

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210493Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review Office

Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210493
Priority or Standard	Standard
Submit Date(s)	04/20/2017
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Division/Office	DGIEP/ODEIII
Reviewer Name(s)	Charles Line MD
Review Completion Date	12/15/2017
Established Name	fosnetupitant/ palonosetron
(Proposed) Trade Name	Akynzeo® for injection
Applicant	Helsinn Healthcare SA
Formulation(s)	235mg fosnetupitant/0.5 mg palonosetron lyophilized powder in single-dose vial for reconstitution
Dosing Regimen	1 vial of Akynzeo; infuse over 30 minutes starting 30 minutes before chemotherapy.
Applicant Proposed Indication(s)/Population(s)	AKYNZEO for injection is indicated for the 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 netupitant (capsules) or fosnetupitant, a pro-drug of netupitant (for injection): palonosetron prevents nausea and vomiting during the acute phase and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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. AKYNZEO for injection is a combination of palonosetron and fosnetupitant, a prodrug of netupitant: 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. Limitations of Use AKYNZEO for injection has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Akynzeo® for injection is a combination antiemetic medication containing 235 mg of fosnetupitant (a NK1 antagonist) and 0.25 milligrams of palonosetron (a 5HT3 antagonist). This product is a lyophilized powder contained in a vial and is reconstituted in 50 milliliters of 5 percent Dextrose Injection, USP or 0.9 % Sodium Chloride Injection, USP.

The proposed dosing recommendations are for administration of one vial as a 30-minute intravenous infusion starting 30 minutes prior to the start of chemotherapy. The proposed dosing recommendations also state that dexamethasone 12 mg should be administered 30 minutes prior to chemotherapy, followed by dexamethasone 8 mg once a day on Days 2 to 4.

The proposed indication of Akynzeo for Injection is “for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy”. It should be noted that the proposed indication also includes a statement that 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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Clinical reviewer, CDTL, Division Director and ODE III Director all recommend approval of NDA 210493 for Akynzeo for injection (fosnetupitant and palonosetron fixed dose combination) for the indication: “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.”; the indication should include a statement that Akynzeo for injection is a fixed combination of palonosetron and fosnetupitant, a pro-drug of netupitant; and should include a statement that 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. Furthermore, the following Limitations of Use statement should be added: “AKYNZEO for injection has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide chemotherapy.”

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Akynzeo for injection (fosnetupitant and palonosetron fixed dose combination) is proposed for an indication in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy or HEC. Akynzeo® for injection is recommended for approval with an indicated population of HEC not including anthracycline/cyclophosphamide (AC) based chemotherapy. The benefit of this product, when used in combination with dexamethasone, is to prevent chemotherapy induced nausea and vomiting (CINV) in this population.

CINV diminishes the quality of life of cancer patients receiving HEC. The current standard of care is for patients about to receive HEC chemotherapy to receive both a 5-HT₃ receptor antagonist and an NK₁ receptor antagonist, in combination with dexamethasone. There are multiple medications with HEC indications (in both IV and oral dosage forms) that represent each of these drug classes; in addition, the oral dosage form of Akynzeo (netupitant and palonosetron) is approved with a HEC indication.

The evidence for the effectiveness of Akynzeo for injection includes:

- (i) Studies that supported the approval of Akynzeo capsules: Akynzeo capsules are indicated for **HEC including AC** in both the acute and delayed phases. The effect of **palonosetron** was demonstrated in the **acute phase**, and the effect of **netupitant** was demonstrated in both the **acute and delayed phases**.
- (ii) Studies that supported the approval of Aloxi (palonosetron) IV: Aloxi (**palonosetron**) **IV** is indicated for **HEC in the acute phase**; and for moderately emetogenic chemotherapy (MEC) in both the acute and delayed phases. It should be noted that the studies supporting this indication were based on a former classification of HEC and MEC where **HEC did not include AC**, and MEC included AC.
- (iii) Studies submitted in the current NDA: These are described below.
 - Non-Inferiority Trial (Palonosetron 30-minute vs. 30 second infusion; Study PALO 15-17): This was a non-inferiority (NI) study in the **acute phase** conducted in a HEC population that did not include patients treated with AC comparing **palonosetron infused over 30 minutes** (as in the proposed product) to palonosetron infused over 30 seconds (as approved for Aloxi IV). Non-inferiority was demonstrated for the Complete Response endpoint in the acute phase.
 - Relative Bioavailability Study (IV fosnetupitant vs. oral netupitant; Study PNET 12-23): This was a relative bioavailability study in healthy subjects which included a comparison of 260 mg of **IV fosnetupitant** (a prodrug of netupitant) with 300 mg of oral netupitant (the dose of netupitant in the approved Akynzeo capsules). Bioequivalence criteria were met (for AUC_{0-120h} and AUC_{0-∞}).

The effect of **palonosetron infused over 30 minutes** was demonstrated in the **acute phase** in the population of **HEC not including AC**, and the effect of **IV fosnetupitant** was demonstrated in the **acute and delayed phases** in the population of **HEC not including AC**. It should be noted that because palonosetron IV has a delayed phase indication in the AC population but palonosetron PO does not, **demonstration of the contribution of fosnetupitant IV in the delayed phase in the AC population would be needed for an Akynzeo IV indication in the delayed phase in the AC population and MEC.**

The following additional study was conducted:

- Active control study (Akynzeo for infusion vs. Akynzeo capsules; NEPA 15-18): This was an active control study (not designed as a NI trial) with four HEC not including AC cycles. The results suggested similar safety between the two arms.

No new safety signals were identified as compared to approved Akynzeo capsules. No risk management strategies beyond product labeling are recommended.

This product is expected to be of benefit to patients receiving HEC not including AC who cannot tolerate oral therapy; these are patients receiving the most emetogenic chemotherapy regimens. Furthermore, the product will provide both 5-HT₃ and NK₁ receptor antagonist therapy with the administration of a single medication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• Chemotherapy induced nausea and vomiting (CINV) especially in patients receiving HEC has a significant impact on the quality of life of cancer patients who are undergoing treatment for their disease.	• Akynzeo® for injection will provide significant benefit by preventing CINV in patients receiving HEC not including AC.
<u>Current Treatment Options</u>	• There are multiple antiemetics with HEC indications (in both IV and oral dosage forms) that represent each of the drug classes in Akynzeo for injection (i.e., 5-HT₃ receptor antagonist and NK₁ receptor antagonist); in addition, the oral dosage form of Akynzeo (netupitant and palonosetron) is approved with a HEC indication.	• Akynzeo® for injection offers additional benefit to the existing treatment options by providing an alternative to cancer patients who cannot tolerate oral medication. Further, per the most recent ASCO guidelines, patients receiving HEC should be treated with both 5HT₃ and NK₁ receptor antagonists to prevent CINV. As a fixed dose combination product, Akynzeo® for injection allows for these patients to be treated with a single infusion instead of two separate infusions of a 5HT₃ inhibitor and another approved NK-1 inhibitor.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The evidence for the effectiveness of Akynzeo for Injection includes: (i) <u>Studies that supported the approval of Akynzeo capsules</u>: Akynzeo capsules are indicated for HEC including AC in both the acute and delayed phases. The effect of palonosetron was demonstrated in the acute phase, and the effect of netupitant was demonstrated in both the acute and delayed phases. (ii) <u>Studies that supported the approval of Aloxi (palonosetron) IV</u>: Aloxi (palonosetron) IV is indicated for HEC in the acute phase; and for moderately emetogenic chemotherapy (MEC) in both the acute and delayed phases. It should be noted that the studies supporting this indication were based on a former classification of HEC and MEC where HEC did not include AC, and MEC included AC. (iii) <u>Studies submitted in the current NDA</u>: These are described below. <u>Non-Inferiority Trial (IV Palonosetron 30 minute vs. 30 second infusion; Study PALO 15-17)</u>: This was a non-inferiority (NI) study in the acute phase conducted in the HEC not including AC population comparing palonosetron infused over 30 minutes (as in the proposed product) to palonosetron infused over 30 seconds (as approved for Aloxi IV). Non-inferiority was demonstrated for the Complete Response endpoint in the acute phase. <u>Relative Bioavailability Study (IV fosnetupitant vs. oral netupitant; Study PNET 12-23)</u>: This was a relative bioavailability study in healthy subjects which included a comparison of 260 mg of IV fosnetupitant (a prodrug of netupitant) with 300 mg of oral netupitant (the dose of netupitant in the approved Akynzeo capsules). Bioequivalence criteria were met (for AUC_{0-120h} and AUC_{0-∞}). The effect of palonosetron infused over 30 minutes was demonstrated in the acute phase in the population of HEC not including AC, and the effect of IV fosnetupitant was demonstrated in the acute and delayed phases in the population of HEC not including AC. It should be noted that because	- The effect of IV palonosetron 30-minute infusion was demonstrated in the acute phase in the population of HEC not including AC. - The effect of IV fosnetupitant was demonstrated in both the acute and the delayed phase in the population of HEC not including AC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	palonosetron IV has a delayed phase indication in the AC population but palonosetron PO does not, <u>demonstration of the contribution of fosnetupitant IV in the delayed phase in the AC population would be needed for an Akynzeo IV indication in the delayed phase in the AC population</u> and for MEC.	
Risk	No new safety signals were identified as compared to approved Akynzeo capsules.	The safety profile is acceptable.
Risk Management	The risks of this product are well-described and there are no uncertainties that need further attention or investigation.	No risk management strategies beyond product labeling are recommended

1.4. Patient Experience Data

Per the applicant:

“The 21st Century Cures Act was enacted 13Dec2016, and the IV NEPA NDA was submitted 20 April 2017, a difference of 129 days. Title III of the Act (attached) states, “*Following the approval of an application that was submitted under section 505(b) of this Act [i.e., an NDA] or section 351(a) of the Public Health Service Act [i.e., certain biologic license applications] at least 180 days after the date of enactment of the 21st Century Cures Act, the Secretary [FDA] shall make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such application.*” [underline added]

Since the 21st Century Cures Act was enacted 13Dec2016 and the IV NEPA NDA was submitted 20April2017, and the timeframe between these dates is 129 days, not the at least 180 days the law states above, the applicant is not required to submit patient experience data.

2 Therapeutic Context

2.1. Analysis of Condition

Chemotherapy-induced nausea and vomiting (CINV), particularly nausea, is still cited by cancer patients as having the highest impact on their quality of life.¹ Risk factors for CINV include young age, female sex, platinum- or anthracycline-based chemotherapy, nondrinker status, emesis in the earlier cycles of chemotherapy, and a previous history of motion/ morning sickness.¹ Patients who are undergoing chemotherapy can experience nausea and vomiting in the acute phase (0-24 hours after chemotherapy initiation), the delayed phase (>24-120 hours after chemotherapy administration), or the overall phase (0-120 hours after chemotherapy administration). The emetogenicity of the chemotherapy also has an impact on CINV. The medications included in highly emetogenic chemotherapy (HEC) include but are not limited to cisplatin, carmustine, cyclophosphamide, dacarbazine, mechlorethamine, and streptozotocin.² In 2011, the American Society of Clinical Oncology (ASCO) reclassified anthracycline-cyclophosphamide (AC) chemotherapy combinations from moderately emetogenic chemotherapy (MEC) to HEC even though the likelihood of emesis on these medications without antiemetic prophylaxis was 85 % while the rest of the medications in HEC were 90% or greater.³ In general, the emetic risk associated with HEC is greater than or equal to 90%. For MEC, the

¹ Lorusso, V. Management of chemotherapy-induced nausea and vomiting by risk profile: role of netupitant/palonosetron. *Therapeutics and Clinical Risk Management*. 2016 Jun 7;12:917-25. doi: 10.2147/TCRM.S89215. eCollection 2016.

² Hesketh, P.J. *et al.* Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 2017 35:28, 3240-3261.

³ www.asco.org/guidelines/antiemetics

emetic risk is from 30-90 percent.

2.2. Analysis of Current Treatment Options

With respect to CINV, there are two main classes of medications that are used: neurokinin 1 (NK₁) receptor antagonists and serotonin (5-HT₃) receptor antagonists. 5-HT₃ antagonists are thought to work in the acute phase whereas NK₁ inhibitors are thought to work in both the acute phase and the delayed phase. The only exception to this is IV palonosetron which has an indication for delayed phase MEC.

The 2017 ASCO guidelines recommend that adult patients who are treated with cisplatin and other high-emetic-risk single agents should be offered the four-drug combination of a NK₁ receptor antagonist, a 5-HT₃ receptor antagonist, dexamethasone, and olanzapine. As per these guidelines, dexamethasone and olanzapine should be continued on days 2 to 4.¹ Adult patients who are treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK₁ receptor antagonist, a 5-HT₃ receptor antagonist, dexamethasone, and olanzapine. Olanzapine should be continued on days 2 to 4.¹ It should be noted that olanzapine is not approved for this indication. The basis of the recommendation in the 2017 ASCO guidelines is a phase 3 randomized controlled trial which suggested that adding olanzapine to antiemetic prophylaxis (dexamethasone, aprepitant or fosaprepitant, and a 5-hydroxytryptamine type 3–receptor antagonist) reduces the likelihood of nausea among adult patients who are treated with high emetic risk antineoplastic agents (patients with no previous chemotherapy who were receiving cisplatin or cyclophosphamide–doxorubicin).⁴ Although olanzapine has not been included in the designs of studies by commercial sponsors for this indication (i.e., “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”), we anticipate that in the future, sponsors will propose that olanzapine also be included in these study designs. Dexamethasone, which currently appears in the dosage and administration instructions in the labels of approved antiemetics as a component of a combination regimen for prevention of chemotherapy induced nausea and vomiting (CINV), also does not have a CINV indication in its product labeling.

The first 5HT₃ inhibitor, intravenous ondansetron was approved in January 1991. Its indication statement did not address HEC or MEC: “prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.” Oral ondansetron was approved in December 1992, and the indication statement did contain language regarding HEC and MEC.

Intravenous granisetron was approved in 1993, and its indication statement contained general language (i.e., “emetogenic cancer therapy”); however, there was also a qualifier included, “including high dose cisplatin.” The Clinical Studies section also had a subsection called “moderately emetogenic chemotherapy study” that specifically described MEC as carboplatin, cisplatin 20-50 mg/m², and cyclophosphamide >600 mg/m².

Oral dolasetron was approved in September 1997 with the indication “prevention of nausea and

⁴ Navari RM, Qin R, Ruddy KJ et al., “Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting”, *N Engl J Med* 2016; 375:134-142.

vomiting associated with moderately emetogenic cancer chemotherapy, including high dose cisplatin.” The NDA had a single MEC study which was described under the header “Cyclophosphamide Based Chemotherapy” and describes the study as primarily enrolling women receiving “moderately emetogenic chemotherapy such as cyclophosphamide based regimens.”

Intravenous palonosetron was approved in July 2003 with indications specifically identifying HEC and MEC. Oral palonosetron was approved in 2008 with an indication limited to MEC. Due to its long half-life, the clinical development plans for both the intravenous and oral versions of this drug included evaluations in the acute and delayed phases. IV palonosetron was demonstrated to show efficacy in the acute and delayed phases of MEC (the majority of the patients received anthracycline plus cyclophosphamide chemotherapy, approximately 60%), but was only shown to be efficacious in the acute phase of HEC. Oral palonosetron has no indication for the delayed phase as oral palonosetron 0.5 mg was not found to be non-inferior to IV palonosetron 0.25 mg.

The treatments for CINV are summarized in Table 1. The regulatory significance will be further discussed in section 3.

Table 1 - Antiemetic Medications with an Indication for CINV

5HT3	Dosage Form	HEC vs MEC, Acute vs Delayed Phase)	Year Approved
Zofran (Ondansetron)	Oral and IV	Oral – HEC and initial and repeat courses of MEC IV - Nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy	IV-1991 Oral -1992
Anzemet (Dolasetron)	Oral and IV	Oral - Initial and repeat MEC in patients ≥ 2 years old IV – indications are for postoperative nausea and vomiting	Oral and IV - 1997
Kytril/ Sustol (Granisetron)	Oral, IV, extended Injection (Sustol)	Kytril (discontinued) - Initial and repeat courses emetogenic cancer chemotherapy, including high dose cisplatin Sustol - prevention of acute and delayed nausea and vomiting with initial and repeat MEC and AC	Kytril - 1993 Sustol - 2016
Aloxi (Palonosetron)	Oral and IV	Oral – MEC acute phase IV - MEC acute and delayed, HEC acute.	Oral – 2008 IV - 2003
NK1	Dosage Form	Indication (HEC vs MEC, Acute vs Delayed	
Emend (aprepitant/fosaprepitant)	Oral and IV	Oral – Initial and repeat courses for acute and delayed HEC. Initial and repeat courses of MEC IV – delayed nausea and vomiting associated with initial and repeat MEC	HEC - 2003 MEC - 2005

Varubi (rolapitant)	Oral and IV	Prevention of delayed nausea and vomiting with initial and repeat courses including but not limited to HEC	Oral – 2015 IV – 2017
5HT3 and NK1	Dosage Form	HEC vs MEC, Acute vs Delayed Phase)	Year Approved
Akynzeo® capsules	Oral	“including but not limited to HEC” acute and delayed phases	2014

(Source – Reviewer’s Table)

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Akynzeo® for injection is proposed as a fixed dose combination product containing fosnetupitant and palonosetron. Akynzeo® capsules (netupitant + palonosetron HCl), which is currently marketed as a fixed dose combination product, was approved in October 2014 (NDA 205718) for the following indication:

“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.”

In addition to being marketed in this country, oral Akynzeo® is also currently being sold abroad (Europe).

The applicant’s proposed indication is for the acute and delayed phase of HEC. There have been no other indications proposed.

3.2. Summary of Presubmission/Submission Regulatory Activity

In 2011, ASCO reclassified anthracycline-cyclophosphamide (AC) chemotherapy combinations from MEC to HEC even though the likelihood of emesis on these medications without antiemetic prophylaxis was 85% while the rest of the medications in HEC were 90% or greater.³ This created several challenges for the Division from a regulatory perspective, in considering the appropriate indication (HEC/MEC) for programs in which the MEC development had focused on patients receiving AC combination chemotherapy. Traditionally, clinical trials designed to obtain MEC indications were designed using patients on anthracycline-cyclophosphamide chemotherapy combinations, predominantly breast cancer patients. In general, females have not been as responsive to antiemetic prophylaxis in the setting of CINV. After reviewing the regulatory history and development programs for products with MEC and/or HEC indications, the Division concluded there was a lack of persuasive evidence that a product effective for HEC would not also be effective for MEC. It seemed reasonable to conclude that if a product was shown to be effective to prevent CINV in the setting of cisplatin based HEC, efficacy would also be expected in the setting of less emetogenic chemotherapy. The Division noted that given the differential treatment effect of intravenous palonosetron in CINV delayed phase between the HEC and MEC settings (it was effective for CINV delayed phase in the setting of MEC, in which 70-80% of patients studied received AC, but was not shown to be effective in CINV delayed phase after cisplatin based HEC, a clinical development program that focuses on HEC, targeting

a general indication (“prevention of CINV, including but not limited to HEC”) should study cisplatin based HEC separately from AC.

A further regulatory consideration involving Akynzeo® for injection involves the Combination Rule. Recalling that Akynzeo® is a combination of palonosetron and netupitant, it was necessary to show that both components of the drug were safe and effective. During the oral Akynzeo® development program, there were two trials designed to show the effect of netupitant, NETU 10-29 and NETU 08-18 (originally designed as a MEC trial) which compared Akynzeo® to oral palonosetron in AC chemotherapy. These two trials established the efficacy of netupitant for acute and delayed phase CINV in the setting of cisplatin based HEC and in the setting of AC combination chemotherapy. An additional trial, PALO 10-01, established noninferiority of oral palonosetron to IV palonosetron in prevention of acute phase of CINV in the setting of HEC. Oral palonosetron does not have an indication for the delayed phase of MEC; however, intravenous palonosetron does. This difference in established efficacy between the oral and palonosetron impacts the conclusions that can be drawn from the clinical development program submitted to support approval of the switch from the oral combination product to an intravenous combination product. For the purposes of the Combination Rule, the effect that oral Akynzeo® had in the delayed phase could be entirely attributed to the effect of the netupitant, given the lack of evidence of efficacy in the delayed phase associated with the oral palonosetron component of the combination. The switch to an intravenous palonosetron component of the combination necessitates a trial to establish that the intravenous netupitant component contributes to efficacy in the delayed phase in the setting of MEC, given that intravenous palonosetron has been shown to be effective for delayed phase of MEC. In the absence of trials to establish the contribution of netupitant to the intravenous fixed combination in the delayed phase of MEC, the applicant proposed an indication stating that it had never been studied in AC chemotherapy. The reference to AC chemotherapy acknowledges the majority of patients enrolled in the clinical trials that established the efficacy of intravenous palonosetron in delayed phase of MEC were treated with AC combination chemotherapy.

