/17
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 12/18/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/18/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 8/21/17

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 4/6/18
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 12/21/17
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/20/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 3/28/18, 12/19/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/19/17 OPQ review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

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

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

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/s/

MARY H CHUNG
04/20/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210493

MID-CYCLE COMMUNICATION

Helsinn Healthcare SA
c/o August Consulting, Inc.
Attention: Craig Lehmann, PharmD.
Authorized Representative
515 Capital of Texas Highway, 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 (fosnetupitant and palonosetron) for injection, for intravenous use.

We also refer to the teleconference between representatives of your firm and the FDA on October 3, 2017. 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, PharmD.
Senior 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: October 3, 2017 10:30- 11:30 AM EST

Application Number: NDA 210493
Product Name: Akynzeo (fosnetupitant and palonosetron) for injection
Indication: Prevention of chemotherapy-induced nausea and vomiting
Applicant Name: Helsinn Healthcare SA

Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director
Hylton Joffe, M.D.	Deputy Director, Acting

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Lisa Soule, M.D.	Associate Director, Acting
Joette Meyer, PharmD.	Associate Director for Labeling
Anil Rajpal, M.D.	Medical Team Lead
Charles Line, M.D.	Medical Officer
David Joseph, Ph.D.	Pharmacology Team Lead
Ke Zhang, Ph.D.	Pharmacology Reviewer
Mary Chung, PharmD.	Regulatory Project Manager

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Team Lead
Elizabeth Shang, Ph.D.	Clinical Pharmacology Reviewer
Xinyuan (Susie) Zhang, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Hitesh Shroff, Ph.D.	Application Team Lead

Division of Biometrics III

Yeh-Fong Chen, Ph.D.	Biostatistics Team Lead
Min Min, Ph.D.	Biostatistics Reviewer

Office of Surveillance and Epidemiology/ Division of Risk Management

Erin South, PharmD.	Reviewer

APPLICANT ATTENDEES
Fabio Trento, Project manager
Marco Palmas, Head of Clinical Development
Alberto Bernareggi, R&D Innovation & Strategy Director
Giada Rizzi, Statistics & Data Management Manager
Emanuela Lovati, Preclinical Development Manager
Claudio Giuliano, Preclinical Development and DMPK Manager
Alessio Venturini, Pharmaceutical Development Manager
Giuseppina Clerici, Drug Safety Deputy Director
Mauro Catena, Regulatory Affairs Manager
Angioletta Navini, Regulatory Affairs Senior Manager
Virginia Cuervo Alvarez, Head of Regulatory Affairs and Drug Safety
Sergio Cantoreggi, Chief Scientific Officer
Richard Bourne, Vice President Regulatory Affairs – Helsinn Therapeutics
Craig Lehmann, U.S. Agent for the NDA

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

The observations of lower exposure of the netupitant metabolites (M1, M2, and M3) in the pro-netupitant IV group compared to the netupitant/palonosetron capsules group in Study PNET-12-23 and lower observed complete response rates (especially in the delayed phase) with IV NEPA FDC compared to oral NEPA FDC in Study NEPA-15-18 raise concerns that the lower exposure of these metabolites (M1, M2, and M3) may adversely impact the efficacy of the IV dosing. The lower response rate was observed in the first cycle of treatment and was replicated in subsequent cycles. These findings raise questions about whether pro-netupitant has comparable efficacy to netupitant in the delayed phase, and whether it is reasonable to conclude that pro-netupitant would be superior to placebo in a comparison of pro-netupitant + palonosetron vs. placebo + palonosetron in the HEC setting.

Discussion Summary:
Sponsor expressed understanding of FDA's issues described above. They stated they will provide a detailed response in writing in the coming week to the application.

3.0 INFORMATION REQUESTS

Not applicable

4.0 MAJOR SAFETY CONCERNS/ RISK MANAGEMENT

There are no safety signals identified to date.

There are no Risk Evaluation and Mitigation Strategies (REMS) identified to date for this application beyond routine draft professional labeling for the product.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee Meeting.

6.0 LATE-CYCLE MEETING/ OTHER PROJECTED MILESTONES

The proposed date for the Late-Cycle Meeting (LCM) is February 6, 2018.

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/s/

MARY H CHUNG
11/02/2017

M E M O R A N D U M

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

DATE: 8/16/2017

TO: Office of New Drugs
Division of Gastroenterology and Inborn Errors Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 210493

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	CRS Clinical Research Services Mannheim GmbH	Grenadierstrasse 1, 68167 Mannheim, Germany
Analytical		(b) (4)

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/s/

ANGEL S JOHNSON
08/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210493

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Craig Lehmann, PharmD

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) dated and received April 20, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosnetupitant and Palonosetron for Injection, 235 mg/0.25 mg.

We also refer to your correspondence, dated and received April 20, 2017, 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 conditionally acceptable.

If any of the proposed product characteristics as stated in your April 20, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nicholas Miles, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7025. For any other information regarding this application, contact Mary Chung, PharmD, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
07/19/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115191

MEETING MINUTES

Helsinn Healthcare SA
c/o August Consulting, Inc.
Attention: Craig Lehmann, PharmD.
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 prodrug and palonosetron hydrochloride for injection.

We also refer to the teleconference between representatives of your firm and the FDA on November 30, 2016. The purpose of the meeting was to discuss your proposed submission plans for your planned NDA.

A copy of the official minutes of the teleconference 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) 796-0260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B, teleconference
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 30, 2016 12:00 PM- 1:00 PM EST
Application Number:	IND 115191
Product Name:	fosnetupitant and palonosetron for injection
Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
Sponsor/Applicant Name:	Helsinn Healthcare, SA
Meeting Chair:	Anil Rajpal, M.D.
Meeting Recorder:	Mary Chung, PharmD.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Anil Rajpal, M.D.	Medical Team Lead
Aisha Johnson, M.D.	Medical Reviewer
Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Mary Chung, PharmD.	Senior Regulatory Project Manager

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Team Lead, Acting
Dilara Jappar, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics III

Wen-Jen Chen, Ph.D.	Biostatistics Reviewer

Office of Product Quality

Friedrich Burnett, Ph.D.	Chemistry Reviewer
Hitesh Shroff, Ph.D.	Chemistry Team Lead

Office of Surveillance and Epidemiology

Jacqueline Sheppard, PharmD.	Risk Management Analyst
Madhuri Patel, PharmD.	Safety Evaluator
Mishale Mistry, PharmD.	Safety Evaluator, Team Lead

Sukhiminder Sandhu, Ph.D. Epidemiology Team Lead

SPONSOR ATTENDEES
Sergio Cantoreggi, Chief Scientific Officer
Angioletta Navini, Senior Manager, Regulatory Affairs
Mauro Catena, Manager, Regulatory Affairs
Richard Bourne, Vice President Regulatory Affairs, Helsinn Therapeutics
Giada Rizzi, Manager, Statistics & Data Management
Fabio Trento, Senior Manager, Project Management
Ruben Giorgino, Head of Drug Development
Alberto Bernareggi, Clinical Pharmacology, Director, Drug Development
Claudio Pietra, Director, Preclinical Development
Emanuela Lovati, Manager, Preclinical Development
Giuseppina Clerici, Deputy Director, Drug Safety
Alessio Venturini, Manager, Corporate Pharmaceutical Development
Daniel Voisin, Manager, Clinical Operations
Christian Bacilieri, Manager, Process Validation & Regulatory Affairs, Helsinn Advanced Synthesis
(b) (4), CMC consultant
(b) (4), Clinical Pharmacology Consultant
Craig Lehmann, Authorized Representative for the IND

1.0 BACKGROUND

On September 15, 2016, Helsinn Healthcare submitted a meeting request to discuss their proposed submission plans for their planned NDA for fosnetupitant and palonosetron injection. Fosnetupitant and palonosetron for injection is the I.V. formulation of NDA 205718 Akynzeo (netupitant and palonosetron) capsules, which was approved on October 10, 2014. Previous meetings held on this development program include the June 6, 2016 meeting, February 4, 2015 meeting, and December 9, 2014 meeting.

