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December 21, 2022

Dr. Jessica J. Lee, MD, MMSc
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology
10903 New Hampshire Avenue, Silver Spring, MD 20993
Building 22, Suite 4177

Subject: **NDA 205718, Sequence 0153**

Product: **Akynzeo® (netupitant-palonosetron hydrochloride) Capsules**

Ref: **RESPONSE TO PREA NON-COMPLIANCE LETTER**

Cross ref: **Palonosetron HCl and Netupitant Fixed Combination, Oral IND 073493 and Akynzeo® (fosnetupitant and palonosetron) for Injection NDA 210493**

Dear Dr. Lee:

Reference is made to Helsinn's New Drug Application (NDA) 205718 for Akynzeo® (netupitant and palonosetron) Capsules approved on October 10, 2014, 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 and to Helsinn's Investigational New Drug (IND) 073493 for Palonosetron HCl and Netupitant Fixed Combination.

Reference is also made to the *Notification of Non-Compliance with PREA* issued by the Agency on November 17th, 2022, for the PREA PMR 2769-3. The purpose of this submission is for the Sponsor to officially respond to the notification mentioned above letter and request the release and the reissue of the PREA PMR 2769-3.

Background

Helsinn initially registered an oral combination product containing netupitant 300 mg and palonosetron 0.5 mg, Akynzeo capsules, and agreed with the Agency to the following listed PREA PMRs:

2769-1 (NETU-14-47) An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone.

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

2769-2 (NEPA-15-31) A PK/PD dose-finding study of netupitant to characterize the netupitant PK/PD relationship for complete response in the delayed phase following oral administration of a single dose of netupitant given concomitantly (in separate formulations) with a single oral administration of palonosetron in pediatric cancer patients ages 0 to17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age-appropriate formulation.

Final Protocol Submission: 11/01/2015: *completed*
Study Completion: 09/30/2019: *completed*
Final Report Submission: 06/30/2020: *completed*

2769-3 (NEPA-Protocol Number To-Be-Determined) An adequate, well-controlled, double-blind, randomized study to evaluate the safety and efficacy of a dose of the netupitant/palonosetron fixed combination compared to standard therapy in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age-appropriate formulation.

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

Helsinn had also registered an intravenous formulation of Akynzeo, a fixed dose combination of fosnetupitant (a water soluble phosphorylated pro-drug of netupitant rapidly converted to netupitant in vivo following IV administration) and palonosetron. Akynzeo IV was initially approved as a powder to be reconstituted prior to dilution (NDA 210493) and then approved as a liquid formulation ready to be diluted, Akynzeo Injection (NDA 210493 S-002).

IV Akynzeo is comprised of 235 mg fosnetupitant (corresponding to 260 mg of fosnetupitant chloride hydrochloride, the dose able to yield exposure to netupitant equivalent to that provided by an oral administration of 300 mg netupitant, registered component of Akynzeo capsules) and 0.25 mg palonosetron (the IV palonosetron dose registered as Aloxi).

Current PREA PMRs studies agreed for Akynzeo for injection are listed here below:

3292-1 (NEPA-21-01) An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with fosnetupitant (pro-netupitant) alone.

Final Protocol Submission: 06/2020: *completed*
Study Completion: 06/2021: *completed*
Final Report Submission: ~~09/2021~~ 01/2022: *completed*

3292-2 (NEPA-Protocol Number Protocol Not yet defined) An open-label, pharmacokinetic and safety study of intravenous fosnetupitant/ palonosetron combination in pediatric cancer patients ages 0-17 years for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

Final Protocol Submission: 01/2022: *Not yet started*
Study Completion: 07/2024: *Not yet started*
Final Report Submission: 12/2024: *Not yet started*

The pediatric clinical development was slower than expected due to many issues encountered in patients' recruitment in the study NEPA-15-31 (PREA PMR 2769-2), especially in the younger age groups (less than one year of age). In fact, in December 2019, the Sponsor requested a deferral for the final report submission of study NEPA-15-31, contextually with a deferral for all milestones related to PREA PMR 2769-3.

FDA replied on February 21, 2020, by granting a deferral for the submission of the final report of NEPA-15-31 (PREA PMR 2769-2) up to June 30, 2020. In the same letter, FDA also stated that "as the protocol for PREA PMR 2769-3 is dependent on the results of PREA PMR 2769-2, our decision on the acceptability of the proposed deferral extension for PREA PMR 2769-3 will be made after our review of the final report you submit to the application for PREA PMR 2769-2".