Akynzeo® capsules were approved on October 10, 2014. Prior to this date, the IV and oral Akynzeo® development programs had been running in parallel. The following table summarizes the trials that were evaluated in the oral Akynzeo® development program. For more information, please refer to the oral Akynzeo® clinical review.

Table 2 – Trials from Oral Akynzeo® Development Program

Trials from Oral Akynzeo® Development Program			
Trial	Comparison	Design	HEC vs MEC Acute vs Delayed phase
NETU 07-07 (Pivotal evidence of netupitant efficacy in HEC)	Palonosetron (oral) vs Palonosetron/ Netupitant (100 mg, 200 mg, or 300 mg) vs Aprepitant/ Ondansetron	Dose finding superiority trial, demonstrated the effect of Netupitant	HEC (cisplatin), acute and delayed phases
NETU 08-18	Akynzeo® (Palonosetron/Netupitant) versus Palonosetron (oral)	Safety and efficacy, demonstrated the effect of Netupitant	MEC (AC) in the acute and delayed phases
PALO 10-01	PO Palonosetron versus IV Palonosetron	Non-inferiority	HEC (cisplatin) in the acute phase
NETU 10-29	Akynzeo® (Palonosetron/Netupitant) versus Palonosetron (oral and IV)	Superiority, multiple cycles, demonstrated the effect of Netupitant	HEC (Cisplatin) and MEC in the acute and delayed phases

(Source – Reviewer’s Table)

The design of the Akynzeo® for injection program was based on a two-fold approach: 1) bridging to the approved Akynzeo capsules through establishing bioequivalence of the netupitant component, and 2) establishing, through a noninferiority trial design, that prolonging the infusion time of palonosetron from 30 seconds (the approved labeled dosing instructions) to 30 minutes retains palonosetron’s efficacy. Safety of the intravenous formulation and fosnetupitant would be evaluated in the bioequivalence trial and in a repeat dosing trial. The key meetings between the FDA and Helsinn where the critical agreements on the Akynzeo for injection development program are summarized in the table below and the text that follows. Based on the FDA’s advice after negotiation, the ultimate requirements for the IV Akynzeo (also referred to as IV NEPA FDC) clinical development program should include a bioequivalence trial (PNET-12-23), a non-inferiority (NI) efficacy trial on the palonosetron component (PALO-15-17), a clinical safety trial (NEPA-15-18) and two clinical pharmacology trials (i.e., PNET-13-63, drug-drug interactions in healthy volunteers; NEPA-15-19, PK in cancer patients).

Table 3 – Pertinent Regulatory History

Date	Event
October 10, 2014	Approval of Akynzeo (palonosetron + netupitant) capsules*
December 9, 2014	Pre-IND/Pre-Phase 3 Meeting (Face to Face)
February 4, 2015	Follow up Meeting (Teleconference)
June 6, 2016	Written Responses Only (WRO) sent
November 30, 2016	Pre-NDA Meeting (Teleconference)

(Source – Reviewer’s Table)

Pre-IND/Pre-Phase 3 Meeting (Face to Face) – December 9, 2014

Dosing

FDA stated the following regarding each component of the combination:

- Fosnetupitant (also referred to as pro-netupitant): “We agree with the doses selected for phase 3 study based on PK and safety data from PNET-12-23 (pro-netupitant).”
- Palonosetron: “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.”

NI Trial (PALO 15-17) Design and Population

FDA stated:

- “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.”

Reason for Concern about Infusion Duration

FDA stated the following:

- “...early palonosetron exposure parameters including C_{max} , $AUC_{0-30\ min}$ (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.”

Safety of Akynzeo IV

FDA stated:

- “You need to have repeat dosing safety with the new [Akynzeo IV] product, given the higher early exposure to netupitant (and the presence of prodrug).”
- “...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.”

Requirements for Demonstration of Efficacy for (b) (4)

FDA stated:

- “The oral Akynzeo program compared the addition of netupitant to oral Aloxi in MEC. Oral Aloxi does not have an indication for delayed phase in MEC. Therefore, 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.”

Reviewer’s Comment: The above underlined sentence refers to MEC, as it is characterized in the label for intravenous palonosetron (and taking into consideration the chemotherapy administered to the patients enrolled in the trials that supported intravenous palonosetron’s approval). Because palonosetron IV has a delayed phase indication in the AC population but palonosetron PO does not, demonstration of the contribution of fosnetupitant IV in the delayed phase in the AC population would be needed for an Akynzeo IV indication in the delayed phase in the MEC population for which intravenous palonosetron carries the indication.

- “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.”

Type B Teleconference – February 4, 2015

PALO 15-17 Design

FDA stated:

- “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.”

Reviewer’s Comment: Note that the “planned primary endpoint” was Complete Response (no emesis and no rescue therapy) in the acute phase (0-24 hours).

- “However, your proposed indication would need to be revised to clarify that (b) (4)

PALO 15-17 Statistical Analysis Plan

- The meeting minutes state, “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.”

NEPA 15-18 Design

- FDA stated, “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.”
- The meeting minutes state, “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.”

Written Responses Only – February 4, 2015

FDA stated:

- “Your proposal to not integrate study results for efficacy analyses appears reasonable...”
- “Your proposal to not provide an integrated safety summary appears reasonable...”

Pre-NDA Meeting (Teleconference) – November 30, 2016

FDA stated:

- “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.”
- “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.”
- “The safety data are adequate to support submission of your planned NDA.”
- “...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.”

3.3. Foreign Regulatory Actions and Marketing History

The fixed dose combination intravenous formulation of fosnetupitant and palonosetron is not approved for marketing in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three clinical investigator (CI) sites and the sponsor were inspected for this application. All CI sites have the classification of no action indicated (NAI) or preliminary NAI. The sponsor has the preliminary classification of NAI. The data generated by this study is acceptable in support of the application. Please see table below.

Table 4 – Sites Inspected

Name and type of inspected entity/Address	Protocol # /Site #/ # of Subjects	Inspection Dates	Classification
CI: Dr. Michael Schenker Sf. Nectarie Oncology Center Department of Medical Oncology 23A Caracal Str., Craiova, Romania	PALO-15-17 Site 1813/ 25 Subjects	October 9 to 12, 2017	NAI
CI: Dr. Miranda Gogishvili LDT High Technology Medical Center University Clinic 9 Tsinandali str., Tbilisi, Georgia	PALO-15-17 Site 1401/ 24 Subjects	October 16 to 18, 2017	NAI
CI: Dr. Katalin Udud Koranyi National Institute of TBC and Pulmonology 6th Department of Pulmonology Piheno ut 1, H-1121, Budapest, Hungary	PALO-15-17 Site 1608/ 18 Subjects	October 9- 13, 2017	*NAI
Sponsor: Helsinn Healthcare SA Via Pian Scairolo 9, 6912 Lugano, Switzerland	PALO-15-17	November 21 to 24, 2017	*NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional

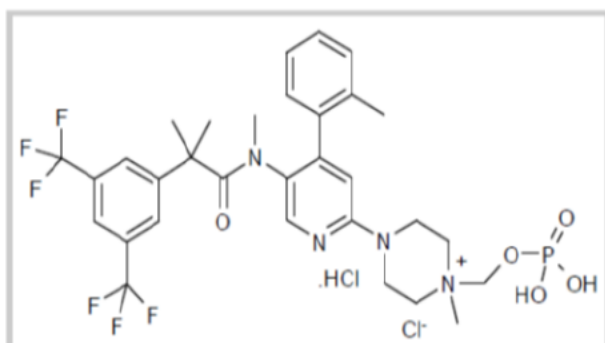
(Source – Clinical Inspection Summary Page 2)

4.2. Product Quality

Akynzeo (fosnetupitant and palonosetron) for Injection, is a lyophilized powder intended for reconstitution and parenteral administration with either 5% dextrose or 0.9% sodium chloride. The lyophilized cake is reconstituted with 20 mL of diluent and the entire constituted solution is removed from the vial and further diluted up to 50 mL for administration.

Each vial contains 235 mg of fosnetupitant (corresponding to 260 mg/vial of fosnetupitant chloride hydrochloride), 0.25 mg of palonosetron (equivalent to 0.28 mg/vial of palonosetron hydrochloride) and the excipients EDTA (b)(4) mannitol (b)(4), and NaOH or HCl as a pH adjuster. There is a (b)(4)% fill excess in each vial in accordance with USP <1151> to permit withdrawal and to achieve the administration of the labeled dose of both actives. See figures below for the chemical structure of the fosnetupitant chloride and palonosetron.

Figure 1 – Structure of 08-PNET



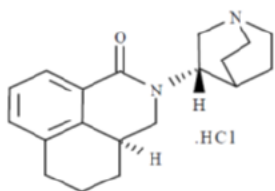
Molecular formula: $C_{31}H_{37}F_6Cl_2N_4O_3P$

Molecular weight: 761.53

USAN: fosnetupitant chloride

(Source – OPQ Report Product Quality Page 6)

Figure 2 – Structure of Palonosetron HCL



Palonosetron HCl, USP contains two chiral centers as shown above, therefore four stereoisomers of the molecule exist. Palonosetron HCl, USP is synthesized (b) (4)

Molecular Formula

$C_{19}H_{24}N_2O \cdot HCl$

Molecular Weight

(Source – OPQ Report Product Quality Page 8)

The various quality aspects, i.e., the drug substance, the drug product, the manufacturing process, the microbiological aspects, the environmental assessment, and labeling have been reviewed by the Office of Pharmaceutical Quality (OPQ) reviewers. OPQ has recommended approval of this application.

The Pharmacology/Toxicology Reviewers in DGIEP reviewed the impurities (including two with positive Ames test) and concurred with the limits set in this NDA. They also reviewed the extractables (b) (4) and determined that there were no concerns associated with exposure to these extractables.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The 4 week IV combination fosnetupitant + palonosetron study in dogs showed QTc prolongation at both mid and high doses (fosnetupitant/palonosetron = 3.95/3 mg/kg and 13.16/10 mg/kg) but this was attributed to palonosetron as it was seen at a dose level of 1 mg/kg in the palonosetron dog study (NDA 21372).

Fosnetupitant was negative in the Ames test, *in vitro* chromosome aberration test in human lymphocytes, and the *in vivo* rat micronucleus test.

In an embryo-fetal development study in rats, intravenous administration of 39.47 mg/kg/day fosnetupitant (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) produced delayed ossification of pubis. No effects on embryo-fetal development were observed with IV administration of up to 13.16 mg/kg/day fosnetupitant in rats (2 times the human AUC for netupitant). In a rabbit embryo-fetal development study, an increase in resorptions was observed with intravenous administration of fosnetupitant at 6.25 mg/kg/day and higher in rabbits (9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). No effects were observed in rabbits at 3.13 mg/kg/day (5.4 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant). In rabbits, the embryo-fetal effects of intravenous fosnetupitant differed from the effects of oral netupitant, and this difference can be attributed to the minimal transformation of fosnetupitant to netupitant in rabbits, in contrast to the rapid metabolism of fosnetupitant in rats and humans.

In a pre-/postnatal study in rats, intravenous administration of 39.47 mg/kg/day fosnetupitant in rats (3 times the human AUC for netupitant) produced lower bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13.16 mg/kg/day (2 times the human AUC for netupitant).

Fosnetupitant produced no effects on fertility or early embryonic development in rats, at doses up to 39.47 mg/kg IV.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK₁) receptors. Fosnetupitant is converted to the active drug, netupitant, through hydrolysis by non-CYP450 enzymes in liver and extrahepatic tissues.

Palonosetron is a 5-HT₃ receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT₃ receptors are located on the nerve terminals of the vagus in the periphery and centrally in

the chemoreceptor trigger zone of the area postrema. Chemotherapeutic agents produce nausea and vomiting by stimulating the release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT₃ receptors located on vagal afferents to initiate the vomiting reflex. The development of acute emesis is known to depend on serotonin and its binding to 5-HT₃ receptors have been demonstrated to selectively stimulate the emetic response.

Delayed emesis has been largely associated with the activation of tachykinin family neurokinin 1 (NK₁) receptors (broadly distributed in the central and peripheral nervous systems) by substance P. As shown in *in vitro* and *in vivo* studies, netupitant inhibits substance P mediated responses.

4.5.2. Pharmacodynamics

NK₁ Receptor Occupancy

The receptor occupancy of netupitant was measured in a human positron emission tomography (PET) study. Netupitant was shown to cross the blood brain barrier with a NK₁ receptor occupancy of 92.5%, 86.5%, 85.0%, 78.0%, and 76.0% in striatum at 6, 24, 48, 72, and 96 hours, respectively, after oral administration of 300 mg netupitant.⁵

Cardiac Electrophysiology

An oral dose 2 times the recommended dose of netupitant (600 mg) and 3 times the recommended dose of palonosetron (1.5 mg) in an AKYNZEO capsule, did not prolong the QT interval to any clinically relevant extent.

The recommended dose of AKYNZEO for injection (235 mg fosnetupitant and 0.25 mg palonosetron), did not prolong the QT interval to any clinically relevant extent.

4.5.3. Pharmacokinetics

Akynzeo for Injection

After single dose administration of AKYNZEO for injection (235 mg fosnetupitant and 0.25 mg palonosetron) administered as a 30-minute infusion to cancer patients, fosnetupitant achieved C_{max} at the end of the infusion with an apparent terminal half-life less than 1 hour. Within 30 minutes of completion of the infusion, the concentration of fosnetupitant decreased to less than 1% of the C_{max}.

Table 5 – PK Parameters (mean and CV%) After Single Dose Administration of AKYNZEO for injection in Healthy Subjects

	Fosnetupitant	Netupitant	Palonosetron
C _{max} (ng/mL)	3478 (45)	590 (28)	0.8 (35)
t _{max} ¹ (h)	0.5 (0.5 – 0.6)	0.6 (0.5 – 4)	0.6 (0.5 – 6)
AUC (ng*h/mL)	1401 (46)	15588 (32)	36 (30)
t _{1/2} (h)	0.75 (54)	144 (50)	58 (47)

¹ median (min-max)

⁵ Content adapted from approved label

Fosnetupitant 260 mg IV vs. Netupitant 300 mg PO: The relative bioavailability (260 mg IV fosnetupitant vs. 300 mg oral netupitant) is discussed in the sub-sections below (“Relative Bioavailability (260 mg IV fosnetupitant vs. 300 mg oral netupitant)” and “Geometric Means of Netupitant Metabolites: IV versus Oral”).

Palonosetron 30 minutes IV vs. Palonosetron 30 seconds IV: The Clinical Pharmacology Review noted the following (*emphasis added*): “Because Akynzeo IV is administered over 30 minutes while Aloxi is administered via IV push over 30 seconds, the ***C_{max} of Aloxi will be higher than that from Akynzeo IV*** while AUC will be comparable because the dose is the same. Therefore, ***safety of the 30-minute infusion of palonosetron is at least comparable if not better than Aloxi administered by IV push.*** On the other hand, the sponsor ***conducted a pivotal phase 3 study to evaluate the potential difference in efficacy due to the lower C_{max}*** and demonstrated that the efficacy of palonosetron IV administered over 30 minutes is not inferior to Aloxi injectable.” See Section 6.1 of this review for a discussion of the non-inferiority study (PALO-15-17) comparing palonosetron IV administered over 30 minutes to Aloxi IV administered over 30 seconds.

Relative Bioavailability (260 mg IV fosnetupitant vs. 300 mg oral netupitant)

The relative bioavailability study (PNET 12-23) included a comparison of 260 mg of IV fosnetupitant with 300 mg of oral netupitant. Bioequivalence criteria were met for AUC_{0-120h} and AUC_{0-∞} for the comparison of 260 mg of IV fosnetupitant (a prodrug of netupitant) with 300 mg of oral netupitant (the dose of netupitant in the approved Akynzeo capsules). The C_{max} for 260 mg IV fosnetupitant was approximately 1.5 times the C_{max} for 300 mg PO netupitant, and exceeds the BE criteria range. Please see table below.

Table 6 – Bioequivalence assessment of 260 mg IV fosnetupitant (Test) vs. 300mg oral netupitant (Reference) based on netupitant PK parameters in Study PNET 12-23.

Netupitant				
Parameter	Treatment	LSM (antilog)	Test (IV) / Reference (Oral) Ratio	90% CI (lower - upper limits)
AUC _{0-∞} last (ng*h/mL)	IV fosnetupitant (Test)	11876	0.94	0.88 - 1.01
	Oral netupitant (Ref)	12621		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	11876	0.94	0.88 - 1.01
	Oral netupitant (Ref)	12621		
AUC _{0-inf} (ng*h/mL)	IV fosnetupitant (Test)	13290 (n=26)	0.88	0.82 - 0.94
	Oral netupitant (Ref)	15073 (n=21)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	825.2	1.51	1.33 - 1.73
	Oral netupitant (Ref)	544.8		

(Source - Elizabeth Shang PhD. – Presentation of PK data from PNET 12-23)

Assuming the efficacy of netupitant is based solely on netupitant levels (see discussion of netupitant major metabolites below), these BE study results indicate that the efficacy of the oral netupitant and the intravenous fosnetupitant component of the two products can be expected to be comparable. However, the safety of the higher netupitant C_{max} associated with the intravenous product must be addressed. The safety was evaluated in Study NEPA 15-18 (see section 8 of this review).

Geometric Means of Netupitant Metabolites: IV versus Oral

The Clinical Pharmacology Reviewer compared the geometric means (AUC_{0-120h}) of netupitant's metabolites (M1, M2, and M3) for IV fosnetupitant versus oral netupitant, and found that the metabolites were lower with IV fosnetupitant (29%, 24%, and 16% lower, respectively) than orally administered netupitant. Similarly, the intravenous product C_{max} of each netupitant metabolite was lower than the oral product (39%, 34% and 25% lower, respectively). See table below.

Table 7 - Comparative exposure to netupitant metabolite M1 following administration of 260mg IV fosnetupitant (Test) vs. 300mg oral netupitant (Reference)⁶

Metabolite M1				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	2325 (n=30)	0.71	0.67 - 0.75
	Oral netupitant (Ref)	3293 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	2325 (n=30)	0.71	0.67 - 0.75
	Oral netupitant (Ref)	3293 (n=30)		
AUC _{0-inf} (ng*h/mL)	IV fosnetupitant (Test)	2931 (n=2)	NE	NE
	Oral netupitant (Ref)	3267 (n=1)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	26.1 (n=30)	0.61	0.58 - 0.65
	Oral netupitant (Ref)	42.4 (n=30)		

n = number of subjects; NE = not-evaluated

⁶ Table is taken from Pages 65 to 66 of the Clinical Pharmacology Review by Elizabeth Shang.

Metabolite M2				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	2295 (n=30)	0.76	0.70 - 0.82
	Oral netupitant (Ref)	3034 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	2402 (n=28)	0.75	0.69 - 0.81
	Oral netupitant (Ref)	3219 (n=27)		
AUC _{0-∞} (ng*h/mL)	IV fosnetupitant (Test)	2567 (n=28)	0.77	0.71 - 0.84
	Oral netupitant (Ref)	3330 (n=28)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	155.3 (n=30)	0.66	0.57 - 0.76
	Oral netupitant (Ref)	235.5 (n=30)		

n = number of subjects

Metabolite M3				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	3389 (n=30)	0.84	0.80 - 0.89
	Oral netupitant (Ref)	4028 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	3389 (n=30)	0.84	0.80 - 0.89
	Oral netupitant (Ref)	4028 (n=30)		
AUC _{0-∞} (ng*h/mL)	IV fosnetupitant (Test)	3790 (n=22)	0.86	0.78 - 0.95
	Oral netupitant (Ref)	4417 (n=15)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	53.0 (n=30)	0.75	0.70 - 0.80
	Oral netupitant (Ref)	70.8 (n=30)		

n = number of subjects

The Clinical Pharmacology Reviewer questioned whether lower metabolite exposure might negatively impact the efficacy of the proposed IV product relative to the oral product. The clinical program submitted to support this NDA did not include an efficacy trial with the primary objective to compare efficacy of fosnetupitant vs. netupitant based on a clinical efficacy endpoint. The objective of Study NEPA 15-18 was to evaluate the safety of the product relative to the approved oral product. It was not designed as a noninferiority trial and was insufficiently powered to answer a comparative efficacy question. However, efficacy was measured in the trial and the Clinical Pharmacology reviewers noted that the observed Complete Response in the Delayed Phase was numerically lower in the IV product arm than in the oral product arm (see Section 6.2.2).