The proposed indication for fosnetupitant and palonosetron injection is prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

The September 15, 2016 Pre-NDA meeting request was granted and the background package was received on October 27, 2016.

2. DISCUSSION

The format of these minutes provides for Helsinn's questions in regular typeface, followed by the Agency's November 28, 2016 responses in **bolded** print. The November 30, 2016 meeting discussion is presented in ***italic and bolded*** print.

Question 1:

Key study results. Data from phase 3 study PALO-15-17 and NEPA-15-18 and Phase 1 PNET-12-23 are provided in this background package in Section #8.1 and Appendices 1, 2 and 3. The sponsor plans to seek the following indication for approval of the IV NEPA FDC in HEC:

> prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy; AKYNZEO for injection is (b) (4) (b) (4) combination of palonosetron and fosnetupitant: palonosetron prevents nausea and vomiting during the acute phase and fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

Sponsor believes that these 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 to Question 1:
For Study PALO-15-17, it is a review issue to determine whether efficacy data from the study is adequate to support the submission of the planned NDA for the target indication.

In addition, in order to assess the validity of efficacy analysis presented in Table 6 at page 22 of the meeting Briefing Package, please submit the following information when you submit the clinical study report for this NDA:

- **Published articles with formula for Wilson score confidence interval method which you used to generate confidence intervals for the non–inferiority analysis;**
- **Publish articles for CMH stratum-adjusted methods proposed by Koch et al. and O'Gorman et al. which you used to test proportion difference in the non-inferiority analysis;**
- **Please conduct the secondary endpoint analyses based upon primary endpoint non-inferiority method using two-sided 99% confidence intervals.**

For Study NEPA-15-18, as the briefing package indicated, since efficacy assessment was a secondary study objective, only descriptive statistics were planned and performed. We would like to remind you that the descriptive analysis results for the efficacy endpoints cannot be claimed in the labeling.

Question 2:
Safety results and overall approach to safety evaluation for the planned NDA. Sponsor believes that the safety data are adequate to support the submission of the planned NDA as demonstrated in this background package in Section#8 and 9. In addition, the safety profile of IV NEPA FDC is similar to that observed for oral Akynzeo, for which a REMS was not required. Therefore, it is proposed not to include a REMS for IV NEPA FDC. Does the Agency agree? Please comment as needed.

FDA Response to Question 2:
The safety data are adequate to support submission of your planned NDA. The adequacy of the safety data to support approval will be determined upon complete review of your NDA. Further, at this time, there is insufficient information to determine whether a risk

evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. We will determine the need for a REMS during the review of your application.

Question 3:

Biopharm/PK data to be included in the NDA. *In-vitro* and *in-vivo* biopharm/PK studies planned to be included in the NDA are summarized in the background package in Section #9. Sponsor believes that overall the biopharm/PK program is adequate to support the submission of the planned NEPA IV NDA. Does the Agency agree? Please comment as needed.

FDA Response to Question 3:

No, we do not agree. See our following comments.

- **You have not conducted a thorough QT study to address the QT prolongation potential of your proposed combination product. We recommend that you submit your plan to address the potential of fosnetupitant to prolong QT interval to FDA's QT-IRT team.**
- **We acknowledge that you have conducted PBPK modeling to predict the in vivo drug interaction potential and concluded that in vivo drug interactions are unlikely between fosnetupitant and substrates for CYP2C9, CYP2C19, OATP1B1, OATP1B3 and P-gp. However, you have not provided any details on how the PBPK modeling supported your conclusion.**
- **On the other hand, based on the in vitro study results, in vivo drug interaction potential by inhibitory effects of fosnetupitant on CYP2C9 (IC_{50} = 27.9 μM), CYP2C19 (IC_{50} = 46.1 μM), P-gp (IC_{50} ~ 50 μM), MATE1 (IC_{50}: 29.48 μM), OATP1B1 (IC_{50}: 19.01 μM) and the OATP1B3 (IC_{50}: 17.37 μM) cannot be ruled out. As Cmax/IC_{50} > 0.1 for these CYP enzymes and transporters, you should follow-up with in vivo clinical drug interaction studies to assess the inhibition potential of fosnetupitant toward these CYP enzymes and transporters.**
- **We recommend that you evaluate potential of fosnetupitant being a substrate for transporters.**
- **We note that co-administration of a single dose of IV fosnetupitant 260 mg increased the exposure of dexamethasone, a substrate of CYP3A4 by 1.5-fold on Day 1 and up to 2.4-fold on Day 4. We recommend that you address the potential duration of inhibitory effect of your proposed product on CYP3A4 activity beyond 4 days after single dose administration of IV Akynzeo.**

Discussion Summary:

Regarding the process of submitting sponsor's proposed plan to address the potential of fosnetupitant to prolong QT interval, FDA clarified that the proposed plan should be submitted to the IND. FDA strongly suggested to submit ECG data from study PNET 12-23 on the 390 mg dose level with the proposed plan. QT IRT team will be consulted. FDA stated they would provide a summary template to guide the submission.

FDA clarified that a response from the QT IRT team regarding whether a tQT study is required is necessary prior to the NDA submission.

Regarding sponsor's clarification provided on their PBPK modeling, FDA clarified that responding comments will be provided upon consultation with the Pharmacometrics team.

FDA indicated sponsor's response regarding the potential duration of inhibitory effect of the proposed product on CYP3A4 activity beyond 4 days after single dose administration of IV Akynzeo appears reasonable, but that this issue would be a review issue. The extent of the inhibition would be 8 days instead of 4 days based on the oral Akynzeo data, which is currently under FDA review.

Post-meeting comment:
We have consulted the PBPK review team. As for your PBPK modeling approach, your approach seems reasonable. We recommend that you provide the study report and relevant model files in the NDA submission. The adequacy of the model and your conclusion will be determined during the NDA review. Please see the guidance for Industry: Physiologically based Pharmacokinetic Analyses- Format and Content for more information
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

Question 4:
Approach to dataset provision for nonclinical studies. In previous Type C meeting minutes (June 6, 2016, minutes available in Appendix #6), regarding dataset provision for nonclinical studies in support of the planned NDA, the Agency clarified that *"We agree with your plan to submit full study reports for all nonclinical studies in the NDA. However, we do not agree with your plan to omit SEND datasets for all nonclinical studies. For nonclinical studies that were started after December 17, 2016, the data must be submitted in SEND format, based on our consultation with the Office of Computational Science".* All non-clinical studies were performed prior to December 17, 2016 (reference to the guideline "Providing Regulatory Submissions in Electronic Format — Standardized Study Data", December 2014), therefore the Sponsor plans not to submit any dataset. However, Helsinn noted that Important Notice "Technical Rejection Criteria For Study Data" was released on October 3rd, 2016, requesting that a Trial Summary dataset (TS.xpt) must be presented for each study in section 4.2, even if the study started prior to December 17, 2016. This seems to be in contrast with the previous Agency feed back.

The Sponsor plan to proceed to submit pdf full study reports with no datasets, based on FDA feedback received on June 6, 2016. Please confirm this approach is acceptable.

FDA Response to Question 4:
Based on the study data technical conformance guide and data standards catalog on the FDA study data standards resources page, if the nonclinical/clinical study starts after 12/16/2016, the sponsor needs to submit the SDTM data (http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm). In order to determine the study start date, we need the TS domain to be submitted after 12/16/2016.