Following the completion of the NEPA-15-31 Clinical Study (PREA PMR 2769-2), the Sponsor has started discussing with the Agency the possibility of shifting the PREA requirement for an adequate and well controlled safety and efficacy study from the oral Akynzeo PREA program to the IV Akynzeo PREA program; the rationale behind this request was based on the below considerations:

- an intravenous formulation of an antiemetic drug is a more convenient treatment option for oncologists since it can be adjusted to the paediatric cancer patient's body weight more easily compared to an oral combination product.
- an intravenous formulation of an antiemetic drug is an important alternative option for paediatric patients who can't swallow orally administered medications
- an intravenous formulation of an antiemetic drug is preferred by paediatric oncologists for better compliance and ease of use since essentially all paediatric cancer patients receiving chemotherapy have a central venous catheter placed for purposes of IV administration
- There is an unmet medical need for IV treatment to prevent chemotherapy-associated nausea and vomiting in children

therefore, data from an adequate and well controlled safety and efficacy PREA study on IV Akynzeo would be more clinically meaninguful than such a trial on oral Akynzeo since a paediatric formulation of IV Akynzeo is expected to better address the clinical needs.

Given the complexity of the proposed changes to the agreed PREA PMRs for both oral and IV Akynzeo, various interactions with the Agency have occurred between mid-2020 and mid-2022, a detailed summary table listing all the interactions between the Sponsor and the FDA is provided in Table 1. Following the last WRO letter dated March 30 2022, the Sponsor has put

forth its best effort to timely submit a draft version of the Clinical Study Protocol (NEPA-22-01) intended to address the future reissued PREA PMR 3292-2.

While working diligently on a draft version of the Clinical Study Protocol proposed for a new PREA PMR 3292-2, the Sponsor failed to promptly submit a request of release of the existing PREA PMR 2769-3 and sincerely apologize.

Table 1: Summary Table of interactions between the Sponsor and FDA related to the revisions of the PREA PMRs.

Date	Helsinn / *FDA Communication*	Type of submission
April 21, 2020	Helsinn	Type C Meeting request submitted within S0129
May 28, 2020	Helsinn	Meeting package submitted within S0130
July 23, 2020	*FDA*	*Meeting Request – Written Responses*
May 10, 2021	Helsinn	Type C Meeting request submitted within S0143
June 7, 2021	Helsinn	Meeting package submitted within S0144
July 23, 2021	*FDA*	*Meeting Request – Written Responses*
January 14, 2022	Helsinn	Type C Meeting request submitted within S0149
February 11, 2022	Helsinn	Meeting package submitted within S0150
March 30, 2022	*FDA*	*Meeting Request – Written Responses*
June 15, 2022	Helsinn[1]	Submission of Draft Clinical Study Protocol NEPA-22-01 under IND 115191
October 3, 2022	*FDA*[2]	*Advice/Information Request received on the draft NEPA-22-01 Protocol*

Request for release and reissue of PREA PMR 2769-3

Helsinn deeply regrets the delay in the pediatric development of Akynzeo, which is also due to the evolving thinking on pediatric development and the Sponsor's intention to offer the medical community a product aligned as much as possible the real medical needs.
As recommended by the Agency in the March 30th, 2022 WRO Letter, the Sponsor is requesting the Agency to release and reissue the PREA PMR 2769-3 as follows:

~~2769-3 An adequate, well-controlled, double-blind, randomized study to evaluate the safety and efficacy of a dose of the netupitant/palonosetron fixed combination compared to standard therapy in pediatric cancer patients ages 0 to17 years undergoing treatment~~

[1] Amendment submitted by the Sponsor under Akynzeo (fosnetupitant and palonosetron) injection IND 115191
[2] Advice/Information request received from FDA under Akynzeo (fosnetupitant and palonosetron) injection IND 115191

~~with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age-appropriate formulation.~~

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

2769-3 A PK, PD, safety, and tolerability study with single and multi-day administration of oral netupitant/palonosetron fixed combination for the prevention of nausea and vomiting in pediatric patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age-appropriate formulation.

Final Protocol Submission: 01/2028
Study Completion: 01/2030
Final Report Submission: 07/2030

The content of this sequence 0153 has been scanned for viruses with AVG Business edition and resulted virus free.

For any questions, please contact me as Authorized Representative for this NDA at 908-285-3057.

Sincerely,

DocuSigned by:
Jason Najdzinowicz
Signer Name: Jason Najdzinowicz
Signing Reason: I approve this document
Signing Time: 19-Dec-2022 | 5:54 PM GMT
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