To address the issue of whether the lower metabolite levels are clinically meaningful, the review team evaluated the evidence to support whether each of these metabolites is active and contributes to the efficacy of netupitant. The pharmacology/toxicology reviewers noted the following:

- The three major metabolites, M1 (Ro 68-1133), M2 (Ro 71-3001), and M3 (Ro 73-1519), also bind to the hNK1 receptor, with pKi values of 9.0, 9.0, and 9.1, respectively.
- Netupitant inhibited NK1 receptor agonist-induced foot-tapping behavior in gerbils in a dose-dependent manner. The metabolites M1, M2, and M3, also blocked the foot-tapping activity in this study. However, the relevance of the effect on foot-tapping activity to the pharmacodynamic activity for the proposed indication (anti-emesis) is unknown.

The pharmacology/toxicology reviewers noted that these nonclinical data do not rule in or rule out a substantive role of these metabolites in the product's efficacy in humans. Given these limitations, the Clinical Pharmacology reviewers further considered available human PK and efficacy data that could inform the question. They identified the dose-ranging trial (Study NETU-07-07) submitted in the NDA for oral Akynzeo capsules as an important resource for addressing the question. This trial was the major trial relied upon to establish the efficacy of oral netupitant in the setting of HEC. The efficacy results of Study NETU-07-07 are summarized in the table below, which is reproduced from Dr. Yeh-Fong Chen's statistical review for NDA 205718. See below.

Table 8. Sponsor's Results for Complete Response Rate in the Delayed Phase, Acute Phase and Overall Phase based on MFAS Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=137)	PALO+NETU 300 mg (N=135)
Delayed phase (25-120 hours)				
Number (%) of Patients	109 (80.1)	122 (90.4)	125 (91.2)	122 (90.4)
Difference from Palo alone (%) with 95 CI		102 (1.9, 18.6)	11.1 (2.9, 19.3)	10.2 (1.9, 18.6)
p-value by logistic regression model*		0.018	0.010	0.018
p-value by CMH test**		0.017	0.008	0.016
Acute phase (0-24 hours)				
Number (%) of Patients	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)
Difference from Palo alone (%) with 95 CI		3.6 (-3.0, 10.2)	3.0 (-3.7, 9.7)	8.8 (3.3, 14.3)
p-value by logistic regression model*		0.278	0.383	0.007
p-value by CMH test**		0.278	0.383	0.002
Overall phase (0-120 hours)				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)
Difference from Palo alone (%) with 95 CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 21.9)
p-value by logistic regression model*		0.018	0.017	0.004
p-value by CMH test**		0.018	0.016	0.003

A flat dose-response (delayed phase) over the dose range of 100 mg to 300 mg PO netupitant (see also Section 7.1.4 Dose and Dose-Response of this Clinical Review) was observed in this trial. As noted in the Statistical review for the current application, the Statistical reviewers evaluated the results of Study NETU-07-07 and concluded that the data support that oral netupitant 100 mg in combination with palonosetron 0.5 mg is superior to palonosetron 0.5 mg for prevention of CINV in the delayed phase. They also concluded the following regarding the comparisons of the three netupitant dose combinations (with a static palonosetron dose) to palonosetron alone in Study NETU-07-07: “ the smallest p-value 0.008 for the comparison between PALO+NETU 200mg and PALO alone is less than 0.05/3, second smallest p-value 0.016 for the comparison between PALO+NETU 100mg and PALO alone is less than 0.05/2 and the largest p-value 0.017 for the comparison between PALO+NETU 300mg and PALO alone is less than 0.05. Based on the Holm-Bonferroni method to control the overall type I error rate due to the three study doses, we can conclude that statistically significant superiority to palonosetron alone was observed for each dose of netupitant.”

Table 9 - The Applicant’s Results for Complete Response (CR) Rate in the Delayed Phase, Acute Phase and Overall Phase based on MFAS Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=137)	PALO+NETU 300 mg (N=135)
Delayed phase (25-120 hours)				
Number (%) of Patients	109 (80.1)	122 (90.4)	125 (91.2)	122 (90.4)
Difference from Palo alone (%) with 95 CI		102 (1.9, 18.6)	11.1 (2.9, 19.3)	10.2 (1.9, 18.6)
p-value by logistic regression model*		0.018	0.010	0.018
p-value by CMH test**		0.017	0.008	0.016
Acute phase (0-24 hours)				
Number (%) of Patients	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)
Difference from Palo alone (%) with 95 CI		3.6 (-3.0, 10.2)	3.0 (-3.7, 9.7)	8.8 (3.3, 14.3)
p-value by logistic regression model*		0.278	0.383	0.007
p-value by CMH test**		0.278	0.383	0.002
Overall phase (0-120 hours)				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)
Difference from Palo alone (%) with 95 CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 21.9)
p-value by logistic regression model*		0.018	0.017	0.004
p-value by CMH test**		0.018	0.016	0.003

Source: Table 4 of Dr. Yeh-Fong Chen’s statistical review for NDA205718

The Statistics Review stated “For the above table 9, the smallest p-value 0.008 for the comparison between PALO+NETU 200mg and PALO alone is less than 0.05/3, second smallest p-value 0.016 for the comparison between PALO+NETU 100mg and PALO alone is less than 0.05/2 and the largest p-value 0.017 for the comparison between PALO+NETU 300mg and PALO alone is less than 0.05. Based on the Holm-Bonferroni method to control the overall type I error rate due to the three study doses, we can conclude that statistically significant superiority to palonosetron alone was observed for each dose of netupitant.”

Given that this trial supported the effectiveness of the 100 mg netupitant dose, the Clinical Pharmacology reviewers identified pharmacokinetic data associated with that dose level to evaluate how the major metabolite levels at that dose compare to the metabolite levels associated with fosnetupitant at the dose proposed for approval. The Clinical Pharmacology Reviewer

noted 260 mg IV fosnetupitant (from studies PNET 12-23 in healthy subjects, PNET 13-63 in healthy subjects, and NEPA 15-19 in cancer patients) is associated with considerably higher M1, M2, and M3 levels (as measured by AUC_{0-120h}) than those associated with 100 mg PO netupitant (from study NP16003 in cancer patients): M1 = 2 to 6 times higher, M2 = 6 to 7.5 times higher, and M3 = 2 to 2.7 times higher. It should be noted that the Clinical Pharmacology Reviewer also presented data from Study NETU-09-07 (in healthy subjects) and Study NETU-10-09 (in cancer patients) which suggest that PK is reasonably similar between healthy subjects and cancer patients.

Conclusion: These results indicate that the lower M1, M2, and M3 exposures (260 mg IV vs. 300 mg PO, see tables above) would not be expected to result in lower efficacy in the delayed phase (Akynzeo IV vs. Akynzeo PO), as the M1, M2, and M3 exposures for fosnetupitant 260 mg IV do not fall below the exposures seen with the lowest effective netupitant PO dose for the delayed phase (100 mg) evaluated in Study NETU-07-07.

QT Evaluation

The reader is referred to the QT-IRT Consult Review for complete information. The QT-IRT concluded that no significant QTc prolongation effect of intravenous administration by 30-minute infusion of IV NEPA FDC (260 mg fosnetupitant⁷ and 0.25 mg palonosetron) is expected based on the totality of the evidence that includes the results from the following four clinical studies (two TQT studies and two studies of IV NEPA FDC):

- A TQT study for IV palonosetron (Aloxi®) showed no clinically significant effect on the QTc interval with a single supratherapeutic dose of 2.25 mg palonosetron IV short infusion. This dose level provides >9-fold exposure margin over the exposures anticipated with therapeutic dosing of 0.25 mg palonosetron given as a 30 min IV infusion in IV NEPA FDC product. (The palonosetron C_{max} associated with the currently approved 30 second infusion is higher than that associated with the proposed 30-minute infusion.)
- A TQT study for Oral NEPA FDC (Akynzeo®; 300 mg netupitant and 0.5 mg palonosetron) showed no clinically significant effect on the QTc interval with single oral supratherapeutic dose of 600 mg netupitant and 1.5 mg palonosetron. The QT-IRT review states that the 600 mg dose of oral netupitant provides similar exposure to netupitant from IV NEPA FDC. Specifically, the netupitant AUC of the proposed IV product is bioequivalent to the AUC of the currently marketed oral product; however, the C_{max} is 50% higher (IV/oral ratio = 1.51; 90% CI: 1.33, 1.73). Therefore, the netupitant C_{max} associated with the 600 mg dose of oral netupitant is similar, if not somewhat lower, than that associated with the proposed IV fosnetupitant product. The QT-IRT review states that the maximum dose evaluated in the previous TQT study of oral netupitant does not cover the worst case scenario of potential increased netupitant exposure expected with hepatic impairment (1.4- fold increase), but points to the lack of QT interval prolongation associated with the intravenous fosnetupitant dose of 390 mg, which was evaluated in Study PNET-12-23 (described in the next bullet), as

⁷ Equivalent to 235 mg fosnetupitant free-base

evidence that this worst case scenario has been adequately addressed in the development program.

- The bioequivalence trial comparing oral netupitant to intravenous fosnetupitant, Study PNET-12-23, included a fosnetupitant dose escalation phase that evaluated a maximum fosnetupitant dose of 390 mg and ECG monitoring associated with PK sampling. It was a single center, randomized, phase 1, double-blind, active-controlled, parallel group study, in which 160 healthy subjects were enrolled: 148 subjects received single ascending IV fosnetupitant (doses from 19.5 mg up to 390 mg with N=8-30 subjects in different dose-groups), and 134 subjects received single dose of oral NEPA FDC. No large (>20 ms) mean increases in baseline-corrected QTcF were observed in the central tendency analysis⁸. None of the subjects in the 260 mg IV fosnetupitant dose group (N=30) had QTcF >450 ms or Δ QTcF >30 ms post-dose. Fosnetupitant is a new molecular entity and has not been studied in any prior TQT studies. The nonclinical cardiac safety studies did not identify any potential issues for fosnetupitant. The 1.5-fold exposure margin provided by the 390 mg IV fosnetupitant dose in this study over the 260 mg therapeutic dose proposed for approval adequately covers the highest clinically relevant exposure of fosnetupitant because fosnetupitant clearance (conversion to netupitant) is likely mediated by non-saturable enzymes, such as phosphatases and esterases, distributed throughout the body and none of the intrinsic/extrinsic factors are expected to increase its exposure. Within this exposure margin, the C-QTc assessment did not show a positive relationship for fosnetupitant.
- Study NEPA-15-18: 202 subjects received oral NEPA FDC and 203 subjects received IV NEPA FDC. No large (>20 ms) mean increases in baseline-corrected QTcF were observed in the central tendency analysis⁹. Similar values for outliers of QTcF and Δ QTcF were seen for the two study arms (IV NEPA FDC and oral NEPA FDC). The cardiac safety profile was also similar between these two study arms.

Furthermore, the sponsor has stated that “oral Akynzeo (oral NEPA FDC) has been marketed for 2 years and after more than 14,000 patient exposures with more than 85,000 doses, no QTc reactions have been reported in the post marketing surveillance data.”

The considerations for exposures and QTc effects for the active drug (netupitant) and metabolite moieties (M1, M2, and M3), that are formed from the pro-drug fosnetupitant, are detailed below:

Netupitant: The C_{max} of fosnetupitant and netupitant occur at the end of the 30-minute infusion of IV NEPA FDC and mean concentrations of netupitant remained at nearly the same level until 4 h post-infusion. The netupitant C_{max} observed with the therapeutic dosing of IV NEPA FDC is ~2-fold of that after oral 300 mg netupitant (823 vs. 421 μ g/L), but is similar to the netupitant C_{max} observed with supratherapeutic dose (600 mg) of netupitant used in TQT study of oral Akynzeo. Although the previous TQT study of oral Akynzeo does not cover the worst case scenario of possible increase in netupitant exposure up to 1.4-fold that could be expected with hepatic impairment, these exposures are covered by the 390 mg IV fosnetupitant (1.5-fold the proposed therapeutic dose of 260 mg fosnetupitant in IV NEPA FDC) that is studied in PNET-

⁸ Because there were no placebo and positive controls for QT evaluation in both studies (PNET-12-23 and NEPA-15-18), the data can be used to exclude only large mean QTc effects (20 ms).

⁹ Because there were no placebo and positive controls for QT evaluation in both studies (PNET-12-23 and NEPA-15-18), the data can be used to exclude only large mean QTc effects (20 ms).

12-23, and data from this study did not show a positive C-QTc relationship for netupitant. These results are consistent with the prior TQT study where no positive C-QTc relationship was identified for netupitant.

Netupitant Metabolites M1, M2 and M3: The intensive PK sampling in Study PNET-12-23 showed that the C_{max} for netupitant metabolites M1, M2 and M3 are around 12 h (steady conc. from 8 to 24 h), 2-3 h and 24 h, respectively. Although the ECG sampling in the two studies (PNET-12-23 and NEPA-15-18) was not adequate to capture the effects near T_{max} of these metabolites, these metabolite exposures with therapeutic dosing of IV NEPA FDC were well covered by the suprathreshold dose of 600 mg netupitant in the TQT study for the approved oral NEPA FDC (2-fold [54 vs. 26 $\mu\text{g/L}$], 1.5-fold [228 vs. 156 $\mu\text{g/L}$] and 1.9-fold [102 vs. 53 $\mu\text{g/L}$] exposure margin for M1, M2 and M3, respectively). Furthermore, there was no statistically significant positive C-QTc relationship seen with each of these 3 metabolites in the prior TQT study for oral Akynzeo. So, further exploration of C-QTc relationships for these metabolites was not carried out in this review and the lack of ECG sampling near T_{max} for these metabolites in the submitted studies (PNET-12-23 and NEPA-15-18) does not impact the overall conclusion.

Effects of Akynzeo IV on S-warfarin

The applicant submitted data from evaluations of the impact of fosnetupitant on transporters and CYP450 enzymes, and vice versa. The reviewers have recommended labeling revisions based on this information. Although modeling suggested that intravenous Akynzeo would not have a substantial impact on S-warfarin (a CYP2C9 substrate), the reviewers recommended inclusion of cautionary language in the label. The applicant did not evaluate INR changes in drug-drug interaction studies. The label will state:

Warfarin

Although it was predicted that co-administration of intravenous AKYNZEO with warfarin would not substantially increase the systemic exposure to S-warfarin (CYP2C9 substrate), the active enantiomer, the effects of AKYNZEO for injection and AKYNZEO capsules on INR and prothrombin time have not been studied. Monitor INR and adjust the dosage of warfarin, as needed with concomitant use of AKYNZEO, to maintain the target INR range.

The reviewers also recommended that the approval letter include the following PMCs:

3292-3 *In vitro* study to evaluate the inhibition potential of fosnetupitant towards MATE2-K

The timetable you submitted on January 10, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2019
Study/Trial Completion:	01/2020
Final Report Submission:	07/2020

3292-4 *In vitro* study to evaluate the potential of fosnetupitant to be a substrate for P-gp/MDR1, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OCT1, and OCT2

The timetable you submitted on January 10, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/2019
Study/Trial Completion: 01/2020
Final Report Submission: 07/2020

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.7. Consumer Study Reviews

This is not applicable to this application.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 9 – Clinical Studies to Support Safety and Efficacy

Study	Design	Regimen	Control	Key Assessments	# of Pts.	Study Population	Other Key Features	# of Centers
PALO 15-17	Randomized, double-blind, non-inferiority trial	IV Palo 30-minute infusion (single dose)	IV Palo 30 second bolus (single dose)	Complete Response in the Acute Phase	441	HEC not including AC	One chemotherapy cycle	76 Centers (multi-national, 9 countries), No studies centers in the USA
NEPA 15-18	Randomized, double-blind, active control trial	IV NEPA FDC (IV Akynzeo), repeat dosing	Oral NEPA FDC (Akynzeo Capsules), repeat dosing	Safety and descriptive efficacy (Complete Response in acute phase, delayed phase, and overall)	405	HEC not including AC	4 chemo-therapy cycles	80 Centers (multi-national, 12 countries including USA)
PNET 12-23	PK study	IV fosnetupitant at various doses	Oral netupitant/palonosetron (Akynzeo Capsules)	Safety at various doses	158	Healthy Subjects (male and female age 18-45)	Includes relative bioavailability study (260 mg IV fosnetupitant vs. 300 mg PO netupitant)	1 Center (Germany)

(Source Reviewer's Table)

5.2. Review Strategy

Efficacy

This review will focus primarily on evaluation of efficacy data from the non-inferiority trial (Study PALO 15-17). In particular, the trial will be reviewed for demonstration of non-inferiority (IV palonosetron 0.25 mg over 30 minutes vs. palonosetron 0.25 mg over 30 seconds) for the primary endpoint of Complete Response (CR) in the acute phase after a single chemotherapy cycle. Study PNET 12-23, the relative bioavailability study which bridges the proposed intravenous product to the approved oral product, based on netupitant exposure, and establishes the efficacy of fosnetupitant for the delayed (and acute) phase of CINV associated with HEC, was presented above in Section 4.5 Clinical Pharmacology.

The descriptive efficacy analyses from Study NEPA 15-18 (Akynzeo IV vs. Akynzeo capsules) will be reviewed and presented for completeness; but these data are not critical to the evaluation of efficacy as the trial was not designed/powerd to demonstrate non-inferiority.

Safety

Safety data from Studies PALO 15-17 and NEPA 15-18 will be reviewed. In addition, safety data from Study PNET 12-23 (which included a relative bioavailability comparison of fosnetupitant 260 mg IV vs. netupitant 300 mg PO) will be reviewed. Key differences between

the products that required randomized, controlled safety assessment in this program include: 1) fosnetupitant is a NME, 2) the netupitant C_{max} associated with the IV product exceeds that of the oral product, and 3) the palonosetron infusion duration is prolonged relative to currently marketed product's dosage and administration labeling.

General Approach

This review will present some analyses performed by the applicant (with the Clinical reviewer's commentary) and some of the Clinical Reviewer's own analyses. These analyses were performed using applicant datasets and the JReview software tool. Tables in which the data are presented will clearly identify the source of the data analyzed.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. PALO 15-17

6.1.1. Study Design

Overview and Objective

PALO 15-17 was titled "A phase 3, single-dose, multicenter, randomized, double-blind, parallel group study to assess the efficacy and safety of palonosetron 0.25 mg administered as a 30-minute IV infusion compared to palonosetron 0.25 mg administered as a 30-second IV bolus for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic chemotherapy."

PALO 15-17 was designed to provide evidence that a 30-minute infusion of IV palonosetron 0.25 mg was non-inferior to the 30-second bolus injection of palonosetron 0.25 mg (the approved posology for Aloxi IV) in the acute phase of CINV. The primary objective of the study was to demonstrate non-inferiority of a single IV dose of palonosetron 0.25 mg administered as a 30-minute infusion versus a single dose of palonosetron 0.25 mg administered as a 30 second IV bolus with oral dexamethasone in terms of a complete response in the acute phase.

Reviewer's Comments: *PALO 15-17 was necessary to establish that the longer palonosetron infusion time associated with the proposed product (relative to the approved palonosetron infusion time) does not negatively impact the efficacy of palonosetron in the acute phase of CINV.*

Trial Design

Overview

PALO 15-17 was a phase 3, multicenter, randomized, double-blind, parallel group, non-inferiority, stratified study assessing the efficacy, safety, and tolerability of a single dose of palonosetron 0.25 mg administered as a 30-minute IV infusion versus a single dose of

palonosetron 0.25 mg administered as a 30-second IV bolus, each administered with oral dexamethasone prior to HEC. It was designed to focus on the acute phase of CINV. (Note that the treatment effect of intravenous palonosetron for CINV was established in the clinical trial in which it was given in combination with dexamethasone.)