For the nonclinical/clinical submission with legacy data or no data, we only require one record in TS domain including study id, TSPARMCD = STSTDTC and TSVAL= xxxx-xx-xx(year-month-day). The define file is not required.

Question 5:

Proposed drug substance and drug product quality program for the planned NDA. Section #11 provides general information on the drug substance synthesis and the proposed commercial drug product formulation, an overview of planned specifications and the stability data package to be submitted in the NDA. Approach to the characterization of genotoxic impurities is the same as that supporting the registration of oral Akynzeo. Sponsor believes that the CMC plan is adequate to support the submission of the planned IV NEPA FDC NDA. Does the Agency agree? Please comment as needed.

FDA Response to Question 5:

We have the following comments on the fosnetupitant API:

- **The synthesis appears reasonable; however, provide information either in the application or a DMF to support designation of (b) (4) as an appropriate starting material. A final determination will be made at the time of the NDA review.**
- **Add tests for Residue on Ignition and Elemental Impurities to the specification, or provide justification for the absence of these tests.**
- **Provide justification for the limit of NMT (b) (4) % for (b) (4)**
- **Provide justification of the limit of NMT (b) (4) ppm for (b) (4) as it is not listed in ICH Q 3C tables.**
- **Your justification for evaluation of genotoxic impurities appears reasonable, but the final determination is a review issue that will be evaluated by both CMC and nonclinical pharmacology.**
- **It is acceptable to provide full CMC information, including the results of stability studies, in a new DMF. We recommend that at least 12 months of long term stability data and 6 months of accelerated stability data on three batches of API be included upon submission of the NDA. Ensure that the DMF is submitted prior to submission of the NDA so that it is available for review.**

The planned update to the DMF for the palonosetron API prior to submission of the NDA submission appears reasonable.

Your proposed drug product formulation, specification and stability study plan appear to be reasonable. However, the drug product expiration dating period will be determined at the time of the NDA review based on the stability data provided in the application.
We recommend that you perform a drug product compatibility study with container closure system, commonly used diluents, dosage devices specified in the drug product labeling and stability testing of the reconstituted drug product at room temperature and refrigerated temperature up to 48 hours. Also, the compatibility of the drug product with likely co-administered drug products should be addressed to provide appropriate and supportive language in the labeling.

Testing for elemental impurities will need to be included in the drug product specification (see ICH Q3D). This should include testing for lead, arsenic, cadmium, mercury, chromium, copper, selenium, manganese, zinc and other metals that are present during the manufacturing process and have the potential to contaminate the drug product.

In addition, please note the below.

[redacted] (b) (4)

(Section 1.6.2; page 13 of 13; Appendix 11). If the reconstituted and further diluted drug product will be held longer than four hours at room temperature and/or 24 hours under refrigerated temperatures, microbiological studies in support of the post-constitution and post-dilution storage time(s) [redacted] (b) (4) **are required. The NDA should include a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions after reconstitution and further dilution with the specified diluents. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Provide a description of the test methods and results of studies that are designed using a minimum countable inoculum (** [redacted] (b) (4) **CFU/mL) to simulate potential microbial contamination that may occur during product constitution and dilution. It is generally accepted that growth is evident when the population increases more than 0.5 $\log_{10}$; however, other evidence of growth may be significant. Perform the test using the storage conditions (temperature and duration) and diluents specified in the proposed product labeling. Provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted or diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. In addition, provide a positive control that demonstrates the viability of the organisms over the duration of the test period.**

Discussion Summary:
Sponsor clarified that the product PI will [redacted] (b) (4) ***limit the use of reconstituted solution within 3 hours. FDA Microbiology and CMC teams concurred with this plan. Sponsor clarified that they would*** [redacted] (b) (4) ***support the 3 hour statement in the labeling. FDA concurred.***

Question 6:
Draft labeling. Approach to draft labeling is described in Section#15 of this background package. Draft labeling is included in the background package as Appendix #11. This draft labeling is representative of the proposed format and content of the information relevant to the IV NEPA FDC itself, and/or to oral Akynzeo and/or each single component of the combination. Does the Agency agree with the proposed approach? Please comment as needed.

FDA Response to Question 6:

You propose to develop Prescribing Information (PI) for fosnetupitant/palonosetron injection that is separate from the netupitant/palonosetron oral PI. We note that you have submitted to IND 115191 the proposed proprietary name, Akynzeo, for Agency review. Although the acceptability of the proposed proprietary name Akynzeo for the proposed product will be a review issue, we do not agree with the proposed separate Prescribing Information (PI) for fosnetupitant/palonosetron injection if you intend to market both formulations under the same proprietary name.

In general, OND discourages sponsors from creating separate PIs for different strengths or dosage forms of the same product unless there is a compelling reason to do so. For example, sometimes there are significant differences between the products (e.g., indications, dosage regimen, safety profile) that cannot be communicated in one labeling document. For example, Revatio (sildenafil tablets, oral suspension, and injection) indicated for the treatment of pulmonary arterial hypertension and Viagra (sildenafil citrate tablets) indicated for the treatment of erectile dysfunction. Also, Botox (onabotulinumtoxinA) and Botox Cosmetic.

Having one PI allows the prescriber access to a comprehensive overview of the strengths, indications, dosage forms, etc. available for the active moiety. In addition, one document allows for easier updating by the sponsor when new information becomes available.

Products with different routes of administration often share a PI. Examples include:

- **Revatio (noted above): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021845s016,022473s010,203109s009lbl.pdf**
- **Sivextro (tedizolid phosphate injection and tablets): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/0205435s001,0205436s001lbl.pdf**
- **Cyclophosphamide injection and tablets: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf**
- **Vimpat (lacosamide tablets, injection and oral solution): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022253s030,022254s022,022255s016lbl.pdf**
- **Bentyl (dicyclomine hydrochloride capsules, tablets and injection): http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/007409s042,008370s033lbl.pdf**

Question 7:

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/3 clinical studies NEPA-15-18, and PALO-15-17 and for the Phase 1 PK and safety study PNET-12-23. Does the Agency agree with the proposed approach? Please comment as needed.

FDA Response to Question 7:

Your plan to include financial certification in the NDA for all applicable investigators in the studies submitted as part of your planned NDA appears reasonable. For further information regarding financial disclosures, see the Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf**)**

Your planned pdufa user fee payment amount which is based on the fee amount for FY2017 is correct, and we do not have additional comments to your proposed plan for pdufa fee payment at this time.

Please note that the final determination regarding user fees will occur when the application is submitted in its entirety to the Agency.

Regarding your proposed propriety name, the final determination will be made under the IND by April 10, 2017.

Question 8:

Proposed content and format of the planned NDA and approach to eCTD format. The proposed draft Table of Contents (ToC) of the NDA is located in Appendix #10. 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. If the submission (planned in April) is done before 12 April 2017, the opinion on the proprietary name under IND 115191 (Serial #0028 of 12 October 2016) may not yet be available. Should this be the case, the Sponsor proposes to submit it as a follow up submissions are planned in the 30-day period after the initial NDA submission during FDA's review of the NDA. Overall, 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 to Question 8:

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

- **Providing Module 1 Table of Contents is not necessary instead, sponsor can submit a linked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application.**
- **The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.**
- **Do not include sections that will not be submitted as part of the application.**

- **Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf**
- **Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs and instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and file tagged as "case report form".**
- **To submit Postmarketing Report (descriptive portion) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Please ensure that the leaf title of the report includes the reporting period (e.g. PADER-Aug01-2015-Aug02-2016), so reviewers can quickly differentiate one year's report, from another.**

Discussion Summary:
FDA clarified that the sponsor should submit the proprietary name review request to the NDA, and reference the IND.