Reviewer's Comments: There were no significant weaknesses to this study. Its design was consistent with prior agreements between the Sponsor and the FDA (please see section 3.2).

Number of Patients

The number of patients to be randomized into the study was 440 equally distributed in the two treatment groups (i.e., 220 patients/group).

Pertinent Inclusion Criteria

1. Signed written informed consent.
2. Male or female patient ≥ 18 years of age.
3. Histologically or cytologically confirmed solid tumor malignancy.
4. Naïve to cytotoxic chemotherapy. Previous biological or hormonal therapy is permitted.
5. Scheduled to receive first course of one of the following reference HEC, alone or in combination with other chemotherapeutic agents* on Day 1:
 - cisplatin administered as a single IV dose of ≥ 70 mg/m²
 - cyclophosphamide ≥ 1500 mg/m²
 - carmustine (BCNU) >250 mg/m²
 - dacarbazine (DTIC)
 - mechlorethamine (nitrogen mustard)

The administration of the reference HEC should not extend beyond 4 hours on study Day 1.

*on Day 1, additional HEC or MEC chemotherapeutic agents have to be administered after the start of the reference HEC administration and their administration must be completed no more than 6 hours after the start of reference HEC infusion. Low, minimally, or not emetogenic chemotherapies can be administered at any time after the start of the reference HEC.¹⁰

6. ECOG Performance Status of 0, 1, or 2.
7. If a patient is female, she shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having negative urine pregnancy test.
8. Hematologic and metabolic status adequate for receiving a HEC regimen and fulfillment of the following criteria:
 - a) Total Neutrophils $\geq 1500/\text{mm}^3$ (Standard units: $\geq 1.5 \times 10^9/\text{L}$)
 - b) Platelets $\geq 100,000/\text{mm}^3$ (Standard units: $\geq 100.0 \times 10^9/\text{L}$)
 - c) Bilirubin $\leq 1.5 \times$ Upper Limit of Normal (ULN)
 - d) Liver enzymes:

¹⁰ MASCC/ESMO Antiemetic Guideline 2013; Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Annals of Oncology 21 (Supplement 5):232-243 (2010). Updated in January 2013: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_english_2014.pdf

- i. Without known liver metastases, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) $\leq 2.5 \times \text{ULN}$
 - ii. With known liver metastases, AST and ALT $\leq 5.0 \times \text{ULN}$
- e) Serum Creatinine $\leq 1.5 \text{ mg/dL}$ (Standard units: $\leq 132.6 \text{ } \mu\text{MOL/L}$) or Creatinine Clearance $\geq 60 \text{ mL/min}$
- 9. If a patient has a known hepatic or renal impairment, he/she may be enrolled in this study at the discretion of the Investigator, provided the inclusion criterion #8 items d) and e) are satisfied.
- 10. If a patient has a known history or predisposition to cardiac conduction interval abnormalities, including QTc, he/she may be enrolled in this study at the discretion of the Investigator.
- 11. Able to read, understand, follow the study procedure and complete patient diary.

Reviewer's Comments: The diagnostic (inclusion) criteria included adult chemotherapy-naïve male and female patients with a diagnosis of malignant solid tumor requiring a first treatment with one of the protocol pre-defined reference HEC regimens. It should be noted that the inclusion criteria did not include patients receiving anthracycline plus cyclophosphamide chemotherapy, which was consistent with the population studied to support intravenous palonosetron's approval for the HEC acute phase CINV indication.

Pertinent Exclusion Criteria

1. Lactating woman.
2. Current use of illicit drugs or current evidence of alcohol abuse.
3. Scheduled to receive moderately emetogenic chemotherapy or highly emetogenic chemotherapy from Day 2 to Day 5.
4. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of the reference HEC administration on Day 1 or between Days 1 to 5.
5. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of the reference HEC administration on Day 1.
6. Symptomatic primary or metastatic CNS malignancy.
7. Active peptic ulcer disease, gastrointestinal obstruction, increased intracranial pressure, hypercalcemia, an active infection or any illness or medical conditions (other than malignancy) that, in the opinion of the Investigator, may confound the results of the study, represent another potential etiology for emesis and nausea (other than chemotherapy-induced nausea and vomiting [CINV]) or pose unwarranted risks in administering the study drugs to the patient.
8. Known hypersensitivity or contraindication to 5-HT₃ receptor antagonists (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron) or dexamethasone.
9. Known contraindication to the IV administration of 50 mL 5% glucose solution.
10. Participation in a previous clinical trial involving palonosetron.
11. Any investigational drugs (other than those given in this study) taken within 4 weeks prior to Day 1, and/or is scheduled to receive any investigational drug during the present study.

12. Systemic corticosteroid therapy at any dose within 72 hours prior to the start of the reference HEC administration on Day 1. However, topical and inhaled corticosteroids are permitted.
13. Scheduled to receive bone marrow transplantation and/or stem cell rescue therapy.
14. Any medication with known or potential antiemetic activity within 24 hours prior to the start of the reference HEC administration on Day 1, including:
 - HT3 receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron)
 - NK1 receptor antagonists (e.g., aprepitant or any other new drug of this class)
 - benzamides (e.g., metoclopramide, alizapride)
 - phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine)
 - benzodiazepines (except if the subject is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1)
 - butyrophenones (e.g., haloperidol, droperidol)
 - anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide)
 - antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine)
 - domperidone
 - mirtazapine
 - olanzapine
 - prescribed cannabinoids (e.g., tetrahydrocannabinol or nabilone)
 - Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications
15. Concurrent medical condition that would preclude administration of dexamethasone for 4 days such as systemic fungal infection or uncontrolled diabetes.

Reviewer's Comments: There were no unreasonable exclusion criteria with respect to laboratory values, lactation, prior trial participation, complicating comorbidities (i.e., CNS malignancy, chronic GI conditions, bone marrow transplantation), allergies/contraindications to study drug administration, or concurrent antiemetic medication use. The main characteristics of the population were similar to the target US population.

Dose Selection

The approved dose of Aloxi (palonosetron) IV for adults of 0.25 mg was used.

Dosing Schedule

The dosing schedule is summarized in the table below.

Table 10 – Dosing Schedule PALO 15-17

STUDY DAY	TIME	GROUP 1 (IV PALO 30-minute infusion)	GROUP 2 (IV PALO Bolus)
DAY 1	30 min before start of HEC	5 tablets, 4 mg dexamethasone each	5 tablets, 4 mg dexamethasone each
	30 min before start of reference HEC, immediately following oral dexamethasone	1 vial, palonosetron placebo IV 30-second bolus	1 vial, 0.25 mg palonosetron IV 30-second bolus
	30 min before start of HEC immediately following IV 30-second bolus	1 vial, 0.25 mg palonosetron IV 30-minute (+/-5 min) infusion	1 vial, palonosetron placebo IV 30-minute (+/-5 min) infusion
DAY 2	(morning) 24 to 26 hours after dexamethasone Day 1 dose	2 tablets, 4 mg dexamethasone each	2 tablets, 4 mg dexamethasone each
	(evening, 8-12 hours after morning dose)	2 tablets, 4 mg dexamethasone each	2 tablets, 4 mg dexamethasone each
DAYS 3-4	morning	2 tablets, 4 mg dexamethasone each	2 tablets, 4 mg dexamethasone each
	evening	2 tablets, 4 mg dexamethasone each	2 tablets, 4 mg dexamethasone each

(Source - Palo 15-17 Protocol (Final Version) Page 45)

Randomization/Stratification

With respect to assignment to treatment, patients were to be randomized per a 1:1 randomization ratio, stratified by country and sex. Treatment assignment was managed through a static central blocked randomization stratified by sex (male, female) and country. The randomization scheme was to be reproducible and prepared prior to study start via a computerized system by the IWRS (Interactive Web Response System) vendor.

Blinding

The blinding of the study medications was guaranteed using identical placebos to the respective active drugs (double-dummy technique). When palonosetron 0.25 mg was to be administered as 30-min IV infusion, a 30-sec IV bolus of placebo was to be administered (Group 1). Conversely, when palonosetron 0.25 mg was administered as a 30-sec IV bolus, a 30-min infusion of placebo was to be administered (Group 2). Therefore, each patient was to receive a 30-sec IV bolus and a 30-min IV infusion, one of which contained the active investigational medicinal product while the other was a placebo.

No blinding was required for dexamethasone, which was administered at the same dose and posology in both treatment groups.

The Investigator had the possibility to unblind the study treatment in case of an emergency, when he/she considered it essential to know what treatments the patient had received.

Administrative Structure

There was no data safety monitoring board (DSMB) for this study. Two contract research organizations (CRO) were involved in this study. PSI CRO AG, based out of Zug, Switzerland, was the clinical CRO, and [REDACTED]^{(b) (4)}, based out of [REDACTED]^{(b) (4)}, was the CRO for Statistics and Data Management (SDM). There were no adjudication committees. There is no suggestion that any third-party entity assessed for safety or efficacy during this study.

Schedule and Procedures

The following table lists the schedule and procedures that occurred during the trial.

Table 10 Schedule and Procedures PALO 15-17

Procedure/assessment	Screening	Day 1 Visit 2	Day 2 ^b Visit 3	Day 6(+2) ^c Visit 4	Day 21(±2) ^d Visit 5
	Day -14 to -1 ^a Visit 1				
Informed consent	X				
Inclusion/exclusion criteria ^e	X	X			
Demography	X				
Medical/surgical history (including cancer history)	X				
ECOG performance status	X				
Urine pregnancy test	X ^f	X ^f			
Serum pregnancy test ^g	X			X	
Prior and concomitant medications	X	X	X	X	X
Physical examination	X ^h		X ⁱ	X ^h	
Vital signs ^j	X	X	X	X	
12-lead ECG ^k	X			X	
Blood chemistry ^l	X			X	
Hematology ^l	X			X	
Urinalysis ^l	X			X	
Randomization		X			
Chemotherapy		X			
Study drugs and dexamethasone administration ^m		X			
Distribution of patient diary and instructions on completion for acute phase of CINV ⁿ		X			
Retrieval of patient diary for acute phase of CINV			X		
Distribution of patient diary and instructions on completion for delayed phase of CINV ⁿ			X		
Retrieval of patient diary for delayed phase of CINV				X	
Adverse events ^o	X	X	X	X	X

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- (a) Day -1 was the day immediately preceding Day 1.
 - (b) Approximately 24 h after the first study drug administration (i.e., intravenous [IV] palonosetron or placebo bolus administration) on Day 1.
 - (c) 120 h after the first study drug administration on Day 1. If Day 6 was a holiday or a weekend day, Visit 4 could have been scheduled within the 2 forthcoming days.
 - (d) Day 21 (± 2), either on-site visit or phone contact.
 - (e) Including check of alcohol and illicit drug consumption.
 - (f) Was to be performed for females of childbearing potential within 24 h prior to the first investigational medicinal product (IMP) administration on Day 1. If the screening visit urine pregnancy test was done within the 24 h before the first IMP administration, no urine pregnancy test was to be performed at Visit 2 (Day 1).
 - (g) Was to be performed for females of childbearing potential (centralized laboratory).
 - (h) Complete physical exam (general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological).
 - (i) Limited physical exam (general appearance, cardiovascular, lungs and abdomen body systems).
 - (j) Vital signs assessments include: pulse rate, systolic and diastolic blood pressure at Visit 1 (screening), Visit 2 (on Day 1 at pre-dose, i.e., before the bolus administration; on Day 1 after the end of the IV study drug infusion, i.e., immediately before to start the reference highly emetogenic chemotherapy (HEC) administration), Visit 3 (24 h ± 2 h after the first study drug administration [i.e., IV palonosetron or placebo bolus administration]) and Visit 4 (120 h -6/+54 h after the first study drug administration), height (only at Visit 1 [screening]), and body weight (at Visit 1, Visit 2, and Visit 4). Pulse rate and systolic and diastolic blood pressure had to be measured after the patient had been in a sitting position for at least 5 min.
 - (k) 12-lead ECG (single recording) was to be recorded at Visit 1 (screening) and Visit 4 (at 120 h -6/+54 h after the first study drug administration), after the patient had been in a supine position for at least 5 min, and was to be assessed in a central laboratory.
 - (l) A centralized laboratory was to be used for hematology, blood chemistry, and urinalysis.
 - (m) Patients were to receive dexamethasone on Days 1 to 4. The first Day 2 dexamethasone dose ("morning" dose) was to be administered between 24 and 26 h after the Day 1 oral dexamethasone administration. Dexamethasone for Day 2 (evening dose, within 8-12 h after morning dose), Day 3, and Day 4 were to be provided to the patient by the Investigator at Visit 3.
 - (n) Patients were to be asked to report date and time of onset of emetic episodes (episodes of retching or vomiting), as well as, date and time of intake of rescue medication on their diary.
 - (o) Adverse events were to be collected from informed consent signature up to the follow-up visit or last patient contact.

(Source – PALO 15-17 Study Report Page 42)

Dietary Restrictions/ Instructions

No specific dietary restrictions/ instructions were included in the study protocol. This was not an issue from a clinical perspective.

Concurrent Medications

With respect to concurrent medications, the only medications that were specifically excluded from the study were drugs that had specific antiemetic activity. This list of medications included but was not limited to 5-HT₃ receptor antagonists, NK₁ receptor antagonists, benzamides, phenothiazines, benzodiazepines, butyrophenones, anticholinergics, antihistamines, domperidone, mirtazapine, olanzapine, prescribed cannabinoids, and over-the-counter antiemetics, cold, or allergy medications, and the exclusion criteria specified that these medications could not be taken within 24 hours prior to the start of the reference HEC administration on Day 1.

Treatment Compliance

A patient was compliant with therapy if he/she took all study drugs (including dexamethasone) provided in the clinical study medication kit.

Rescue Medication

Rescue medication was defined as any antiemetic medication taken for treatment of emesis (vomiting, retching) and nausea in the 0-120 hours from start of reference chemotherapy administration. It was permitted on an as-needed basis to alleviate established, refractory, or persistent nausea or vomiting. Rescue medication was not allowed for prevention of emesis, nor to increase the expected anti-emetic effects of the study medication. The Investigator was to be provided with enough rescue medication, e.g., metoclopramide tablets, to be distributed to the patient on an as-needed basis. However, the Investigator was authorized to use an alternative rescue medication, based on his/her judgment. The Investigator was to ensure that rescue medication was made available to patients whenever needed. NK1 receptor antagonists were not allowed and 5-HT₃ receptor antagonists were not to be used as rescue medications. Commercial palonosetron (Aloxi®, Onicit®, Paloxi®) was not allowed.

Subject Completion, Discontinuation, or Withdrawal

Completion: A patient will be defined as having “completed” the study if he/she completes Visit 5 (either on-site or phone contact).

Discontinuation: Termination of the study before Visit 5 (or before the relative phone contact) will be considered as a premature discontinuation.

Replacement: Patients who discontinued after randomization were not to be replaced.

Follow-up Procedures and/or Assessments: If a subject discontinued from the study after treatment with the investigational product, the Investigator must try his/her best to contact the subject within 20(±2) days after the first treatment on Day 1 (i.e., at approximately the same date when Visit 5 was to be scheduled), in view of completing the safety assessment by collecting information that may be suggestive of AEs.

Missing Data

Any patients who do not provide data about occurrence of emetic episodes and rescue medication intake or do not provide a full set of these data throughout the 24 hours after HEC administration will be considered as treatment failures (i.e., non-responders) for the primary efficacy analysis.

Study Endpoints

For a discussion of how the primary endpoint for PALO 15-17 was determined, please refer to the regulatory history discussion in Section 3.2.

Primary Endpoint

The primary endpoint for this study was:

- the proportion of patients with a complete response (CR) in the acute phase of CINV.

CR in the acute phase is defined as:

- **no emetic episode** and **no rescue medication** during the **0-24 hours** after the start of HEC administration on Day 1.

Secondary Endpoints

The secondary endpoints were the proportion of patients with CR during the delayed and overall phases, the proportion of patients with no emetic episodes during the acute, delayed, and overall phases, and the proportion of patients with no rescue medications during the acute, delayed, and overall phases.

Definition of Emetic Episode

An emetic episode was defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Emetic episodes were considered distinct if separated by absence of vomiting and retching for at least 1 minute. All patients were asked to document in patient diaries (one for the acute phase and one for the delayed phase) all details about their emetic episodes during the 120 hours after the start of administration of the reference HEC (0-24 hours in the diary for acute phase and >24 to 120 hours in the one for delayed phase). These details included each episode of retching or vomiting, date of each retching or vomiting episode, and exact time of onset of each retching or vomiting episode. Each emetic episode, as well as date and time of occurrence, was then be documented on the eCRF (electronic case report forms) in accordance with the patient diary records.

Statistical Analysis Plan

Definitions of Analysis Populations

The following definitions of analysis populations were used:

- “All Randomized Patients”: “All Randomized Patients” includes all patients who have been randomized to treatment.
- Full Analysis Set (FAS): The Full Analysis Set (FAS) includes all patients who have been randomized to treatment and received HEC regimen and active study drug (including partial infusion). Following the intent to treat principle, patients were assigned to the study treatment group per the treatment to which they have been randomized. FAS was to be used for demography, other baseline characteristics, for primary efficacy analysis, and all efficacy analyses.
- Per-Protocol (PP) Population: The Per-Protocol (PP) population included all patients from the FAS, who had completed the 0-24 hour study period and with no major protocol violations (i.e., those affecting the primary efficacy endpoint). All the protocol violations (e.g., wrong inclusion, poor compliance, missing diaries, forbidden

concomitant medications, mis-randomizations) will be reviewed and discussed case by case during the blind data review meeting (BDRM) and decisions described in the blind data review document/minutes which will be finalized prior to database lock. Patients will be assigned to study treatment groups per the actual treatment received. PP population was also used for demography, other baseline characteristics, and for the primary efficacy analysis.

Primary Efficacy Analysis and NI Margin

To test the null hypothesis, the lower limit of the two-sided 99% CI for the difference in proportion of patients with CR in the acute phase between palonosetron IV 30-minute infusion and palonosetron IV 30-second bolus will be compared to the **pre-set noninferiority margin set at -15%**.

The null hypothesis can be written as:

$$H_0: \pi_T - \pi_C \leq -\Delta$$

H_0 will be tested against the alternative hypothesis:

$$H_1: \pi_T - \pi_C > -\Delta$$

Where π_T is the proportion of patients with CR in the test group (PALO IV 30-minute infusion), π_C is the proportion of patients with CR in the control group (PALO IV 30-second bolus) and Δ is the non-inferiority margin which is fixed at 15%.

Reviewer's Comment: Per the regulatory history, the Sponsor and FDA agreed upon a -15 % non-inferiority margin with two-sided 99% confidence interval. This is based on the previous precedent of FDA's acceptance of the 15% noninferiority (NI) margin in the PALO-10-01 study from the oral Akynzeo development program. See additional discussion in the Statistical Analysis Plan – Basis for Selection of NI Margin section below.

Missing Data

With respect to missing data, any patients who did not provide data about the occurrence of emetic episodes and rescue medication intake or that did not provide a full set of these data throughout the 24 hours after HEC administration were considered as treatment failures (i.e., non-responders) for the primary efficacy analysis. For consistency, the same approach for handling missing data as described for the primary efficacy analysis was also applied to emetic episodes and rescue medication intake.

Adjustment for Multiplicity

No adjustment for multiplicity was made in the study. All secondary efficacy endpoints were intended to provide supportive evidence related to the primary objective or additional clinical characterization of treatment effect, the results on these were interpreted in only a descriptive manner.

Basis for Selection of NI Margin

21 CFR 314.126(a)(2)(iv) states the following:

“If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.”

The Guidance “Non-Inferiority Clinical Trials to Establish Effectiveness” states the following:¹¹
“The goal of the study is to show that the effect of the test drug (T) is not inferior to the effect of the active control (C) by a specified amount, called the NI margin, or M.”

For anti-emetics, the Applicant notes the following:

“Ideally, the margin should be identified based on past experience in placebo-controlled studies. However, for many years, the use of placebo antiemetics has not been considered ethical in patients undergoing HEC. Consequently, there are no CINV studies directly comparing IV palonosetron and placebo.”

The Applicant notes that in Study PALO-99-05 (trial for the Aloxi IV program; NDA 21372), a “modeled historical placebo” (i.e., literature-based meta-analysis (PALO-01-23)) was used. This Reviewer notes that this approach was deemed acceptable based on the Clinical Review of that NDA.¹² The Clinical Review under NDA 21372 stated the following regarding PALO-01-23:

“Since the use of placebo is not ethically acceptable in the CINV subject population, a literature-based meta-analysis (PALO-01-23) was performed to provide historical placebo control data. Since dolasetron performed similarly to the modeled historical dolasetron and far better than in the modeled historical placebo, the applicant demonstrated validity of the trial for the 24 hour end-point.”

The Applicant states the following regarding the “modeled historical placebo” (PALO-01-23) (*emphasis added*):

“Data were collected on potential important covariates (e.g., treatment, age, sex, naivety, coadministration of corticosteroids, country/region of study sites location, single versus multicenter, type practice setting, analysis population, dosing route, distribution of cancer treated, chemotherapy emetogenicity, specific chemotherapeutic agents used) which might have predicted CR. The meta-analysis database was comprised of 78 treatment arms from published trials and included data from 7,274 patients (the above-mentioned studies using placebo were part of the database as well). Using this database, a logistic regression was performed to identify which covariates were predictive of CR. Using the relevant covariates from the meta-analysis, an equation was produced to determine the predicted CR rate for any given patient population (i.e., any given combination of relevant covariates). Relevant covariates from PALO-99-05 were entered into this equation (model) to produce the predicted historical placebo CR in the acute phase for the patient population of that study. The effect of the ***modeled historical placebo estimated by this equation indicated a proportion of patients with CR in the acute phase of 11.8% (95% CI: 8.7% to 15.8%)***.”

¹¹ <https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf> (accessed December 11, 2017)

¹² https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-372_Alox.cfm (accessed December 10, 2017)

The Applicant states the following regarding the choice for M1 (*emphasis added*):

The entire effect of the active control drug assumed to be present in this non-inferiority trial (M1) is estimated by the difference between the lower limit of the 95% CI for the IV palonosetron 0.25 mg (i.e., 52.4%) and the upper limit of the 95% CI for the modeled historical placebo (i.e., 15.8%). Therefore, the non-inferiority margin for the current study should not exceed 36.6% (M1).

The Applicant states the following regarding the choice for M2 (*emphasis added*):

Based also on clinical judgment, it was considered that a substantial portion of M1 (at least 50%) should be preserved, leading to a value of about 18%. To be as conservative as possible, a further additional adjustment is applied to reflect uncertainties and the non-inferiority margin is reduced to 15% (M2, the largest clinically acceptable difference of the test drug compared to the control drug).

In addition to the precedent of Trial PALO-99-05 (trial conducted for Aloxi IV with a 15 % NI margin and a 97.5 % confidence interval) (see Clinical Review of NDA 21372),¹³ this Reviewer notes that the NI Margin of 15% (99% confidence interval) was used in Trial PALO-10-01 (efficacy of oral palonosetron 0.50 mg in the HEC setting using palonosetron 0.25 mg IV bolus as active control drug) for Akynzeo capsules (see Clinical Review of NDA 205718). The Applicant also cited other precedents where the 15% NI Margin was used, which included: (1) Dolasetron study MCPR0031 (versus ondansetron, 95 % CI) and study 73147-3-S-093 (versus granisetron, 95 % CI); (2) Palonosetron MEC studies 99-03 and 99-04 (both with 97.5 % CI; and (3) trial for Sancuso granisetron transdermal patch (95% CI).

Reviewer's Comment: This Clinical Reviewer agrees with the 15% NI Margin with the use of a two-sided 99% confidence interval and the basis for selection of this NI Margin using the "modeled historical placebo" (PALO-01-23) given the precedents described above.

Interim Analysis

No interim analysis was performed for this study.

Planned Subgroup Analyses

It was felt that sex and the country in which the study was being performed would affect the primary endpoint. As such, the subgroups that were explored included:

- Sex- (Male, Female)
- Country- (Belarus, Bosnia and Herzegovina, Bulgaria, Georgia, Greece, Hungary, Lithuania, Romania, Russia)

Please refer to the statistical review for a more complete discussion involving the statistical analysis plan.

¹³ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-372_Alox.cfm (accessed December 10, 2017)

Protocol Amendments

The Sponsor submitted two protocol amendments. The first, dated October 19, 2015, was submitted to correct minor inconsistencies between the synopsis and the rest of the protocol. None of these revisions changed the essential aspects of the protocol. The second amendment, dated January 25, 2016 was implemented to update general information to current status, to specify in detail time windows for study drug, additional non-investigational study drug, and reference chemotherapy administration, vital signs and 12-lead ECG measurements, to align the wording related to the study drug storage conditions with the text reported on study drug label, to unequivocally clarify the meaning of the wording “first study drug”/“post-dose” in some sections, and to correct minor typing errors. Here again, these revisions did not change the essential aspects of the protocol.

Data Quality and Integrity: Sponsor’s Assurance

The study was performed per the CRO’s and Sponsor’s SOPs. These included study conduct and the archiving of essential documents in accordance with ICH-GCP guidelines.

Monitoring

The study was monitored by the CRO’s adequately qualified and trained clinical monitors on a regular basis throughout the study period, to ensure the proper conduct of the clinical trial. The purposes of the clinical trial monitoring were to verify that the rights and well-being of study patients were protected, that the reported trial data were accurate, complete, and verifiable against the source documents, and that the study was conducted in accordance with the current protocol, GCP guidelines, and applicable regulatory requirements. During the monitoring visits, monitors were to verify the following information (including but not limited to): patient informed consent, patient’s eligibility, safety data and reporting, quality of source documents, and eCRF data against patient’s medical records. If inconsistencies were identified, the corresponding corrections to the eCRF data were to be made by the Investigator. Monitors were to also check patient compliance, accrual, drug handling, including dispensing procedures, and accountability logs, delegation of responsibilities within the Investigator’s team, relevant communications with family doctors, if any, ancillary equipment and facilities, including refrigerators, local labs, etc. The Investigator and other site staff involved in the study had to allocate enough time to the monitor during these visits.

A total of 16 on-site audits were performed by the CRO (9 audits) as well as by the Sponsor (7 audits) to ensure that the study followed GCP, applicable regulatory requirements, and the study protocol. Additional audit activities may also have been conducted after study completion.

In addition, Regulatory Authorities could conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notified the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator had to inform the study Sponsor and CRO immediately. The Investigator was to make all efforts to facilitate the conduct of the audits and inspections, giving access to all necessary facilities, data and documents.

Laboratory Accreditation

All samples were sent to a qualified central laboratory for analyses.

Data Reporting and Management

Electronic case report forms (eCRFs) were to be used for recording patient's study data using a validated web-based Electronic Data Capture (EDC) system. It was the responsibility of the Investigator to ensure that the eCRFs were properly and filled in. The eCRFs had to be completed for all patients who were included in the study.

Each authorized site personnel were assigned a login and password to enter the EDC system via a secure network.

Data Clarification Forms (DCFs) were to be used to validate/clarify data entered on an eCRF page.

Discrepancies raised were to be reviewed online to determine the corrective action needed. Changes were to be made directly by authorized site staff.

Patients' source documentation (i.e., hospital charts) were to be maintained at the clinic. Source data to be recorded directly onto the eCRFs were to be communicated in advance.

Paper patient diaries covering the acute and delayed phases of CINV were to be used to collect emetic episodes (i.e., retching and vomiting episodes), and rescue medication intake.

The medical (hospital) files of trial patients were to be retained in accordance with national legislation (and in accordance with the maximum period of time permitted by the hospital (or institution/private practice)).

6.1.2. Study Results

Compliance with Good Clinical Practices

Palo 15-17 was conducted in compliance with good clinical practices with the CFR regarding protection of human subjects, Institutional Review Boards, and obligations of clinical investigators.

This study was also in accordance with the European Union (EU) clinical Trial Directive 2001/20/EC, the United States (US) Code of Federal Regulations 313.32, and the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and ICH E2A Guidance on Clinical Safety Management.

Financial Disclosure

A review of this study revealed no financial conflicts of interest. Please see financial disclosure

forms in Section 13.2. The applicant provided adequate documentation to show that there were no financial conflicts of interest between themselves and the 274 Investigators that participated in this study.

Patient Disposition

A total of 441 patients were randomized.

The 441 patients randomized to the study were distributed between treatment groups as follows: 225 patients randomized to palonosetron 0.25 mg as a 30-minute IV infusion (“infusion group”) and 216 patients randomized to 0.25 mg as a 30-second IV bolus (“bolus group”).

Four-hundred forty (440) (99.8%) patients were treated (225 [100%] patients in the infusion group, and 215 [99.5%] in the bolus group); and 424 (96.1%) patients completed the study (218 [96.9%] patients in the infusion group, and 206 [95.4%] in the bolus group).

Of the 17 (3.9%) patients who withdrew from the study prematurely, 13 (2.9%) patients died (6 [2.7%] patients in the infusion group, and 7 [3.2%] in the bolus group); 2 (0.5%) patients were lost to follow-up (one patient in each treatment group); and 2 (0.5%) patients chose to withdraw (both patients in the bolus group).

See the table below.

Table 9 – Patient Disposition PALO 15-17

Patient Disposition	IV PALO Infusion (N=225) n (%)	IV PALO Bolus (N=216) n (%)	Overall (N=441) n (%)
Randomized patients	225 (100.0)	216 (100.0)	441 (100.0)
Not treated patients	0 (0.0)	1 (0.5)	1 (0.2)
Treated patients	225 (100.0)	215 (99.5)	440 (99.8)
Patients who completed the study	218 (96.9)	206 (95.4)	424 (96.1)
Withdrawals	7 (3.1)	10 (4.6)	17 (3.9)
Primary reason for premature study termination			
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Death	6 (2.7)	7 (3.2)	13 (2.9)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (0.4)	1 (0.5)	2 (0.5)
Withdrawal by subject	0 (0.0)	2 (0.9)	2 (0.5)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)
Randomization code broken	0 (0.0)	0 (0.0)	0 (0.0)

(Source – PALO 15-17 Study Report Page 129)

Protocol Violations/Deviations

Overall, 15 (3.4%) patients in the FAS had major protocol deviations: 11 (4.9%) in the infusion group and 4 (1.9%) in the bolus group. The most common (affecting 9 [2.0%] patients) major protocol deviation referred to “dexamethasone not administered within the time window on the morning of Day 2”. All remaining major protocol deviations either referred to a HEC dosage

outside of the reference range (3 [0.7%] patients) or to the use of medication with potential anti-emetic effects within 24 h after starting the reference HEC (3 [0.7%] patients). Please see the table below.

Table 11 – Major Protocol Deviations PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus	Total
	N = 225	N = 215	N = 440
	n (%)	n (%)	n (%)
All patients with major protocol deviations	11 (4.9)	4 (1.9)	15 (3.4)
Major protocol deviation description:			
The dose per administration does not meet the protocol-described reference HEC dosage	3 (1.3)	0	3 (0.7)
Morning Day 2 administered dexamethasone date/time is not 24 h (plus/minus allowed time window) after the first intake of dexamethasone on Day 1	5 (2.2)	4 (1.9)	9 (2.0)
Use of a medication with potential anti-emetic effects in the 24 h after start of reference HEC	3 (1.3)	0	3 (0.7)

(Source PALO 15-17 Study Report Page 72)

Demographics

The patient demographics were comparable in each study arm. Please see the table below.

Table 12 – Demographics Table PALO 15-17

Palonosetron 0.25 mg IV		30-min Infusion	30-sec Bolus	Total
		N = 225	N = 215	N = 440
		n (%)	n (%)	n (%)
Gender	Male	151 (67.1)	144 (67.0)	295 (67.0)
	Female	74 (32.9)	71 (33.0)	145 (33.0)
Race	White	225 (100.0)	215 (100.0)	440 (100.0)
Age (years)^a	Mean (SD)	59.9 (8.7)	58.9 (8.5)	59.4 (8.6)
	Median	61.0	59.0	60.0
	Min, Max	25, 78	34, 79	25, 79
Baseline weight (kg)	Mean (SD)	73.85 (16.54)	74.44 (14.87)	74.14 (15.73)
	Median	72.00	73.00	73.00
	Min, Max	44.0, 128.0	43.2, 120.0	43.2, 128.0
Baseline height (cm)	Mean (SD)	168.5 (8.4)	169.6 (8.7)	169.0 (8.6)
	Median	170.0	170.0	170.0
	Min, Max	145, 188	145, 190	145, 190
BMI (kg/m²)^b	Mean (SD)	26.03 (5.53)	25.94 (5.21)	25.99 (5.37)
	Median	25.20	25.10	25.15
	Min, Max	13.0, 43.7	16.3, 44.6	13.0, 44.6
BSA (m²)	Mean (SD)	1.849 (0.225)	1.864 (0.205)	1.856 (0.215)
	Median	1.830	1.860	1.850
	Min, Max	1.39, 2.55	1.37, 2.35	1.37, 2.55

(Source PALO 15-17 Study Report Pages 76-77)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

At study entry, primary cancer location was similar between treatment groups, with the most frequent primary cancer location being lung and respiratory tract (51.1%), followed by “other” (19.8%), and head and neck (17.3%). Median time since diagnosis was 42 day for both treatment groups.

The extent of cancer at study entry was categorized as either primary, metastatic, or locally recurrent, with no notable differences between the treatment groups in the proportions of patients assigned to each category. The majority of patients had primary (52.0%) or metastatic (43.4%) disease. For metastatic cancer, the most commonly reported sites for metastases were lymph nodes (23.9%), “other” (13.2%), and lung (12.0%). A small proportion of patients (4.5%) had locally recurrent cancer. Please see table below.

Table 13 – Cancer History PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus	Total
	N = 225 n (%)	N = 215 n (%)	N = 440 n (%)
Primary Cancer Location			
Gastric	8 (3.6)	12 (5.6)	20 (4.5)
Head and neck	32 (14.2)	44 (20.5)	76 (17.3)
Lung and respiratory tract	119 (52.9)	106 (49.3)	225 (51.1)
Ovarian	13 (5.8)	11 (5.1)	24 (5.5)
Bladder	4 (1.8)	4 (1.9)	8 (1.8)
Other	49 (21.8)	38 (17.7)	87 (19.8)
Extent			
Primary	113 (50.2)	116 (54.0)	229 (52.0)
Metastatic	101 (44.9)	90 (41.9)	191 (43.4)
Local recurrence	11 (4.9)	9 (4.2)	20 (4.5)
If metastatic, site(s) of metastasis			
Bone	17 (7.6)	10 (4.7)	27 (6.1)
Adrenal gland / Kidney	13 (5.8)	6 (2.8)	19 (4.3)
Liver	13 (5.8)	10 (4.7)	23 (5.2)
Lung	32 (14.2)	21 (9.8)	53 (12.0)
Lymph nodes	57 (25.3)	48 (22.3)	105 (23.9)
Other	31 (13.8)	27 (12.6)	58 (13.2)
Time since diagnosis (days)^a			
n	225	215	440
Mean (SD)	114.4 (353.3)	83.1 (201.7)	99.1 (289.4)
Median	42.0	42.0	42.0
Q1, Q3	23, 67	23, 71	23, 70
Min, Max	6, 3640	2, 2460	2, 3640

(Source – PALO 15-17 Study Report Page 79)

Chemotherapy

Reference Chemotherapy

All patients in the study received reference chemotherapy which is summarized in the following table.

Table 14– Reference Chemotherapy PALO 15-17

Palonosetron 0.25 mg IV		30-min Infusion	30-sec Bolus	Total
		N = 225	N = 215	N = 440
Cisplatin, mg/m ²	n (%)	217 (96.4)	211 (98.1)	428 (97.3)
	Mean (SD)	76.74 (8.17)	76.96 (7.51)	76.85 (7.85)
	Median	75.00	75.00	75.00
	Min, Max	56.1, 103.0	64.1, 100.5	56.1, 103.0
Dacarbazine, mg/m ²	n (%)	8 (3.6)	4 (1.9)	12 (2.7)
	Mean (SD)	849.69 (217.37)	989.57 (24.95)	896.32 (187.03)
	Median	912.85	1000.00	987.03
	Min, Max	375.3, 1039.0	952.4, 1005.9	375.3, 1039.0

(Source – PALO 15-17 Study Report Page 81)

Concomitant Chemotherapy

Concomitant chemotherapy is summarized in the following table.

Table 15– Concomitant Chemotherapy PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus	Total
	N = 225	N = 215	N = 440
	n (%)	n (%)	n (%)
Any concomitant chemotherapy	191 (84.9)	180 (83.7)	371 (84.3)
No concomitant chemotherapy started up to Day 5	34 (15.1)	35 (16.3)	69 (15.7)
Concomitant chemotherapy on Day 1 only	121 (53.8)	114 (53.0)	235 (53.4)
Concomitant chemotherapy on Days 1-5	70 (31.1)	66 (30.7)	136 (30.9)
Concomitant chemotherapy Days 1-5 by type			
Bevacizumab*	1 (0.4)	0	1 (0.2)
Bleomycin	1 (0.4)	2 (0.9)	3 (0.7)
Bleomycin Sulfate	1 (0.4)	0	1 (0.2)
Capecitabine	10 (4.4)	12 (5.6)	22 (5.0)
Cyclophosphamide*	13 (5.8)	5 (2.3)	18 (4.1)
Docetaxel	9 (4.0)	5 (2.3)	14 (3.2)
Doxorubicin*	10 (4.4)	3 (1.4)	13 (3.0)
Doxorubicin hydrochloride*	0	2 (0.9)	2 (0.5)
Epirubicin hydrochloride*	1 (0.4)	0	1 (0.2)
Epirubicin*	2 (0.9)	1 (0.5)	3 (0.7)
Etoposide	45 (20.0)	31 (14.4)	76 (17.3)
Fluorouracil	21 (9.3)	32 (14.9)	53 (12.0)
Gemcitabine	38 (16.9)	31 (14.4)	69 (15.7)
Gemcitabine hydrochloride	15 (6.7)	6 (2.8)	21 (4.8)
Methotrexate*	0 (0.0)	1 (0.5)	1 (0.2)
Paclitaxel	14 (6.2)	15 (7.0)	29 (6.6)
Pemetrexed*	8 (3.6)	13 (6.0)	21 (4.8)
Pemetrexed disodium*	4 (1.8)	3 (1.4)	7 (1.6)
Vinblastine sulfate*	1 (0.4)	0	1 (0.2)
Vincristine*	1 (0.4)	0	1 (0.2)
Vinorelbine	2 (0.9)	2 (0.9)	4 (0.9)
Vinorelbine tartrate	10 (4.4)	19 (8.8)	29 (6.6)
Any chemotherapy after Day 5^b	57 (25.3)	51 (23.7)	108 (24.5)
Bleomycin	0	1 (0.5)	1 (0.2)
Bleomycin sulfate	1 (0.4)	0	1 (0.2)
Carboplatin	1 (0.4)	2 (0.9)	3 (0.7)
Cisplatin	8 (3.6)	4 (1.9)	12 (2.7)
Dacarbazine citrate	1 (0.4)	0	1 (0.2)
Doxorubicin	1 (0.4)	0	1 (0.2)
Etoposide	0	2 (0.9)	2 (0.5)
Gemcitabine	28 (12.4)	25 (11.6)	53 (12.0)
Gemcitabine hydrochloride	13 (5.8)	3 (1.4)	16 (3.6)
Paclitaxel	1 (0.4)	0 (0.0)	1 (0.2)
Pemetrexed	3 (1.3)	1 (0.5)	4 (0.9)
Pemetrexed disodium	1 (0.4)	2 (0.9)	3 (0.7)
Vinorelbine*	1 (0.4)	1 (0.5)	2 (0.5)
Vinorelbine tartrate*	9 (4.0)	16 (7.4)	25 (5.7)

(Source – PALO 15-17 Study Report Pages 82 and 83)

Treatment Compliance, Prior Medications, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

There were no significant differences in treatment compliance between the two study arms. Please see the table below.

Table 16 – Treatment Compliance – FAS, PALO 15-17

		IV PALO Infusion (N=225)	IV PALO Bolus (N=215)	Overall (N=440)
Number of compliant patients	n (%)	222 (98.7)	212 (98.6)	434 (98.6)
Number of non-compliant patients	n (%)	3 (1.3)	3 (1.4)	6 (1.4)

(Source PALO 15-17 Study Report Page 310)

Prior Medications

Considering the Safety Population, use of prior medications was recorded for 42.7% of patients in the study.