Question 9:
Overall planned NDA. Please advise us of any matters we have not addressed regarding the planned NDA, since we do not wish to miss anything. Please comment as needed.

FDA Response to Question 9:
Please see comments provided above.

3.0 ADDITIONAL COMMENTS

Additional Clinical Pharmacology Comments:

- **For all of the PK/PD studies that you plan submit in the NDA submission, please provide datasets containing individual plasma concentrations and PD data as well as datasets for individual PK and PD parameters along with its corresponding define files. For the datasets containing PK and PD parameters, please provide the files in a readily analyzable format with each PK parameter in a distinct column. In addition, the PK parameter dataset should also include subject ID, treatment, period, and sequence in different columns.**

Discussion Summary:

Sponsor provided their proposed plan in their meeting background (See attached). FDA clarified that all PK datasets (concentration profile dataset and PK parameter dataset) would need to be provided when the NDA is submitted. Sponsor confirmed to comply with the FDA comments above.

3.0 ADDITIONAL COMMENTS

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator

c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

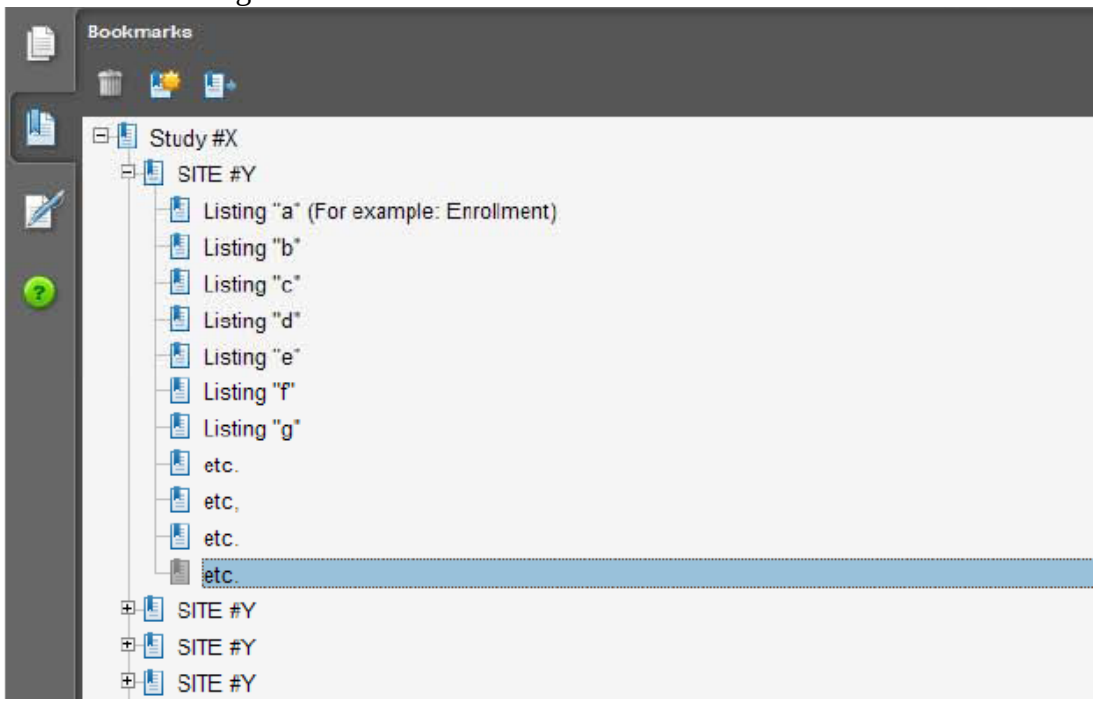
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA

inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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

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

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ATTACHMENTS AND HANDOUTS

Attached below are handouts sponsor provided for the November 30, 2016 meeting.

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

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/s/

MARY H CHUNG
12/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 115191

MEETING MINUTES

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

Dear Dr. Lehmann:

Please refer to your Pre-Investigational New Drug Application (PIND) file for netupitant prodrug and palonosetron hydrochloride fixed combination for injection.

We also refer to the telecon between representatives of your firm and the FDA on February 4, 2015. The purpose of the meeting was to discuss your planned phase 3 development program in follow-up to the face-to-face meeting held December 9, 2014.

A copy of the official minutes of the telecon 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) 796-0260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Teleconference
Meeting Category:	Pre-IND/ Pre-Phase 3
Meeting Date and Time:	February 4, 2015 11:00 AM- 12:00 PM
Application Number:	PIND 115191
Product Name:	Netupitant prodrug and palonosetron hydrochloride fixed combination for injection
Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy
Sponsor/Applicant Name:	Helsinn Healthcare SA (Helsinn)
Meeting Chair:	Ruyi He, M.D.
Meeting Recorder:	Mary Chung, PharmD.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Dragos Roman, M.D.	Deputy Director (Acting)
Ruyi He, M.D.	Medical Team Lead
Laurie Muldowney, M.D.	Medical Reviewer
Mary Chung, PharmD.	Regulatory Project Manager

Division of Biometrics III

Mike Welch, Ph.D.	Deputy Division Director
Yeh-Fong Chen, Ph.D.	Statistical Team Lead

SPONSOR ATTENDEES

Sergio Cantoreggi, Ph.D., Chief Scientific Officer, Head of R&D, Helsinn
Ruben Giorgino, M.D., Ph.D., Director, Head of Drug Development, Helsinn
Marco Palmas, M.D., Director, Head of Corporate Clinical Development, Helsinn
Alberto Bernareggi, MSc, PharmD., Director, Pharmacokinetics and Metabolism, Helsinn
Daniel Voisin, MSc, Manager, Corporate Clinical Development, Helsinn
Fabio Trento, MPharm, Senior Manager, Project Management, Helsinn
Angioletta Navini, MSc, Ph.D., Senior Manager, Corporate Regulatory Affairs, Helsinn
Cecilia Moresino, MSc, Senior Manager, Head of Statistics and Data Management
Giada Rizzi, MSc, Manager, Statistics and Data Management, Helsinn
Dario Ceriani, Director, Corporate Regulatory Affairs, Helsinn

Craig Lehmann, PharmD., IND Representative
(b) (4) Statistical Consultant
(b) (4)., Clinical Pharmacology Consultant
Stacie O'Sullivan, MSc, Sr. Manager Global Regulatory Affairs, EISAI US
(b) (4)., Medical Oncology Consultant

1.0 BACKGROUND

On August 4, 2014, Helsinn Healthcare submitted a meeting request to discuss their planned phase 3 development program and nonclinical program for netupitant prodrug and palonosetron hydrochloride fixed combination for injection. This meeting was granted and held December 9, 2014. During this meeting, sponsor presented their clinical development plan, which has been revised since the Type B, Pre-IND meeting held September 26, 2012, in light of the approval of NDA 205718 Akynzeo (netupitant palonosetron fixed combination capsule).

Akynzeo, netupitant/palonosetron fixed combination capsule, was approved on October 10, 2014 by the FDA. Netupitant is a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron is a serotonin-3 (5-HT3) receptor antagonist. Akynzeo is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC). Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

On December 23, 2014, sponsor submitted a follow-up teleconference meeting request to discuss their phase 3 development plans, which have been revised per December 9, 2014 discussion with FDA, to support a revised proposed indication. This meeting was granted and scheduled for February 4, 2015.

2.0 DISCUSSION

Question 1:
Adequacy of PALO-15-XX to support the efficacy of the IV 30- minute infusion palonosetron component in IV Akynzeo in the acute phase.