The most commonly reported classes of medications (ATC level 4 headings) used prior to study entry were heparin group (7.0%), other opioids (6.1%), and beta blocking agents, selective (5.5%).

Concomitant Medications

Use of concomitant medications was recorded for 81.8% of patients in the study.

As expected due to the specific patient population and administration of cytotoxic cancer chemotherapy, solutions producing osmotic diuresis as (mannitol) (37.7%), electrolyte solutions (19.3%), solutions affecting electrolyte balance (17.5%) and solutions for parenteral nutrition (16.6%) were very commonly reported classes of medications (ATC level 4 headings) during the present study.

In addition, other commonly reported classes of medications (ATC level 4 headings) used concomitantly during the study were selective beta-blocking agents (15.9%), plain sulfonamides diuretics (furosemide and indapamide) (14.5%), heparin group (10.5%), H2-receptor antagonists (10.0%), platelet aggregation inhibitors excluding heparin (8.9%), proton pump inhibitors (8.6%), colony stimulating factors (7.5%), folic acid (7.5%), glucocorticoids (7.5%), other opioids (7.5%), serotonin (5-HT₃) antagonists (7.3%), calcium (6.6%), dihydropyridine derivatives (6.4%), angiotensin II antagonists, plain (5.7%), HMG-CoA reductase inhibitors (5.7%), iron bivalent oral preparations (ferrous sulfate) (5.7%), propulsives (5.7%), and other cardiac preparations (5.5%).

Rescue Medication Use

Rescue medication use was generally similar between the two treatment arms. See table below.

Table 17 – Anti-Emetic Rescue Medication Use – FAS, PALO 15-17

WHO ATC terms WHO Preferred Term	IV PALO Infusion (N=225) n (%)	IV PALO Bolus (N=215) n (%)	Overall (N=440) n (%)
Number Of Patients With At Least One Rescue Medication	52 (23.1)	44 (20.5)	96 (21.8)
Antivertigo Preparations	0 (0.0)	1 (0.5)	1 (0.2)
Dimenhydrinate	0 (0.0)	1 (0.5)	1 (0.2)
Other Antiemetics	0 (0.0)	1 (0.5)	1 (0.2)
Chlorobutanol	0 (0.0)	1 (0.5)	1 (0.2)
Other Plain Vitamin Preparations	0 (0.0)	1 (0.5)	1 (0.2)
Pyridoxine	0 (0.0)	1 (0.5)	1 (0.2)
Propulsives	52 (23.1)	44 (20.5)	96 (21.8)
Metoclopramide	33 (14.7)	24 (11.2)	57 (13.0)
Metoclopramide Dihydrochloride	1 (0.4)	0 (0.0)	1 (0.2)
Metoclopramide Hydrochloride	20 (8.9)	20 (9.3)	40 (9.1)
Serotonin (5ht3) Antagonists	1 (0.4)	1 (0.5)	2 (0.5)
Ondansetron	1 (0.4)	1 (0.5)	2 (0.5)

(Source PALO 15-17 Study Report Page 306)

Efficacy Results

Primary Endpoint

The analysis of FAS revealed that 186 (82.7%) patients in the infusion group reported CR in the acute phase, as did 186 (86.5%) patients in the bolus group. The stratum-adjusted CMH method for difference in proportions, stratified by sex and country, with associated two sided 99% CI was used for non-inferiority testing. The difference in proportion between **the 30-minute infusion and 30-second bolus treatment groups was -3.8% (99% CI: -12.2%, 4.7%)**.

Since the lower limit of the two-sided 99% CI for the difference in proportions was greater (i.e., closer to zero) than the pre-defined non-inferiority margin of -15%, **non-inferiority of palonosetron 30-min infusion vs. 30-sec bolus was demonstrated**. Please see table below.

Table 18 - Complete Response in the Acute Phase (FAS and PP) PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Full Analysis Set	N = 225	N = 215
Responder, n (%)	186 (82.7)	186 (86.5)
[95% confidence interval] ^a	[77.2, 87.1]	[81.3, 90.4]
CMH risk difference % (Infusion – Bolus) [99% CI] ^b		-3.8 [-12.2; 4.7]
P-value ^b		p<0.001
Per-Protocol Population	N = 214	N = 211
Responder, n (%)	177 (82.7)	182 (86.3)
[95% confidence interval] ^a	[77.1, 87.2]	[81.0, 90.3]
CMH risk difference % (Infusion – Bolus) [99% CI] ^b		-3.4 [-12.0; 5.2]
P-value ^b		p<0.001

(Source – PALO 15-17 Study Report Page 86)

Secondary and Other Relevant Endpoints

The secondary endpoints of this trial did not have any bearing on the proposed indication or labeling. Intravenous palonosetron (30 sec) has not been shown to be effective in the delayed phase of HEC and currently does not carry this indication. Therefore, no meaningful conclusions can be drawn from these analyses. Intravenous palonosetron is approved for prevention of delayed phase of CINV associated with MEC. It might be reasonable to extrapolate the observation from this trial to the MEC setting, should the applicant pursue a MEC indication in the future; however, there was no prespecified noninferiority margin agreed upon for the delayed phase and there was no plan to control alpha for multiplicity to account for these additional analyses. The results for these endpoints are presented here only for descriptive purposes. (see Section 6.1.1). Please see tables below.

Table 19 – Complete Response in the Delayed and Overall Phases PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
Delayed Phase (>24-120 h)		
Responder, n (%)	170 (75.6)	165 (76.7)
[95% confidence interval] ^a	[69.5; 80.7]	[70.7; 81.9]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-1.2 [-8.7; 6.3]
Overall Phase (0-120 h)		
Responder, n (%)	150 (66.7)	156 (72.6)
[95% confidence interval] ^a	[60.3; 72.5]	[66.2; 78.1]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-6.0 [-14.1; 2.1]

(Source – PALO 15-17 Study Report Page 87)

Table 20 – No Emetic Episodes in the Acute, Delayed, and Overall Phases PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
Acute Phase (0-24 h)		
Responder, n (%)	186 (82.7)	190 (88.4)
[95% confidence interval] ^a	[77.2; 87.1]	[83.4; 92.0]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-5.6 [-11.9; 0.6]
Delayed Phase (>24-120 h)		
Responder, n (%)	176 (78.2)	168 (78.1)
[95% confidence interval] ^a	[72.4; 83.1]	[72.1; 83.1]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		0.1 [-7.2; 7.4]
Overall Phase (0-120 h)		
Responder, n (%)	155 (68.9)	160 (74.4)
[95% confidence interval] ^a	[62.6; 74.6]	[68.2; 79.8]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-5.6 [-13.6; 2.4]

(Source – PALO 15-17 Study Report Page 89)

The observed treatment difference for No Emetic Episodes in the Acute Phase was similar to that for Complete Response in the Acute Phase.

Table 21 – No Rescue Medications in the Acute, Delayed, and Overall Phases PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion N = 225	30-sec Bolus N = 215
Acute Phase (0-24 h)		
Responder, n (%)	200 (88.9)	195 (90.7)
[95% confidence interval] ^a	[84.1; 92.4]	[86.1; 93.9]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-1.7 [-7.0; 3.7]
Delayed Phase (>24-120 h)		
Responder, n (%)	183 (81.3)	176 (81.9)
[95% confidence interval] ^a	[75.7; 85.9]	[76.2; 86.4]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-0.7 [-7.6; 6.3]
Overall Phase (0-120 h)		
Responder, n (%)	173 (76.9)	169 (78.6)
[95% confidence interval] ^a	[71.0; 81.9]	[72.6; 83.6]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-2.0 [-9.3; 5.4]

(Source – PALO 15-17 Study Report Page 91)

The observed treatment difference for No Rescue Medications in the Acute Phase was similar to that for Complete Response in the Acute Phase.

Subgroup Analyses

Sex

A logistic regression model to test the interaction of treatment by sex was performed and is summarized below. No treatment-by-sex interaction was detected (p=0.409). It should be noted that the observed treatment difference was numerically greater in females than males, and the lower bound of the confidence interval for the difference was numerically lower; however, the sample size was small (only approximately 70 female patients per treatment group). See the table below.

Table 22 - Exploratory Analysis of Complete Response in the Acute Phase by Sex (Population: Full Analysis Set)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
Male	n = 151	n = 144
Responder, n (%)	134 (88.7)	129 (89.6)
[95% confidence interval] ^a	[82.7; 92.9]	[83.5; 93.6]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-0.8 [-7.8; 6.2]
Female	n = 74	n = 71
Responder, n (%)	52 (70.3)	57 (80.3)
[95% confidence interval] ^a	[59.1; 79.5]	[69.6; 87.9]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-9.8 [-23.2; 3.6]

Source: Summary Tables 14.2.1.5 and 14.2.1.7

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup.

(a) Wilson score method confidence interval.

(b) CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O’Gorman et al.

Table above is taken from Page 95 of the PALO 15-17 CSR

Country

A logistic regression to test the treatment-by-country interaction was performed and is summarized for the FAS in the table below. No treatment-by-country interaction was detected (p=0.817).

Table 23 - Exploratory Analysis of Complete Response in the Acute Phase by Country (Population: Full Analysis Set)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
Bulgaria	n = 19	n = 19
Responder, n (%)	16 (84.2)	17 (89.5)
[95% confidence interval] ^a	[62.4; 94.5]	[68.6; 97.1]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-5.3 [-25.5; 15.0]
Georgia	n = 21	n = 21
Responder, n (%)	19 (90.5)	20 (95.2)
[95% confidence interval] ^a	[71.1; 97.3]	[77.3; 99.2]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-5.2 [-20.8; 10.4]
Hungary	n = 50	n = 48
Responder, n (%)	39 (78.0)	42 (87.5)
[95% confidence interval] ^a	[64.8; 87.2]	[75.3; 94.1]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-9.8 [-23.9; 4.3]
Romania	n = 46	n = 45
Responder, n (%)	40 (87.0)	37 (82.2)
[95% confidence interval] ^a	[74.3; 93.9]	[68.7; 90.7]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		4.7 [-10.0; 19.5]
Russian Federation	n = 68	n = 65
Responder, n (%)	53 (77.9)	56 (86.2)
[95% confidence interval] ^a	[66.7; 86.2]	[75.7; 92.5]
CMH risk difference % (Infusion – Bolus) [95% CI] ^b		-8.1 [-20.7; 4.6]

Source: Summary Tables 14.2.1.6 and 14.2.1.8

Abbreviations: CMH = Cochran-Mantel-Haenszel; CI = confidence interval; IV = intravenous; N = number of patients in a given group; n = number of patients in a given subgroup.

(a) Wilson score method confidence interval.

(b) CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O’Gorman et al.

Table above is taken from Page 97 of the PALO 15-17 CSR

Data Quality and Integrity – Reviewers’ Assessment

Please refer to OSI analysis in Section 4.1. There were no anomalies in the results with respect to different study sites. No other concerns with the study results were identified.

Dose/Dose Response

Dose/Dose response was not specifically addressed in this trial.

Durability of Response

Durability of response was not specifically addressed in this trial.

Persistence of Effect

Persistence of effect was not specifically addressed in this trial.

Additional Analyses Conducted on the Individual Trial

No additional analyses were required for this study.

6.2. NEPA 15-18

6.2.1. Study Design

Overview and Objective

NEPA 15-18 was titled “A phase 3, multicenter, randomized, double-blind, active control study to evaluate the safety and efficacy of IV pro-netupitant/ palonosetron (260mg/0.25mg) combination for the prevention of chemotherapy induced nausea and vomiting in repeated chemotherapy cycles in patients receiving highly emetogenic chemotherapy.”

The primary objective of this study was to assess the safety and tolerability of a single dose of IV NEPA FDC (260 mg/0.25 mg) infused over 30 min, with oral dexamethasone, in initial and repeated cycles of HEC. The secondary objective of this study was to describe the efficacy of a single dose of IV NEPA FDC (260 mg/0.25 mg) infused over 30 min, with oral dexamethasone, during the acute (0-24 h), delayed (>24-120 h) and overall (0-120 h) phases of initial and repeated cycles of HEC.

Reviewer’s Comment: The critical aspect to understand about NEPA 15-18 is that it was designed to be a safety trial. Efficacy was a secondary objective, and the study was not designed or powered to be a non-inferiority trial. Only descriptive statistics were used in the efficacy analysis.

Trial Design

Overview

NEPA 15-18 was a phase 3 multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, parallel group, stratified study conducted in patients receiving HEC. The study evaluated repeat dosing during 4 cycles of HEC chemotherapy.

IV NEPA FDC (Akynzeo® for injection) was compared to oral NEPA FDC (Akynzeo®) as a control.

Number of Patients

The number of patients to be randomized into the study was 400 equally distributed in the two treatment groups (i.e., 200 patients/group).

Pertinent Inclusion Criteria

Cycle 1:

1. Signed written informed consent.
2. Male or female patient ≥ 18 years of age.
3. Histologically or cytologically confirmed solid tumor malignancy.
4. Naïve to cytotoxic chemotherapy. Previous biological or hormonal therapy is permitted.
5. Scheduled to receive at least 4 repeated consecutive cycles of the following highly emetogenic reference chemotherapies (HEC), alone or in combination with other chemotherapeutic agents* on Day 1:
 - cisplatin administered as a single IV dose of $\geq 70 \text{ mg/m}^2$
 - cyclophosphamide $\geq 1500 \text{ mg/m}^2$
 - carmustine (BCNU) $>250 \text{ mg/m}^2$
 - dacarbazine (DTIC)
 - mechlorethamine (nitrogen mustard)

*on Day 1, additional chemotherapeutic agents have to be administered after the start of the reference HEC administration and their administration must be completed no more than 6 hours after the start of reference HEC infusion. Low, minimally, or not emetogenic chemotherapies can be administered at any time from Day 2 onwards.

6. ECOG Performance Status of 0, 1, or 2.
7. If a patient is female, she shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having negative urine pregnancy test.
8. Hematologic and metabolic status adequate for receiving a HEC regimen and fulfillment of the following criteria:
 - a) Total Neutrophils $\geq 1500/\text{mm}^3$ (Standard units: $\geq 1.5 \times 10^9/\text{L}$)
 - b) Platelets $\geq 100,000/\text{mm}^3$ (Standard units: $\geq 100.0 \times 10^9/\text{L}$)
 - c) Bilirubin $\leq 1.5 \times$ Upper Limit of Normal (ULN)
 - d) Liver enzymes:
 - iii. Without known liver metastases, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN
 - iv. With known liver metastases, AST and ALT $\leq 5.0 \times$ ULN
 - e) Serum Creatinine $\leq 1.5 \text{ mg/dL}$ (Standard units: $\leq 132.6 \text{ } \mu\text{MOL/L}$) or Creatinine Clearance $\geq 60 \text{ mL/min}$
9. Able to read, understand, follow the study procedure and complete patient diary.

Cycles 2 to 4:

1. Participation in the study during the next cycle of chemotherapy is considered appropriate by the Investigator and does not pose unwarranted risk to the patient.
2. Scheduled to receive the same chemotherapy regimen as Cycle 1 or one of the reference chemotherapies as defined in Inclusion criterion #5 for Cycle 1.
3. If a patient is female, she shall be: a) of non-childbearing potential or b) of childbearing

potential using reliable contraceptive measures and having a negative urine pregnancy test.

4. Adequate hematologic and metabolic status according to the Investigator's opinion.

Pertinent Exclusion Criteria

Cycle 1:

1. Lactating woman.
2. Active infection or uncontrolled disease except for malignancy that may pose unwarranted risks in administering the study drugs to the patient.
3. Current use of illicit drugs or current evidence of alcohol abuse.
4. Scheduled to receive moderately emetogenic chemotherapy or highly emetogenic chemotherapy from Day 2 to Day 5.
5. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of the reference HEC administration on Day 1 or between Days 1 to 5.
6. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of the reference chemotherapy administration on Day 1.
7. Symptomatic primary or metastatic CNS malignancy.
8. Known hypersensitivity or contraindication to 5-HT₃ receptor antagonists (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron) or dexamethasone.
9. Known contraindication to the IV administration of 50 mL 5% glucose solution.
10. Previously received an NK-1 receptor antagonist.
11. Participation in a previous clinical trial involving IV pro-netupitant or oral netupitant administered alone or in combination with palonosetron.
12. Any investigational drugs (other than those given in this study) taken within 4 weeks prior to Day 1, and/or is scheduled to receive any investigational drug during the present study.
13. Systemic corticosteroid therapy at any dose within 72 hours prior to the start of the reference HEC administration on Day 1. However, topical and inhaled corticosteroids are permitted.
14. Scheduled to receive bone marrow transplantation and/or stem cell rescue therapy.
15. Scheduled to receive any strong or moderate inhibitor of CYP3A4 or its intake within 1 week prior to Day 1.
16. Scheduled to receive any of the following CYP3A4 substrates within 1 week prior to Day 1: terfenadine, cisapride, astemizole, pimozone.
17. Received within 4 weeks prior to Day 1 or scheduled to receive any CYP3A4 inducer.
18. Any medication with known or potential antiemetic activity within 24 hours prior to the start of the reference HEC administration on Day 1, including:
 - 5-HT₃ receptor antagonists (e.g., ondansetron, granisetron, dolasetron, tropisetron, ramosetron, palonosetron)
 - NK1 receptor antagonists (e.g., aprepitant or any other new drug of this class)
 - benzamides (e.g., metoclopramide, alizapride)
 - phenothiazines (e.g., prochlorperazine, promethazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine)
 - benzodiazepines (except if the subject is receiving such medication for sleep or anxiety and has been on a stable dose for at least seven days prior to Day 1)

- butyrophenones (e.g., haloperidol, droperidol)
 - anticholinergics (e.g., scopolamine, with the exception of inhaled anticholinergics for respiratory disorders, e.g., ipratropium bromide)
 - antihistamines (e.g., cyclizine, hydroxyzine, diphenhydramine, chlorpheniramine)
 - domperidone
 - mirtazapine
 - olanzapine
 - prescribed cannabinoids (e.g., tetrahydrocannabinol or nabilone)
 - Over the Counter (OTC) antiemetics, OTC cold or OTC allergy medications
19. History or predisposition to cardiac conduction abnormalities, except for incomplete right bundle branch block.
 20. History of Torsade de Point or known history of risk factors for Torsade de Point (heart failure, hypokalemia, family history of Long QT Syndrome).
 21. Severe cardiovascular diseases diagnosed within 3 months prior to Day 1 of first cycle, including myocardial infarction, unstable angina pectoris, significant valvular or pericardial disease, history of ventricular tachycardia, symptomatic Congestive Heart Failure (CHF) NYHA class III-IV, and severe uncontrolled arterial hypertension.
 22. Any illness or condition that, in the opinion of the Investigator, may confound the results of the study or pose unwarranted risks in administering the investigational product to the patient.
 23. Concurrent medical condition that would preclude administration of dexamethasone such as systemic fungal infection or uncontrolled diabetes.

Cycles 2 to 4:

1. Lactating woman.
2. Active infection or uncontrolled disease except for malignancy that may pose unwarranted risks in administering the study drugs to the patient.
3. Started any of the restricted medications.
4. Any vomiting, retching, or nausea (grade ≥ 1 as defined by National Cancer Institute) within 24 hours prior to the start of reference chemotherapy administration on Day 1.
5. Received or is scheduled to receive radiation therapy to the abdomen or the pelvis within 1 week prior to the start of the reference chemotherapy administration on Day 1 or between Days 1 to 5.
6. Symptomatic primary or metastatic CNS malignancy.

Reviewer's Comments: The inclusion/ exclusion criteria for NEPA 15-18 were similar to those of PALO 15-17. There was additional language about active infection and conduction abnormalities as exclusions. In addition, there were inclusion/ exclusion criteria assessments that were applied to cycle 1 with abbreviated criteria applied to cycles 2-4 (lactation, active infection/ uncontrolled disease, restricted medication, vomiting, retching, or nausea grade ≥ 1 as defined by the National Cancer Institute), received or scheduled radiation therapy to the abdomen or pelvis within 1 week of the start of reference chemotherapy administration, symptomatic primary or metastatic CNS malignancy. The inclusion/ exclusion criteria are otherwise identical to that found in PALO 15-17. Please refer to Section 6.1.1.

Dose Selection

Fosnetupitant Dose: The dose of fosnetupitant in the IV NEPA FDC was selected based on the results of a relative bioavailability study in healthy volunteers (PNET-12-23). In PNET-12-23, a dose of 257 mg fosnetupitant was compared to the netupitant dose contained in oral NEPA FDC (i.e., 300 mg netupitant). Bioequivalence criteria were met (for AUC_{0-120h} and $AUC_{0-\infty}$). The dose of IV fosnetupitant was then rounded to 260 mg for further development of the IV NEPA FDC.

Palonosetron Dose: The approved dose of Aloxi (palonosetron) IV for adults of 0.25 mg was used.

Dosing Schedule

IV NEPA FDC Infusion: The 30-minute (+/-5 minutes) IV NEPA FDC infusion (or placebo) was started 30 minutes prior to the start of the reference chemotherapy administration. The IV infusion was completed before starting chemotherapy administration.

NEPA FDC Capsule: Oral NEPA FDC capsule (or placebo) was administered 60 minutes prior to the start of the reference chemotherapy administration.

Dexamethasone: Oral dexamethasone administration was performed in open fashion. Dexamethasone dose and schedule were identical between test and control treatments, i.e., 12 mg oral dexamethasone once on Day 1, then 8 mg oral dexamethasone once daily on Days 2 through 4. On Day 1, oral dexamethasone (3 tablets of 4 mg, for a total daily dose of 12 mg) was taken 30 minutes prior to the start of the reference chemotherapy administration (immediately before the start of the IV NEPA FDC or placebo infusion). On Days 2 to 4, oral dexamethasone was taken in the morning (2 tablets of 4 mg, for a total daily dose of 8 mg).

Please see table below for overall treatment administration schedule.

Table 24 – Treatment administration schedules NEPA 15-18

	Group 1 (Test)	Group 2 (Control)
Day 1	1 capsule NEPA FDC placebo p.o., 60 minutes before start of reference chemotherapy administration	1 capsule NEPA FDC (300 mg netupitant/0.50 mg palonosetron), p.o., 60 minutes before start of reference chemotherapy administration
	3 tablets, 4 mg dexamethasone 30 minutes before start of reference chemotherapy (immediately before the start of the IV NEPA FDC infusion)	3 tablets, 4 mg dexamethasone 30 minutes before start of reference chemotherapy (immediately before the start of the IV NEPA FDC placebo infusion)
	1 vial, 260 mg pro-netupitant/ 0.25 mg palonosetron reconstituted with 50 mL 5% glucose solution and administered by IV as a 30-minute (+/- 5 minutes) infusion, starting 30 minutes before reference chemotherapy administration	1 vial, pro-netupitant/palonosetron placebo reconstituted with 50 mL 5% glucose solution and administered by IV as a 30-minute (+/- 5 minutes) infusion, starting 30 minutes before reference chemotherapy administration
Days 2-3-4	2 tablets, 4 mg dexamethasone p.o., morning	2 tablets, 4 mg dexamethasone p.o., morning

(Source - NEPA 15-18 Protocol page 60)

Randomization/Stratification

Randomization was used to avoid bias in assigning treatments to patients. Randomized treatment assignments and maintenance of the blind were continued beyond initial cycle throughout all repeated cycles in this trial. Treatment assignment was managed through a static central blocked randomization stratified by sex (male, female) and country. The randomization scheme was reproducible and was prepared prior to start of the study via a computerized system by the IWRS vendor.

Blinding

The blinding of the study drugs was guaranteed by the use of identical placebos to the respective active drugs (double-dummy technique).

The Investigator had the possibility to unblind the study treatment in case of an emergency, when he/she considered it essential to know what treatments the patient had received.

Administrative Structure

A Data Safety Monitoring Board (DSMB) was to be convened for the evaluation of safety data in the study. The DSMB was to periodically review safety data during the conduct of the study. The DSMB was to not include employees of the sponsor and was to be comprised of two clinicians who are not investigators in the study and one statistician.

Two contract research organizations (CRO) were involved in this study. PSI CRO AG, based out of Zug, Switzerland, was the clinical CRO, and (b) (4) based out of (b) (4) was the CRO for Statistics and Data Management (SDM). There were no adjudication committees.

Schedule and Procedures

The following table from the study report lists the schedule and procedures that occurred during the trial.

Table 25 – Schedules and Procedures NEPA 15-18

Cycle 1 / Repeated Cycles					
Procedure/assessment	Screening Day -14 to -1 ^a (Cycle 1 only) /-7 to Day 1 ^a	Day 1 ^a	Day 2 ^b	Day 6 (+2) ^c	Day 21(±2) ^d
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed consent	X ^a				
Inclusion / Exclusion Criteria ^f	X	X			
Demography	X ^a				
Medical/surgical history (including cancer history)	X ^a				
ECOG Performance Status	X				
Urine pregnancy test	X	X ^g			
Serum pregnancy test ^h	X			X	
Prior and concomitant medications	X	X	X	X	X
Physical examination ⁱ	X		X	X	
Vital signs ^j	X	X	X	X	
12-lead ECG ^k	X ^l	X ^l	X ^l	X ^l	
Blood chemistry ^m	X		X	X	
Hematology ^m	X		X	X	
Urinalysis ^m	X		X	X	
Randomization		X ^o			
Study drugs and dexamethasone administration ⁿ		X ^o			
Chemotherapy		X			
Patient diary ^o and instructions on completion		to be completed from Day 1 and collected at Visit 4			
Adverse Events ^p	X	X	X	X	X

- a) Day -1 is the day immediately preceding Day 1.
- b) Approximately 24 hours after the oral capsule administration on Day 1.
- c) 120 hours after the oral capsule administration on Day 1. If Day 6 is a holiday or a weekend day, Visit 4 may be scheduled within the two forthcoming days.
- d) Day 21(±2), either on-site visit or phone contact. The follow-up visit of one cycle and the screening visit of the subsequent cycle may coincide.
- e) Only at Cycle 1.
- f) Including check of alcohol and illicit drugs consumption.
- g) To be performed for females of childbearing potential within 24 hours prior to the oral capsule administration on Day 1 of each cycle. If the screening visit urine pregnancy test has been done within the 24 hours before the oral capsule administration, no urine pregnancy test is to be performed at Visit 2 (Day 1) of the referred cycle.
- h) Serum pregnancy test will be performed at the central laboratory, as well as for urinalysis, hematology and blood chemistry.
- i) Complete Physical examination at Visits 1 and 4, Limited Physical examination at Visit 3.
- j) Vital signs assessments include: pulse rate, systolic blood pressure, and diastolic blood pressure at Visit 1 (Screening), Visit 2 (on Day 1 at pre-dose (i.e., before the oral capsule administration), after the end of IV study drug or placebo infusion (i.e., immediately [within 10 minutes] before to start the reference chemotherapy administration) and after 5 hours (+/- 1 hour) from the oral capsule administration, Visit 3 (24 hours [+/- 2 hours] after the oral capsule administration), and Visit 4 (120 hours [-6/+54 hours] after the oral capsule administration). Pulse rate and systolic and diastolic blood pressure have to be measured after the patient has been in the sitting position for at least 5 minutes. Height has to be measured only at Visit 1 of Cycle 1. Weight has to be measured at Visit 1, Visit 2 and Visit 4.
- k) 12-lead ECG (single recording) will be assessed in a central laboratory.
- l) 12-lead ECG will be recorded, for each cycle, at screening, pre-dose, end of IV study drug infusion (i.e., immediately [within 10 minutes] before the start of reference chemotherapy), 5 hours (+/- 1 hour) after the oral capsule administration, 24 hours [+/- 2 hours], and 120 hours [from 114 hours to 174 hours, i.e., -6/+54 hours] after the oral capsule administration on Day 1. 12-lead ECG (single recording) will be recorded after the patient has been in the supine position for at least 5 minutes.
- m) A central laboratory will be used for urinalysis, haematology and blood chemistry analysis throughout the entire study. For study inclusion (Cycle 1), central laboratory haematological results are mandatory and should satisfy the inclusion criterion #8. For Investigator's decision about patient's inclusion in Cycles 2 to 4, local laboratory results are acceptable; nevertheless, central laboratory data will need to be collected at each cycle.
- n) Patients will either receive IV NEPA FDC infusion (and placebo capsule) or oral NEPA FDC capsule (and placebo infusion) on Day 1, and dexamethasone on Days 1 to 4. Dexamethasone for Days 3 and 4 will be provided to the patient by the Investigator at Visit 3.
- o) Patients will be asked to report date and time of onset of emetic episodes (episodes of retching or vomiting), date and time of intake of rescue medication and nausea intensity assessed by VAS on their diary. Intake of dexamethasone on Day 3 and Day 4 will also be recorded on patient diary.
- p) Adverse Events will be collected from Informed Consent signature to the follow-up visit of last cycle or last patient contact.
- q) In repeated cycles (i.e., cycles no. 2, 3 or 4), the Visit 1 may be performed from Day -7 up to study Day 1 inclusive (i.e., Visit 1 and Visit 2 may occur on the same day on study Day 1). In that case, the assessments planned at both Visit 1 and Visit 2 have to be performed only once at Day 1.

(Source - NEPA 15-18 Study Report page 47)

It should be noted that severity of nausea was evaluated by the patient in the patient diary for each day of the 0-120 hour interval (Days 1 to 5, inclusive), using a 100-mm horizontal visual analogue scale (VAS). The left end of the scale (0 mm) was labeled as 'no nausea' and the right end of the scale (100 mm) was labeled as 'nausea as bad as it could be'.

Dietary Restrictions

No specific dietary restrictions/ instructions were included in the study protocol. This was not an issue from a clinical perspective.

Concurrent Medications

Information on prior and concomitant medications was to be collected from 14 days prior to Day 1 of the first cycle up to the end of the study. The use of any medication for the prevention of nausea and vomiting or to increase the expected preventive effects of the study medication, or any medication with potential antiemetic effects within 24 h prior to the start of the reference chemotherapy and for the following 120 h was prohibited. A complete list of prohibited medications was listed in the exclusion criteria. The use of rescue medication was permitted.

According to the protocol, at each cycle, systemic corticosteroid therapy (including but not limited to dexamethasone, hydrocortisone, methylprednisolone, or prednisolone) taken at any dose within 72 hours prior to the start of the reference chemotherapy administration on Day 1 and until 120 hours afterwards was not permitted; use of these prohibited medications during Cycle 1 was reported as a major protocol deviation (minor in subsequent cycles). Drugs that

were moderate and strong CYP3A4 inhibitors were not permitted within 1 week prior to Cycle 1 Day 1; use of these prohibited medications during Cycle 1 was also considered a major protocol deviation. If the moderate CYP3A4 inhibitor was stopped 1 week or more before Day 1 of any cycle, no protocol deviation was reported. If the moderate CYP3A4 inhibitor was taken within 1 week of a repeated cycle but not within 1 week of Cycle 1 Day 1, this was reported as a minor deviation.

Overall on Day 1 of Cycle 1, 387 (95.8%) patients received cisplatin (overall mean [SD] dose was 144.86 [22.98] mg). Fourteen (3.5%) patients received dacarbazine (overall mean [SD] dose was 1757.52 [391.67] mg) and 3 (0.74%) patients received cyclophosphamide (overall mean [SD] dose was 3003.33 [332.65] mg). In general, the mean (SD) doses of cisplatin, dacarbazine, and cyclophosphamide received on Day 1 of Cycles 2, 3, and 4 were similar to those on Day 1 of Cycle 1 for both overall and for each treatment group. No patient was treated with cyclophosphamide in the IV NEPA FDC group on Day 1 of Cycle 4 compared with 1 patient in the Oral NEPA FDC group, and no patient was treated with any of the remaining pre-defined reference HEC (carmustine or mechlorethamine).

Similar proportions of patients in each treatment group received chemotherapy concomitantly with their reference HEC up to Day 5 (inclusive) during each cycle (overall, 92.6% of patients during Cycle 1, 89.6% during Cycle 2, 88.2% during Cycle 3 and 89.5% during Cycle 4), mostly on Day 1 only (overall, 67.1% of patients during Cycle 1, 62.5% during Cycle 2, 62.3% during Cycle 3, and 65.3% during Cycle 4), with between 24.3% and 27.0% of patients overall receiving it on Days 1-5. Overall, between 22.6% and 30.4% of patients overall received chemotherapy after Day 5. Overall, the most commonly administered concomitant chemotherapy agents up to Day 5 (inclusive) in each cycle were etoposide (between 24.9% and 25.7% of patients), cyclophosphamide (between 15.1% and 19.7%), fluorouracil (between 11.1% and 11.8%), gemcitabine (between 9.2% and 10.9%), vinorelbine (between 7.0% and 8.4%), vinorelbine tartrate (between 5.9% and 7.9%), doxorubicin (between 5.0% and 7.1%), and gemcitabine hydrochloride (between 4.6% and 5.7%). Overall, the most commonly administered concomitant chemotherapy agents after Day 5 in each cycle were gemcitabine (between 8.2% and 10.1% of patients) and gemcitabine hydrochloride (between 3.8% and 5.2%) and vinorelbine (between 5.8% and 7.0%) and vinorelbine tartrate (between 3.3% and 6.4%).

Treatment Compliance

A patient was considered to be compliant with therapy if he/she took all study drugs (including dexamethasone) provided in the clinical study medication kit. Compliance was defined overall and for each cycle.

Rescue Medication

The protocol stated “Rescue medication should be administered to alleviate established, refractory or persistent nausea or vomiting and will be permitted on an as-needed basis.” Rescue medication was not allowed for prevention of emesis, or to increase the expected antiemetic effects of the study medication. The patient was to record in the patient diary the drug name, dosage and date/time of intake for each medication taken for the treatment of nausea and

vomiting during the 0-120 hour interval (Day 1 to Day 5). Each rescue medication trade or generic name, dosage and route of administration, as well as the time and date of intake, was documented on the eCRF in accordance with the patient diary records. NK-1 receptor antagonists, commercial palonosetron (Aloxi®, Onicit®, Paloxi®) and commercial Akynzeo® were not allowed as rescue medications. Other 5-HT3 receptor antagonists were not be used as rescue medications.

The Investigator was to be provided with a sufficient amount of rescue medication, e.g., metoclopramide tablets, to be distributed to the patients on an as-needed basis. However, the Investigator was authorized to use an alternative rescue medication, based on his/her judgment. The Investigator was to ensure that rescue medication was made available to patients whenever needed. NK1 receptor antagonists were not allowed and 5-HT3 receptor antagonists were not to be used as rescue medications. Commercial palonosetron (Aloxi®, Onicit®, Paloxi®) was not allowed as rescue medication.

Subject Completion, Discontinuation, or Withdrawal

Completion: A patient was defined as “completed” if s/he completed Visit 5 (either as on-site visit or telephone contact) of Cycle 4.

“Completed Cycle, Not Continuing”: A patient was defined as “completed cycle, not continuing” if s/he completed Visit 5 (either as on-site visit or telephone contact) of any cycle before Cycle 4 without continuing in the subsequent cycle.

Discontinuation: Study termination at a different time point (including screening visit for one of the repeated cycles) was considered as study discontinuation.

Replacement: Patients who discontinued after randomization were not to be replaced.

Follow-up Procedures and/or Assessments: If a subject was discontinued from the study after treatment with the investigational product, the Investigator tried his/her best to contact the subject 20 ($\pm$ 2) days after Day 1 of the last study cycle (i.e., at approximately the same date when Visit 5 (Day 21) was to be scheduled), in view of completing the safety assessment by collecting information that may have been suggestive of AEs.

Missing Data

Any patients who did not provide data about occurrence of emetic episodes and rescue medication intake or did not provide a full set of these data throughout the 120 h after HEC administration (including a diary available but not covering the whole 0-120 h) were considered as treatment failures (i.e., non-responders) for the efficacy analysis of CR in the overall phase. The same approach was applied to analysis of CR in the acute (0-24 h) and delayed (>24-120 h) phases. For consistency, the same approach for handling missing data as described for CR was applied to emetic episodes and rescue medication intake.

Study Endpoints

Time-related efficacy study parameters assessment started at “time 0,” defined as the start time of the reference chemotherapy agent administration on Day 1 of each cycle. Efficacy parameters were evaluated at each cycle in the acute phase (0-24 h after the start of reference chemotherapy), delayed phase (>24-120 h after the start of reference chemotherapy), and overall phase (0-120 h after the start of reference chemotherapy).

The following efficacy endpoints were defined:

- proportion of patients with CR (no emetic episodes and no rescue medication) during the acute, (0-24 h after the start of reference chemotherapy), delayed (>24-120 h after the start of reference chemotherapy), and overall (0-120 h after the start of reference chemotherapy) phases
- proportion of patients with no emetic episodes during the acute, delayed, and overall phases
- proportion of patients with no significant nausea (VAS <25 mm) during the acute, delayed, and overall phases (since VAS was assessed daily, for delayed and overall phases the maximum VAS value in the relevant phase was to be considered)

Statistical Analysis Plan

Definitions of Analysis Populations

The following definitions of analysis populations were used:

- **All-Randomized Population:** The All Randomized population included all patients who were randomized to treatment. Patients were assigned to the treatment group to which they were randomized. The All Randomized population was used for patient disposition.
- **Full Analysis Set:** The Full Analysis Set (FAS) included all randomized patients who received the HEC regimen and active study drug (including partial infusion). Following the intent-to-treat principle, patients were assigned to the treatment group to which they were randomized. The FAS was used for demography, other baseline characteristics, and all efficacy analyses.
- **Safety Population:** The Safety population included all patients who received at least one dose of active study drug (including partial infusion). Patients were assigned to treatment groups according to the actual treatment received. Safety population was used for demography, other baseline characteristics, and all safety analyses.

Efficacy Analyses

The assessment of efficacy was a secondary objective of the study. **Only descriptive statistics were planned for the efficacy endpoints.** At each cycle, for each phase (acute, delayed and overall), numbers and percentages (including 95% confidence interval [CI] using the Wilson score method) of patients with CR, with no emetic episodes, with no rescue medications, and with no significant nausea were to be summarized by treatment. CR was also to be summarized

by treatment and sex and by treatment and country. Difference between groups in response rate and 95% CI for difference were presented using Newcombe-Wilson's method and also the stratum-adjusted (sex and country as strata) Cochran-Mantel-Haenszel (CMH) method for the risk difference. Results were to be interpreted only in a descriptive manner.

The stratum-adjusted CMH method for difference in proportions used for efficacy analyses was to include sex (male, female) and country (Austria, Croatia, Czech Republic, Germany, Israel, Italy, Poland, Serbia, Spain, Ukraine, and United States) as strata. These were the same factors to be taken into account at the randomization level.

The procedure for handling missing data was applied to the FAS. Any patients who did not provide data about occurrence of emetic episodes and rescue medication intake or did not provide a full set of these data throughout the 120 h after HEC administration (including a diary available but not covering the whole 0-120 h) were considered as treatment failures (i.e., non-responders) for the efficacy analysis of CR in the overall phase. The same approach was to be applied to analysis of CR in the acute (0-24 h) and delayed (>24-120 h) phases. For consistency, the same approach for handling missing data as described for CR was to be applied to emetic episodes and rescue medication intake. For data recorded on the patient diary, a patient was considered as having CR only if there was documented evidence of both no occurrence of emetic episodes and no rescue medication intake. Otherwise the patient was considered as a failure. Episodes of either emesis or of rescue medication intake confirmed to have occurred outside the time window of 0-120 h with reference to start of chemotherapy administration were kept as they were and not used for the statistical analysis of CR.

Adjustment for Multiplicity

No adjustment for multiplicity was made in the study.

Interim Analysis

No interim analysis was performed for this study.

Planned Subgroup Analyses

Subgroups that were to be explored include:

- Sex (Male, Female)
- Country (Austria, Croatia, Czech Republic, Germany, Israel, Italy, Poland, Serbia, South Africa, Spain, Ukraine and USA)

Protocol Amendments

There were 3 amendments to the NEPA 15-18 protocol: Amendment #1 dated July 27, 2015, Amendment #2 dated October 19, 2015, and Amendment #3 dated March 21, 2016. There were also 2 amendments for Germany only: Amendment #1 dated December 3, 2015 and Amendment #2 dated March 21, 2016.

Amendment #1 dated July 27, 2015 documented the use of a Data Safety Monitoring Board

(DSMB) to periodically review the safety data.