Details of PALO-15-XX study are given in Section 3.1. Study PALO-15-XX is a phase 3 single-cycle non-inferiority study assessing the efficacy and safety of a single dose of palonosetron 0.25 mg (Aloxi) administered as a 30 minute I.V. infusion versus a single dose of FDA-approved palonosetron 0.25 mg (Aloxi) administered as a 30 second I.V. bolus, each administered with oral dexamethasone prior to HEC. The primary objective is to demonstrate the non-inferiority of the I.V. 30-minute palonosetron infusion compared to the FDA-approved I.V. 30-second palonosetron bolus, as FDA requested.

Key Features of this Study are:

- Study population: adult chemotherapy-naïve male or female patients with a malignant solid tumor scheduled to receive their first course of HEC, similar to the patient population

enrolled in I.V. Aloxi pivotal study PALO-99-05 which supported FDA approval of I.V. Aloxi in HEC.

- Primary endpoint: CR (no emesis and no rescue therapy) in the acute phase (0-24 hours), as per FDA request
- NI margin: -15%, consistent with registration studies PALO-99-05 (Study 3 in IV Aloxi label), PALO-10-01 (Study 4 in oral Akynzeo label) and other pivotal studies supporting the registration of 5-HT_3 receptor antagonists.

Does the Agency agree that the design of study PALO-15-XX is adequate to support efficacy in the acute phase of the palonosetron component infused over 30 minutes in the I.V. Akynzeo, for purposes of the planned NDA? Please comment as needed.

FDA Response to Question 1:

We agree that the design of study PALO-15-XX is adequate to support efficacy of the palonosetron component infused over 30 minutes in I.V. Akynzeo. Specifically, we agree with the planned primary endpoint. However, your proposed indication would need to be revised to clarify that combination anthracycline and cyclophosphamide regimens are not included in the HEC indication. For example, the indication could be revised to state Akynzeo I.V. is indicated for prevention of acute and delayed nausea and vomiting associated with HEC, not including anthracycline plus cyclophosphamide chemotherapy, or with a limitation of use stating that it has not been studied in the setting of anthracycline plus cyclophosphamide chemotherapy.

Regarding the non-inferiority margin, we understand that we accepted your proposed 15% margin for the analysis of Study PALO-10-01. However, we cannot agree to this margin for your proposed new study. Because the margin used for the original comparison of I.V. palonosetron 0.25 mg/30 second infusion to ondansetron in Study PALO-99-05 was 15%, allowing for a margin of 15% for the current proposed comparison would allow as much as 30% inferiority of I.V. palonosetron 0.25 mg/30 minute infusion to ondansetron.

To ensure the efficacy of intravenous palonosetron 0.25 mg/30 minute infusion will not be more than 15% inferior to ondansetron (the same standard used in Study PALO-99-05), we recommend you use ondansetron as a comparator; or if you choose to study the 30 minute infusion with a comparator arm of intraveous palonestron 0.25 mg/30 second bolus, we recommend the margin should be 6% (=15-9), since the lower bound of the 97.5% confidence interval of I.V. palonosetron 0.25 mg/30 second bolus effect from Study PALO-99-05 was 9%, when it was compared to ondansetron. To account for the variability associated with reliance on evidence from one historical trial, if you choose to pursue a comparison of the two palonosetron infusions, we recommend the margin be 10%.

Discussion Summary:

Based on previous precedent of FDA's acceptance of the 15% noninferiority (NI) margin in the PALO-10-01 study, which was a NI study comparing IV and oral palonosetron (FDA agreement to NI margin indicated in the SPA no agreement letter issued June, 18, 2010, in response to May 4, 2010 SPA request for PALO-10-01), FDA and sponsor agreed that the NI margin of 15% is acceptable based on sponsor's plan to use a two sided 99% confidence interval for the PALO-15-XX study.

Question 2:
Adequacy of phase 3 study NEPA-15-YY to describe the safety of I.V. Akynzeo over repeated cycles.

Details of NEPA-15-YY study are given in Section 3.2. Study NEPA-15-YY is a phase 3 clinical study assessing the safety of the I.V. pro-netupitant / palonosetron (260 mg / 0.25 mg) FDC for the prevention of chemotherapy-induced nausea and vomiting in four repeated consecutive chemotherapy cycles.

Key features of the study are:

- Study population: adult chemotherapy naïve male and female patients with a diagnosis of malignant solid tumor requiring treatment with HEC or MEC regimens on Day 1 of each cycle. The Sponsor proposes to enroll both patients receiving HEC (as proposed by FDA) (b) (4)

- Sample size: 400 patients will be randomized according to a randomization ratio 1:1, stratified by chemotherapy regimen and gender. It is expected that the number of patients randomized to the test group, i.e. 200, will allow more than 100 patients to be treated with the test drug for 4 cycles. Based on 100 patients treated at cycle 4 with the pro-netupitant and palonosetron (260 mg/0.25 mg) combination, if a given Adverse Event (AE) is not observed, an AE incidence of 3% or greater can be excluded with 95% confidence.

- Comparator: Oral Akynzeo, as per FDA's suggestion

- Study duration: four consecutive cycles

- Safety Assessment: recording of adverse events (AEs). Other safety assessments will include physical examination, vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology, blood chemistry, and urinalysis).

Does the Agency agree that the design of study NEPA-15-YY is adequate to describe the safety of I.V. Akynzeo, for purposes of the planned NDA submission? Please comment as needed.

FDA Response to Question 2:
We agree with the design of study NEPA-15-YY to describe the safety of I.V. Akynzeo. Specifically, we agree with the choice of comparator, study duration, and planned safety assessments. As your proposed indication is for HEC only, you need to have adequate number of patients who will receive HEC in this study, (b) (4)

Should a safety signal be found, additional studies and/or patients may be required.

Discussion Summary:
Sponsor indicated they will enroll HEC patients only (i.e. 400 HEC patients) in study NEPA-15-YY considering FDA input received during December 9, 2014 type B meeting and FDA responses to question #1 and #2 above. FDA agreed.

Question 3:
Adequacy of the overall I.V. Akynzeo clinical program for the HEC setting.

Details on the planned NDA program are given in Section 3.3. As discussed with FDA during the Pre-IND/Pre Phase 3 Meeting held December 9, 2014, the IV Akynzeo NDA clinical program is proposed to be comprised of the following studies. Each of these trials are described in Section 3.3.

- PALO-15-XX (described in Section 3.3 and Appendix #1 herein)
- NEPA-15-YY (described in Section 3.3 and Appendix #2 herein)
- PNET-12-23 (see Section 3.3. For a full description, please see the 9Dec2014 meeting background package, section 3.4.1.1, PIND 115191, submitted Nov2014)
- PNET-13-63 (see Section 3.3. For a description, please see the 9Dec2014 meeting background package, section 3.4.1.2, PIND 115191, submitted Nov2014)
- A full PK study with IV Akynzeo in cancer patients.

For purposes of the planned NDA submission, does the Agency confirm the adequacy of this clinical program for I.V. Akynzeo for the indication of "prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Akynzeo is a (b) (4) ***combination of palonosetron and*** (b) (4) ***netupitant: palonosetron prevents nausea and vomiting during the acute phase and*** (b) (4) ***netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy"?***

FDA Response to Question 3:
Yes, we agree the planned clinical development program appears adequate for NDA submission, as proposed. The adequacy of the submission for the indication proposed will be a review issue. See response to question 1.

3.0 FDA ADDITIONAL COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

4.0 ATTACHMENTS AND HANDOUTS

Attached is sponsor provided handout referenced during the sponsor meeting.

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/s/

MARY H CHUNG
02/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND115191

MEETING MINUTES

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

Dear Dr. Lehmann:

Please refer to your Pre-Investigational New Drug Application (PIND) file for netupitant prodrug and palonosetron hydrochloride fixed combination for injection.

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2014. The purpose of the meeting was to discuss your nonclinical program and planned phase 3 development program.

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) 796-0260.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-IND/Pre-Phase 3
Meeting Date and Time:	December 9, 2014 10:00 AM -11:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	PIND 115191
Product Name:	Netupitant prodrug and palonosetron hydrochloride fixed combination for injection
Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of [redacted] (b) (4) highly emetogenic chemotherapy.
Sponsor/Applicant Name:	Helsinn Healthcare SA (Helsinn)
Meeting Chair:	Ruyi He, M.D.
Meeting Recorder:	Mary Chung, PharmD.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Dragos Roman, M.D.	Deputy Director (Acting)
Ruyi He, M.D.	Medical Team Lead
Laurie Muldowney, M.D.	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
Sandhya Apparaju, Ph.D.	Clinical Pharmacology Reviewer

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

Marie Kowblansky, Ph.D.	Chemistry Team Lead

Division of Biometrics III

Yeh-Fong Chen, Ph.D.	Statistical Reviewer

Pediatric and Maternal Health Staff

Erica Radden, M.D.	Medical Officer
Matthew Bacho	Senior Regulatory Project Manager

Controlled Substance Staff

Katherine Bonson	Reviewer

SPONSOR ATTENDEES

Sergio Cantoreggi, Ph.D., Chief Scientific Officer, Head of R&D, Helsinn
Ruben Giorgino, M.D., Ph.D., Director, Head of Drug Development, Helsinn
Marco Palmas, M.D., Director, Head of Corporate Clinical Development, Helsinn
Alberto Bernareggi, MSc, PharmD., Director, Pharmacokinetics and Metabolism, Helsinn
Daniel Voisin, MSc, Manager, Corporate Clinical Development, Helsinn
Fabio Trento, MPharm, Senior Manager, Project Management, Helsinn
Angioletta Navini, MSc, Ph.D., Senior Manager, Corporate Regulatory Affairs, Helsinn
Emanuela Lovati, Ph.D., Manager, Research and Preclinical Department, Helsinn
Giada Rizzi, MSc, Manager, Statistics and Data Management, Helsinn
Alessio Venturini, Mphaarm, Manager, Pharmaceutical Development, Helsinn
Roberta Cannella, Mpharm, Director, Pharmaceutical Development, Helsinn
Dario Ceriani, Director, Corporate Regulatory Affairs, Helsinn

Craig Lehmann, PharmD., IND Representative
(b) (4) Statistical Consultant
(b) (4) Clinical Pharmacology Consultant
(b) (4) CMC/QA Consultant
Stacie O'Sullivan, MSc, Sr. Manager Global Regulatory Affairs, EISAI US
(b) (4) Medical Oncology Consultant

1.0 BACKGROUND

On August 4, 2014, Helsinn Healthcare submitted a meeting request to discuss their nonclinical program and their planned phase 3 development program for netupitant prodrug and palonosetron hydrochloride fixed combination for injection.

Akynzeo, netupitant/palonosetron fixed combination capsule, was approved on October 10, 2014 by the FDA. Netupitant is a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron is a serotonin-3 (5-HT3) receptor antagonist. Akynzeo is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (HEC). Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

Oral palonosetron (Aloxi 0.5 mg oral capsules) is approved for the prevention of acute chemotherapy induced nausea and vomiting associated with moderately emetogenic cancer chemotherapy (CINV MEC). Intravenous palonosetron (Aloxi 0.25 mg I.V.) is approved for the prevention of acute CINV HEC, and acute and delayed CINV MEC.

On September 26, 2012, a type B, Pre-IND meeting was held between Helsinn Healthcare and FDA to discuss the development program for netupitant prodrug and palonosetron hydrochloride fixed combination for injection. Sponsor had since revised the clinical development approach in light of the recent Akynzeo approval. The sponsor proposes to move forward with the development of an intravenous dosage form of Akynzeo, which consists of 260 mg pro-netupitant (a netupitant pro-drug) + FDA approved 0.25 mg palonosetron as fixed combination (b) (4).

The August 4, 2014 meeting request was submitted by Helsinn Healthcare to discuss their updated development plans. Sponsor proposed to discuss with the FDA their nonclinical program, and clinical development plan (which included the scope and design of phase 1 program, the pro-netupitant dose selection strategy, and planned efficacy and safety study). Sponsor also aimed to present and discuss pro-netupitant drug substance and drug product CMC information to support planned clinical studies. This meeting was granted and scheduled December 9, 2014, according to meeting dates requested by the sponsor.

2.0 DISCUSSION

Question 1:
Pro-netupitant and palonosetron doses selected for Phase 3 - The dose of the pro-netupitant component in IV Akynzeo has been determined to be 260 mg based on PK and safety data from phase 1 study PNET-12-23, described in section 3.4.1.1. The dose of the IV palonosetron component in IV Akynzeo is 0.25 mg, the FDA-approved dose for Aloxi injection, as requested by the FDA at the pre-IND meeting held on September 26, 2012. The selected doses are intended to be used in the planned phase 3 pivotal efficacy and safety study NEPA-15-XX, described in section 3.4.2. Does the Agency agree on the pro-netupitant and palonosetron doses in the IV Akynzeo to be used in the planned phase 3 study?

FDA Response to Question 1:
We agree with the doses selected for phase 3 study based on PK and safety data from PNET-12-23 (pro-netupitant). Although we agree with the FDA-approved dose for Aloxi injection (0.25mg); we have concerns regarding the proposed change in duration of Aloxi infusion. See response to Question 2 below.

Question 2:
Adequacy of NEPA-15-XX as the sole efficacy study to support the IV Akynzeo NDA- Given that the IV Akynzeo program is a line- extension of the recently FDA-approved Akynzeo capsules (NDA 205718), NEPA-15-XX is planned to be the sole phase 3 clinical efficacy and safety trial in the IV Akynzeo NDA program (see section 3.4.2). Key features of the proposed pivotal study are as follows:

- Superiority design
- Palonosetron 0.25 mg IV (Aloxi) as the comparator

- CR in the delayed phase as the primary endpoint; CR in the overall and acute phases as the key secondary efficacy endpoints tested in hierarchical order (CR in the overall phase first and then CR in the acute phases)
- Study population: cancer patients scheduled to receive the first cycle of either cisplatin or AC/EC based chemotherapy

Does the Agency agree that the above listed key features of study NEPA-15-XX are adequate to support the target indication (see section 1.4)? Please comment as needed.

FDA Response to Question 2:

- **We agree with complete response (CR) in the delayed phase as primary endpoint; however, we do not agree with the order of testing for the secondary endpoints. CR acute phase should be tested before CR overall phase, as secondary endpoints.**
- (b) (4) (b) (4) **you must demonstrate the contribution of netupitant I.V. to efficacy in the delayed phase when it is combined with Aloxi I.V. The indication for Aloxi I.V. in HEC is limited to acute phase; therefore, it is not necessary to show the contribution of intravenous netupitant to delayed phase in HEC.**
- **We also recommend that you conduct an additional study, with a noninferiority design comparing the efficacy of the two palonosetron infusions (palonosetron 0.25 mg I.V. infusion for 30 min vs. palonosetron 0.25 mg I.V. infusion for 30 seconds), in the setting of HEC. The primary endpoint should be CR in the acute phase, and the primary objective should be to demonstrate noninferiority of the efficacy of the new proposed infusion time compared to the approved rapid infusion. The best source of information supporting the presumed comparable efficacy of the proposed prolonged infusion regimen for Aloxi 0.25 mg is the multi-arm oral Aloxi study that was the basis for approval of oral Aloxi for MEC. In that trial, the low dose oral Aloxi arm (0.25 mg), although not approved, was designated noninferior for CR acute phase, relative to intravenous Aloxi (0.25 mg). However, this was a MEC trial. In addition, the higher dose, 0.5 mg oral Aloxi, was the dose selected for approval. Your population PK/PD analysis report concludes that early palonosetron exposure parameters including Cmax, $AUC_{0\text{-}30\ min}$ (based on simulated early concentrations) were not correlated to responder status, but other observed AUCs of interest and dose were also not correlated with response. This lack of correlation with any exposure parameter of relevance was unexpected and therefore does not directly address our concern regarding the potential impact of differences in infusion rates (30 minutes for proposed vs. 30 seconds for approved Aloxi I.V.) on the efficacy of palonosetron in the acute phase. In addition, while we acknowledge that the Cmax following oral 0.5 mg palonosetron was lower than that of Aloxi I.V. bolus (considering the noninferiority comparison of approved doses of IV Aloxi 0.25**

mg and oral Aloxi 0.5 mg in the setting of HEC), the AUC parameters for the oral route were approximately 2-fold higher for the oral dose, which may have compensated for the lower Cmax. The AUC following the 30 minute infusion of palonosetron is expected to be similar to that following approved Aloxi I.V. bolus, and therefore may not compensate for any loss of efficacy due to lower Cmax due to slowed infusion.

(b) (4)

Question 3

Efficacy of palonosetron infused over 30 minutes in the acute phase- Akynzeo IV will be infused over 30 minutes while the comparator Aloxi IV will be administered as a bolus over 30 seconds, as per the approved Aloxi PI. At the pre-IND meeting held on September 26, 2012, the Agency asked the Sponsor to evaluate the impact of the increased administration time of palonosetron on the efficacy in the acute phase (0-24h). The Sponsor is providing in this package the results of PK/PD analyses on palonosetron showing lack of correlation between Cmax and Complete Response in the acute phase (see section 3.4.1.8 and Appendix #10). In addition, the Sponsor is presenting evidence that the palonosetron plasma concentrations after 30-second bolus (given as per the Aloxi PI approx. 30 minutes before the start of chemotherapy) or 15/30 minutes infusion are comparable at the time of the start of chemotherapy administration and afterwards (see section 3.4.1.8). These data indicate that the duration of IV administration (30-second bolus versus infusion up to 30 minutes) does not influence the efficacy of palonosetron 0.25 mg. Lastly, non-inferiority of 0.25 mg oral vs. 0.25 mg IV bolus palonosetron in preventing CINV in the acute phase was demonstrated in spite of a markedly different PK profile. In conclusion, the Sponsor believes that no further clinical data are needed to address the efficacy of palonosetron infused over 30-minute in the acute phase and that the proposed superiority design is able to isolate the contribution of the individual components to the efficacy of the Akynzeo IV combination product. Does the Agency agree? Please comment as needed.

FDA Response to Question 3:
See response to Question 2.

Question 4:

Safety evaluation for the NDA- As described in Section 3.4.3, the proposed single-cycle phase 3 trial NEPA-15-XX will enroll approximately 1000 patients of which 500 will be exposed to Akynzeo IV. The Akynzeo IV NDA will also include 178 healthy subjects exposed to IV pro-netupitant in Phase 1 studies PNET-12-23 and PNET-13-63. In addition, being Akynzeo IV a line-extension of oral Akynzeo, its safety evaluation will be also supported by the safety database obtained with netupitant and palonosetron in Akynzeo capsules (NDA 205718), including patients exposed to a large number of multiple chemotherapy cycles. Does the Agency agree on the adequacy of the proposed overall safety database for purposes of the planned NDA of Akynzeo IV? Please comment as needed.

FDA Response to Question 4:

The patient numbers described above may be acceptable. However, we cannot agree with

(b) (4)

- **You need to have repeat dosing safety with the new product, given the higher early exposure to netupitant (and the presence of prodrug).**

For these reasons we recommend a randomized, controlled, multi-cycle safety trial that enrolls patients receiving HEC. The control arm could be oral Akynzeo. The trial does not need to be powered to evaluate a specific safety parameter; however, you should propose the sample size and targeted duration of study that will adequately describe the safety of the new product.

Question 5:

Evaluation of pro-netupitant drug-drug interaction potential- Pro-netupitant showed limited exposure in human plasma after 30-min IV infusion. Most of the administered dose was rapidly converted into netupitant (PNET-12-23, section 3.4.1.1.2). Therefore, the in vitro and in vivo drug-drug interaction studies performed with netupitant and submitted in the Akynzeo capsules NDA are expected to obviate the need for further in vitro and in vivo drug-drug interaction investigations with pro-netupitant. Besides the in vivo interaction study between pro-netupitant and dexamethasone (PNET-13-63), the Sponsor has planned a set of pro-netupitant *in vitro* drug-drug interaction studies, including CYP isoform reversible and time dependent inhibition and drug transporter inhibition (see section 4.4.10.4 and 3.4.1.6.2), according to the recommendations of the FDA "Guidance for Industry on Drug Interaction Studies". Does the Agency agree on the acceptability of this plan to evaluate pro-netupitant drug-drug interaction potential in the planned Akynzeo IV NDA? Please comment as needed.

FDA Response to Question 5:

Your plan to address pro-netupitant drug interactions on major CYP450 enzymes and transporters by means of in vitro studies appears reasonable. In vivo studies may also be needed depending on the findings from the in vitro studies. You will also need to address the drug interaction potential of pro-netupitant with concomitantly dosed palonosetron.

Question 6:
PK evaluation in cancer patients and overall biopharm/PK NDA Program- To complete the clinical biopharm/PK program, in addition to clinical studies PNET-12-23 and PNET-13-63 and the planned in vitro drug-drug interaction studies, as an alternative to a Pop PK study for the reasons explained in section 3.4.1.5, the Sponsor proposes a standard full PK clinical study with dense sampling in a separate group of cancer patients, as described in section 3.4.1.5. This study will be performed in parallel to phase 3 study NEPA-15-XX. This study will adequately characterize the PK profile of the combination of a 260 mg IV pro-netupitant with a 0.25 mg palonosetron IV infusion in the target population. The effects of demographic, physiopathological and treatment related covariates on PK parameters and on their variability have already been investigated for palonosetron, netupitant and its metabolites M1, M2, M3 in the Pop PK study (NETU-10-12) submitted with the Akynzeo capsules NDA. Does the Agency agree on the acceptability of this plan to evaluate PK in cancer patients and on the overall acceptability of the proposed biopharm/PK plan to support the Akynzeo IV NDA? Please comment as needed.

FDA Response to Question 6:
Yes, we agree.

Question 7:
Nonclinical Abuse Liability- The oral combination of netupitant and palonosetron (submitted in the Akynzeo capsules NDA 205718) has been extensively studied in a battery of behavioural test in baboons (see section 4.4.4). More recently, additional studies have been conducted with netupitant alone (self-administration test; NETU-13-74) and with the oral combination with higher doses of palonosetron (NETU-11-24). The overall results suggest a lack of abuse or dependence potential of netupitant and of the combination. Since preclinical data on the combination of pro-netupitant and palonosetron indicate a rapid conversion of pro-netupitant into netupitant (see section 4.4.3), additional abuse liability pharmacology studies on pro-netupitant alone and on the combination pro-netupitant + palonosetron are not planned. Does the Agency agree? Please comment as needed.

FDA Response to Question 7:
We agree that nonclinical abuse-related studies will not be required for pro-netupitant alone or for the combination of pro-netupitant + palonosetron via the intravenous route of administration.

Question 8:
Carcinogenicity Studies- FDA letter dated July 22, 2008, (IND 73,493) regarding the oral Akynzeo NDA program, confirmed that, "*Per the Executive CAC committee's recommendation dated July 7, 2008, the Division of Gastroenterology Products agrees that netupitant rat and mouse carcinogenicity studies will not be required to support the chemotherapy induced nausea*

and vomiting (CINV) indication." Consistent with this earlier FDA feedback, since IV Akynzeo is a line-extension of oral Akynzeo targeted for the same indication, and pro-netupitant is rapidly converted into netupitant in preclinical studies (please see section 4.4.6 and 4.4.7), carcinogenicity studies are not planned. Does the Agency agree? Please comment as needed.

FDA Response to Question 8:
Yes, we agree. However, if you seek approval for other indications, carcinogenicity studies may be needed.

Question 9:
Overall Pharm/Tox Data to Support the Planned Akynzeo IV IND for Clinical Study NEPA-15-XX and the planned NDA- In the planned Akynzeo IV IND, to support clinical study NEPA-15-XX the Sponsor plans to reference and rely on (1) palonosetron safety pharmacology, pharmacology, toxicology, mutagenicity, reprotox and carcinogenicity studies included in previously FDA-approved IV Aloxi NDA 21-372; (2) netupitant and netupitant + palonosetron safety pharmacology, pharmacology, toxicology, mutagenicity and reprotox studies included in previously FDA-approved Akynzeo capsules (NDA 205718) described in Appendix #4b and (3) on the pro-netupitant and pro- netupitant + palonosetron pharm/tox studies described in section 4.4 and Appendix #4a. The NDA program will be completed with the pre- and post-natal development study in rats (Segment 3) as requested by the Agency during the pre-IND meeting held on September 26, 2012. This study will be performed in parallel with the phase 3 study NEPA-15-XX. Does the Agency agree on the adequacy of this pharm/tox program to support the Akynzeo IV IND and NDA? Please comment as needed.

FDA Response to Question 9:
Your proposed nonclinical program appears adequate to support the proposed clinical study under the IND, and an NDA submission. However, determination of whether the toxicology studies provide a reasonable assurance of safety for the proposed clinical study will be based on our review and evaluation of the full study reports.

If the commercial formulation contains excipients that were not included in the previous formulations tested in animals and humans, it is possible that a nonclinical local tolerance study and additional nonclinical studies will be needed to support an NDA submission. We recommend that you consult with the Agency about this issue prior to submitting an NDA.

Question 10:
Pro-netupitant Drug Substance- As described in section 5.2.1.2, the sponsor is proposing that (b) (4) are designated as starting materials for the (b) (4) synthesis. Does the Agency agree with the proposed starting material designation?

FDA Response to Question 10:
(b) (4) **they should be acceptable as starting materials in the synthesis of** (b) (4)**. For** (b) (4)**, since it is**

(b) (4) **, it also should be an acceptable starting material. The key factor that will be considered in determining the acceptability of each of these starting materials will be the impurity specification limits that are defined and the fate of these impurities in the synthesis.**

Question 11:
Akynzeo IV Drug Product- As described in section 5.3.2, the sponsor is considering conducting the phase 3 clinical study NEPA-15-XX using an IV fixed dose combination prepared extemporaneously at the time of administration. The formulation consists of pro-netupitant formulated as a lyophilized powder (the same product used in phase 1 studies PNET-12-23 and PNET-13-63) and Aloxi injection (Palonosetron 0.25 mg). The two components will be compounded at the time of administration: the lyophilized powder will be dissolved with 0.9% NaCl or 5% glucose, combined with Aloxi injection and diluted to a final volume of 50 mL for the administration. The intended commercial Akynzeo IV will consist in a vial containing pro-netupitant and palonosetron HCl formulated together *either* as a lyophilized powder for reconstitution *or* a ready to use solution. The commercial formulation is still under development and therefore the sponsor does not plan to introduce it in the phase 3 trial.

Based on the rationale provided in section 5.3.2, does the Agency agree that the change in formulation from the phase 3 extemporaneous solution to the intended commercial drug product will not require any additional clinical study? Please comment as needed.

FDA Response to Question 11:
Yes – we agree that no additional clinical study will be required, since both formulations contain the same components (b) (4)

Question 12:
The Sponsor plans to submit an initial Pediatric Study Plan according to the FDA Guidance "*Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*", dated July 2013. Because the Akynzeo IV program does not involve a phase 2 study and sponsor plans to open an IND with submission of IV Akynzeo phase 3 protocol NEPA-15-XX, the Sponsor proposes to submit an initial Pediatric Study Plan after submission of the IND but before start of enrollment in study NEPA-15-XX. Does the Agency agree? Please comment as needed.

FDA Response to Question 12:
Yes, we agree.

3.0 ADDITIONAL FDA COMMENTS

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input

from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

4.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts were used during the discussion at the meeting.

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
12/17/2014

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210493

LATE-CYCLE MEETING MINUTES

Helsinn Healthcare SA
c/o August Consulting, Inc.
Attention: Craig Lehmann, PharmD.
Authorized Representative
515 Capital of Texas Highway, Suite 150
Austin, TX 78746

Dear Dr. Lehmann:

Please refer to your New Drug Application (NDA) dated April 20, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Akynzeo (fosnetupitant and palonosetron) for injection, for intravenous use.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 6, 2018.

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}

Anil Rajpal, 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: February 6, 2018 1:00 PM EST
Meeting Location: Teleconference

Application Number: NDA 210493
Product Name: Akynzeo (fosnetupitant and palonosetron) for injection, for intravenous use
Indication: Prevention of chemotherapy-induced nausea and vomiting
Applicant Name: Helsinn Healthcare SA
Meeting Chair: Anil Rajpal, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Joette Meyer, PharmD.	Associate Director for Labeling
Anil Rajpal, M.D.	Medical Team Lead
Charles Line, M.D.	Medical Reviewer
Mary Chung, PharmD.	Senior Regulatory Project Manager

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Clinical Pharmacology Team Lead
Elizabeth Shang, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Hitesh Shroff, Ph.D.	Application Team Lead

Division of Biometrics III

Yeh-Fong Chen, Ph.D.	Statistical Team Lead
Min Min, Ph.D.	Statistics Reviewer

Office of Surveillance and Epidemiology

Erin South	Reviewer, Division of Risk Management

APPLICANT ATTENDEES

Sergio Cantoreggi, Chief Scientific Officer
Alberto Bernareggi, Clinical R&D, Clinical Pharmacology Director
Giada Rizzi, Statistics & Data Management Manager

Emanuela Lovati, Preclinical Development Manager
Claudio Giuliano, Preclinical Development and DMPK Manager
Alessio Venturini, Pharmaceutical Development Manager
Giuseppina Clerici, Drug Safety Deputy Director
Mauro Catena, Regulatory Affairs Manager
Angioletta Navini, Regulatory Affairs Senior Manager
Virginia Cuervo Alvarez, Head of Regulatory Affairs and Drug Safety
Jason Najdzinowicz, Executive Director, Quality Assurance, Regulatory Affairs and Drug Safety – Helsinn Therapeutics
Craig Lehmann, U.S. Agent for the NDA

1.0 BACKGROUND

NDA 210493 was submitted on April 20, 2017 for Akynzeo (fosnetupitant and palonosetron) for injection, for intravenous use.

Proposed indication(s): Akynzeo for injection is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

PDUFA goal date: April 20, 2018

FDA issued a Background Package in preparation for this meeting on January 24, 2018.

2.0 DISCUSSION

1. Introductory Comments

2. Review Plans
   PDUFA goal date: April 20, 2018

3. Wrap-up and Action Items

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/

ANIL K RAJPAL
03/08/2018