Amendment #2 dated October 19, 2015 was implemented to correct a minor inconsistency present in the protocol Synopsis and in section 4.3.2, as well as to simplify study procedure during the repeated cycles (i.e., Cycles 2, 3 or 4) by allowing unification of the Visit 1 (Screening Visit) and Visit 2 (Day 1), whenever possible.

Amendment #3 dated March 21, 2016 was implemented to update general information to current status, to specify in detail and improve description of time windows for the study drug, additional non-investigational study drug and reference chemotherapy administration, and vital signs 12-lead ECG measurements. Additionally, minor editorial improvements were implemented with no impact on the meaning of the sentences.

Amendment #1 dated December 3, 2015, Germany only, was implemented to address the requests of the competent authority (German CEC) provided with their letter dated November 11, 2015 following the review of the study documentation:

- Added Exclusion criterion in Synopsis and in Section 4.3.3: (Pre-dose) QTcF Interval >470 ms at Screening in all Cycles.
- Added the sentence in Section 6.4 Premature Discontinuation: In addition, any patient with post-dose QTcF >500 ms or with QTcF increase >60 ms compared to last value before study drug intake in the cycle will complete the current cycle, but will not be allowed to enter any additional study cycle.

Amendment #2 dated December 3, 2015, Germany only, was implemented to update general information to current status, to specify in detail and improve the description of time windows for the study drug, additional non-investigational study drug and reference chemotherapy administration, vital signs and 12-lead ECG measurements. Additionally, minor editorial improvements were implemented with no impact on the meaning of the sentences.

Data Quality and Integrity: Sponsor's Assurance

Monitoring

The study was monitored by CRO's adequately qualified and trained clinical monitors on a regular basis throughout the study period to ensure the proper conduct of the clinical trial. The purposes of clinical trial monitoring were to verify that the rights and well-being of study patients were protected, that the reported trial data were accurate, complete, and verifiable against the source documents, and that the study was conducted in accordance with the current protocol, Good Clinical Practice guideline and applicable regulatory requirements. During the monitoring visits, monitors verified the following including but not limited to: patient informed consent, patient's eligibility, safety data and reporting, quality of source documents, and eCRF data against patient's medical records. If inconsistencies were identified, the corresponding corrections to the eCRF data had to be made by the Investigator. Monitors also checked patient compliance, accrual, drug handling, including dispensing procedures and accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with

family doctors, and if any, ancillary equipment and facilities, including refrigerators and freezers, local labs, etc. The Investigator and other site staff involved in the study allocated enough time to the monitor at these visits.

Audits were performed by the CRO as well as by the Sponsor. Upon request by the Sponsor, or following the CRO's audit plan, on-site study audits were conducted to ensure that the study was following GCP, applicable regulatory requirements, and the study protocol. The auditing activities may have also been conducted after study completion.

In addition, Regulatory Authorities may have conducted on-site inspections (during the study or after its completion). If a Regulatory Authority notified the Investigator of an inspection or visited the site unannounced for purposes of conducting an inspection, the Investigator had to inform the study Sponsor and CRO immediately. The Investigator facilitate the conduct of the audits and inspections, giving access to all necessary facilities, data and documents.

Laboratory Accreditation

An accredited central laboratory was used for urinalysis, hematology, and blood chemistry analysis throughout the entire study. For study inclusion (Cycle 1), central laboratory hematological results were mandatory and were to satisfy the inclusion criterion #8. For Investigator's decision about patient's inclusion in Cycles 2 to 4, accredited local laboratory results were acceptable; nevertheless, central laboratory data were to be collected at each cycle.

Data Reporting and Management

Electronic CRFs (eCRFs) were used for recording patient's study data using a validated web-based Electronic Data Capture (EDC) system. It was the responsibility of the Investigator to ensure that the eCRFs were properly and filled in. The eCRFs had to be completed for all patients who were included in the study.

Each authorized site personnel were assigned a login and password to enter the EDC system via a secure network. Each login was to uniquely identify the user and appropriate permissions were set-up per the user role. The access to the system was granted once the user's training had been completed and documented.

Data Clarification Forms (DCFs) were used to validate/clarify data entered on an eCRF page. Some DCFs were generated automatically by the system when the user saved data that did not meet the criteria pre-defined for the data field. In addition, other DCFs were created manually in the eCRF and sent to the Investigator either by the study monitor (as result of SDV) or by Clinical Data Management.

Discrepancies raised were reviewed online to determine the corrective action needed. Changes were made directly by authorized site staff. The EDC system's audit trail was to keep track of any information entered, modified, and deleted. The audit trail was to include, as a minimum, what was entered/changed/modified, who made the action, and when the action was made. Any answered DCF was reviewed and closed by authorized users. The Investigator was to

electronically sign the eCRF to validate the content.

Patient's source documentation (i.e., hospital charts) were to be maintained at the clinic. Source data to be recorded directly onto the eCRFs were to be communicated in advance. In cases where source documents were not eCRFs, the information on the eCRFs had to match the source documents. Source data verification was regularly performed by the study monitor.

Paper patient diaries were used to collect episodes of retching and vomiting, rescue medication intake, daily nausea assessment and dexamethasone intake at home. Considering the patient population, the short re-call period and the fact that rescue medication intake and emetic episodes are objective data, the paper diary was considered as a reliable method of data collection and as the most suitable method for this patient population. At each visit, the Investigator was to review the filled-in paper diary and discuss with the patient any issues or missing/incomplete data, so that the patient was enabled to make all necessary corrections, if any, during the visit. The Investigator (or designee) was to review, sign, date, and collect the complete patient diaries after they were returned at Visit 4 and also to transfer all data from each paper diary to the respective eCRF. The paper diaries were to be kept at the trial site and considered as source documents.

The medical (hospital) files of trial patients were to be retained in accordance with national legislation (and in accordance with the maximum period permitted by the hospital or institution/private practice). If the Investigator wished to assign the study documentation to another party or to move to another location, the Sponsor was to be promptly notified. No study documentation could be destroyed without prior written approval from the Sponsor.

The Sponsor had to ensure that it was specified in the protocol or other written agreement that the Investigator(s)/institution(s) would permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s), providing direct access to source data/documents.

6.2.2. Study Results

Compliance with Good Clinical Practices

NEPA 15-18 was conducted in compliance with good clinical practices with the CFR regarding protection of human subjects, Institutional Review Boards, Independent Ethics Committees, and obligations of clinical investigators.

Reporting of suspected unexpected serious adverse reactions (SUSARs) to the relevant IRB/IEC, was in accordance with the European Union (EU) Clinical Trial Directive 2001/20/EC, the United States (US) Code of Federal Regulations 313.32, the International Council for Harmonisation (ICH) E6 Guidance on Good Clinical Practices (GCP), and ICH E2A Guidance on Clinical Safety Management and was also the responsibility of the Sponsor (or Sponsor's designee).

Financial Disclosure

A review of this study revealed no financial conflicts of interest. Please see financial disclosure

forms in Section 13.2. The applicant provided adequate documentation to show that there were no financial conflicts of interest between themselves and the 362 Investigators that participated in this study.

Patient Disposition

A total of 405 patients were randomized, and 404 (99.8%) received study treatment. The number of patients randomized into each treatment group, patient disposition, and the reasons for early discontinuation from the study are summarized in the tables below.

The 405 patients randomized were distributed between treatment groups as follows: 203 patients randomized to IV NEPA FDC and 202 patients to Oral NEPA FDC. As shown in the table below, 404 (99.8%) patients were treated (203 [100%] patients in the IV NEPA FDC group, and 201 [99.5%] patients in the Oral NEPA FDC group). One randomized patient (patient ID 8270417) in the Oral NEPA FDC group did not receive active study drug or reference HEC. The FAS and the safety populations were the same in this study.

Table 26 – Analysis Populations and Reasons for Exclusion NEPA 15-18

Patient Disposition	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=202) n (%)	Overall (N=405) n (%)
All randomized patients	203 (100.0)	202 (100.0)	405 (100.0)
FAS	203 (100.0)	201 (99.5)	404 (99.8)
Reason for exclusion from FAS			
No active study drug received and no HEC received	0	1 (0.5)	1 (0.2)
Safety population	203 (100.0)	201 (99.5)	404 (99.8)
Reason for exclusion from safety population			
No active study drug received	0	1 (0.5)	1 (0.2)

(Source - NEPA 15-18 Study Report Page 76) Disposition Across the Four Cycles

A total of 237 (58.5%) patients completed the four study cycles (120 [59.1%] patients in the IV NEPA FDC group, and 117 [57.9%] patients in the Oral NEPA FDC group).

Eighty-three (20.5%) patients (41 [20.2%] patients in the IV NEPA FDC group, and 42 [20.8%] patients in the Oral NEPA FDC group) completed a cycle (Cycle 1, 2, or 3) but did not continue on the subsequent study cycle.

Eighty-five (21.0%) patients (42 [20.7%] patients in the IV NEPA FDC group, and 43 [21.3%] patients in the Oral NEPA FDC group) discontinued from the study during a cycle, either before receiving study drug (45 patients) or after receiving study drug (40 patients).

Overall, 168 (41.5%) patients did not complete the study (either completed a cycle and did not continue on the subsequent one [83 (20.5%) patients] or discontinued from the study during a cycle [85 (21.0%) patients]). The most frequent ($\geq 5\%$ of patients overall) reasons for

discontinuation from the study were the following: overall study closure in 43 (10.6%) patients (24 [11.8%] patients in the IV NEPA FDC group, and 19 [9.4%] in the Oral NEPA FDC group), AE in 34 (8.4%) patients (16 [7.9%] patients in the IV NEPA FDC group, and 18 [8.9%] in the Oral NEPA FDC group), death in 25 (6.2%) patients (10 [4.9%] patients in the IV NEPA FDC group, and 15 [7.4%] in the Oral NEPA FDC group), and physician decision in 20 (4.9%) patients (8 [3.9%] patients in the IV NEPA FDC group, and 12 [5.9%] in the Oral NEPA FDC group). Other less frequent reasons for premature discontinuation were inclusion/exclusion criteria not met for a repeated cycle, withdrawal by subject, patient lost to follow-up, and other reasons (see table below for details).

Table 27 – Disposition NEPA 15-18

Patient Disposition	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=202) n (%)	Overall (N=405) n (%)
Randomized Patients	203 (100.0)	202 (100.0)	405 (100.0)
Treated patients	203 (100.0)	201 (99.5)	404 (99.8)
Completed the study	120 (59.1)	117 (57.9)	237 (58.5)
Completed a cycle, but not continuing in the study	41 (20.2)	42 (20.8)	83 (20.5)
Discontinued during a cycle ^a	42 (20.7)	43 (21.3)	85 (21.0)
Patients who entered cycle 1	203 (100.0)	202 (100.0)	405 (100.0)
Discontinued cycle 1 before study treatment	0	1 (0.5)	1 (0.2)
Treated cycle 1	203 (100.0)	201 (99.5)	404 (99.8)
Completed cycle 1	187 (92.1)	182 (90.1)	369 (91.1)
Completed cycle 1, not continuing	6 (3.0)	11 (5.4)	17 (4.2)
Discontinued cycle 1 after study treatment	10 (4.9)	8 (4.0)	18 (4.4)
Patients who entered cycle 2	187 (92.1)	182 (90.1)	369 (91.1)
Discontinued cycle 2 before study treatment	8 (3.9)	5 (2.5)	13 (3.2)
Treated cycle 2	179 (88.2)	177 (87.6)	356 (87.9)
Completed cycle 2	167 (82.3)	159 (78.7)	326 (80.5)
Completed cycle 2, not continuing	9 (4.4)	10 (5.0)	19 (4.7)
Discontinued cycle 2 after study treatment	3 (1.5)	8 (4.0)	11 (2.7)
Patients who entered cycle 3	167 (82.3)	159 (78.7)	326 (80.5)
Discontinued cycle 3 before study treatment	4 (2.0)	9 (4.5)	13 (3.2)
Treated cycle 3	163 (80.3)	150 (74.3)	313 (77.3)
Completed cycle 3	134 (66.0)	123 (60.9)	257 (63.5)
Completed cycle 3, not continuing	26 (12.8)	21 (10.4)	47 (11.6)
Discontinued cycle 3 after study treatment	3 (1.5)	6 (3.0)	9 (2.2)

Patient Disposition	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=202) n (%)	Overall (N=405) n (%)
Patients who entered cycle 4	134 (66.0)	123 (60.9)	257 (63.5)
Discontinued cycle 4 before study treatment	12 (5.9)	6 (3.0)	18 (4.4)
Treated cycle 4	122 (60.1)	117 (57.9)	239 (59.0)
Completed cycle 4	120 (59.1)	117 (57.9)	237 (58.5)
Discontinued cycle 4 after study treatment	2 (1.0)	0	2 (0.5)
Primary reason for premature study termination or for not continuing:	83 (40.9)	85 (42.1)	168 (41.5)
Overall study closure	24 (11.8)	19 (9.4)	43 (10.6)
Adverse event	16 (7.9)	18 (8.9)	34 (8.4)
Death ^b	10 (4.9)	15 (7.4)	25 (6.2)
Physician decision	8 (3.9)	12 (5.9)	20 (4.9)
Withdrawal by subject	8 (3.9)	7 (3.5)	15 (3.7)
I/E criteria not met for a repeated cycle	10 (4.9)	5 (2.5)	15 (3.7)
Other	5 (2.5)	6 (3.0)	11 (2.7)
Lost to follow-up	2 (1.0)	3 (1.5)	5 (1.2)

(Source: NEPA 15-18 Study Report page 72)

Protocol Violations/Deviations

Protocol deviations that were considered as having a major impact on efficacy at Cycle 1 are summarized for FAS in the table below. Overall, 27 (6.7%) patients in the FAS had protocol deviations with a major impact on efficacy at Cycle 1: 13 (6.4%) patients in the IV NEPA FDC group and 14 (7.0%) patients in the Oral NEPA FDC group. The most common (affecting 10 [37.0%] patients) protocol deviation referred to “use of medications with potential antiemetic effects or use of CYP3A4 strong or moderate inhibitors, use of CYP3A4 inducers or substrates during Cycle 1 in the interval 0-120 h after start of reference HEC.” All remaining protocol deviations with a major impact on efficacy at Cycle 1 were related to use of prohibited prior or concomitant medications, improper administration of study medication or dexamethasone, improper completion or collection of the diary, or inclusion criterion not met. Please see table below.

Table 28 – Protocol Deviations with a Major Impact on Efficacy at Cycle 1, NEPA 15-18

Patients with deviation	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Patients with deviation having a major impact on efficacy at Cycle 1*	13 (6.4)	14 (7.0)	27 (6.7)
Protocol deviation			
Use of medications with potential antiemetic effects or use of CYP3A4 strong or moderate inhibitors, CYP3A4 inducers or substrates during Cycle 1 in the interval 0-120 h after start of reference HEC	6 (46.2)	4 (28.6)	10 (37.0)
Any medication with known or potential antiemetic activity has been used within 24 h prior to the start of the reference HEC administration on Day 1.	2 (15.4)	3 (21.4)	5 (18.5)
The patient received within 1 week prior to Day 1 or is scheduled to receive any strong or moderate inhibitor of CYP3A4.	3 (23.1)	1 (7.1)	4 (14.8)
Systemic corticosteroid therapy has been used at any dose within 72 h prior to the start of the reference HEC administration on Day 1.	1 (7.7)	2 (14.3)	3 (11.1)
During Cycle 1, the capsule NEPA FDC is not taken 60 min prior to the start of the reference HEC infusion.	0	3 (21.4)	3 (11.1)
During Cycle 1, start time of IV NEPA FDC infusion is not 30 min prior to start of reference chemotherapy.	3 (23.1)	0	3 (11.1)
At least one inclusion criterion has not been replied as expected for Cycle 1 and the subject has been randomized.	0	1 (7.1)	1 (3.7)
During Cycle 1, administered dexamethasone dose is not 2 tablets in the morning.	1 (7.7)	0	1 (3.7)
During Cycle 1, fosnetupitant/palonosetron IV infusion duration is less than 25 min or more than 35 min.	1 (7.7)	0	1 (3.7)
Diary not retrieved during Cycle 1.	1 (7.7)	0	1 (3.7)
Diary not completed at all or both leading questions not completed for emetic episodes and for rescue medications intake during Cycle 1.	0	1 (7.1)	1 (3.7)
Diary not covering the 0-120 h Cycle 1.	1 (7.7)	0	1 (3.7)

(Source – NEPA 15-18 Study Report Page 74)

Demographic Characteristics

Demographics are summarized in the table below for the safety population. The safety population was comprised of 214 (53.0%) male patients and 190 (47.0%) female patients, equally distributed between treatment groups. In terms of race, the majority (99.3%) of patients were Caucasian (white).

As expected, demographic and other baseline characteristics were similar between the two treatment groups. The profiles were also consistent for the FAS and for FAS excluding patients with violations having a major impact on efficacy at Cycle 1. Please see table below.

Table 29 – Demographics NEPA 15-18

		IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Gender	Male	107 (52.7)	107 (53.2)	214 (53.0)
	Female	96 (47.3)	94 (46.8)	190 (47.0)
	Childbearing potential	15 (15.6)	22 (23.4)	37 (19.5)
Race	Asian	0	1 (0.5)	1 (0.2)
	Black Or African American	2 (1.0)	0	2 (0.5)
	White	201 (99.0)	200 (99.5)	401 (99.3)
Age (years)^a	Mean (SD)	60.0 (9.7)	58.9 (10.6)	59.5 (10.2)
	Median	61.0	60.0	61.0
	Min, Max	28, 81	25, 82	25, 82
	Weight (kg)	Mean (SD)	73.02 (15.85)	71.92 (14.45)
	Median	71.00	70.00	70.25
	Min, Max	37.0, 137.0	44.0, 123.0	37.0, 137.0
Height (cm)	Mean (SD)	166.9 (9.7)	167.4 (8.7)	167.2 (9.2)
	Median	167.0	168.0	167.0
	Min, Max	147, 193	147, 192	147, 193
	BMI (kg/m²)^b	Mean (SD)	26.20 (5.22)	25.66 (4.83)
	Median	25.80	25.10	25.40
	Min, Max	14.3, 44.2	16.6, 37.4	14.3, 44.2
		IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
BSA (m²)^c	Mean (SD)	1.831 (0.224)	1.821 (0.206)	1.826 (0.215)
	Median	1.810	1.810	1.810
	Min, Max	1.29, 2.65	1.37, 2.51	1.29, 2.65

(Source NEPA 15-18 Study Report Page 78)

Other Baseline Characteristics

Cancer history is summarized for the safety population in the table below. At study entry, primary cancer location was similar between treatment groups, with the most frequent primary cancer location being lung and respiratory tract (54.9%), followed by other location (18.8%), and ovarian (12.1%). The overall median time since diagnosis was 33 days.

The extent of cancer at study entry was categorized as either primary, metastatic, or locally recurrent, with no notable differences between the treatment groups in the proportions of patients in each category. The majority of patients had primary (47.0%) or metastatic (51.5%) disease. For metastatic cancer, the most commonly reported sites for metastases were lymph nodes (31.9%), lung (17.1%), other sites (10.9%), and liver (10.1%). A small proportion of patients (1.5%) had locally recurrent cancer. Please see table below.

Table 30 – Cancer History NEPA 15-18

	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Primary Cancer Location			
Gastric	12 (5.9)	12 (6.0)	24 (5.9)
Head and neck	11 (5.4)	11 (5.5)	22 (5.4)
Lung and respiratory tract	115 (56.7)	107 (53.2)	222 (54.9)
Ovarian	27 (13.3)	22 (10.9)	49 (12.1)
Bladder	4 (2.0)	7 (3.5)	11 (2.7)
Other	34 (16.7)	42 (20.9)	76 (18.8)
Extent			
Primary	94 (46.3)	96 (47.7)	190 (47.0)
Metastatic	107 (52.7)	101 (50.2)	208 (51.5)
Local recurrence	2 (1.0)	4 (2.0)	6 (1.5)
If metastatic, site(s) of metastasis			
Adrenal gland / Kidney	14 (6.9)	11 (5.5)	25 (6.2)
Bone	11 (5.4)	15 (7.5)	26 (6.4)
Liver	18 (8.9)	23 (11.4)	41 (10.1)
Lung	42 (20.7)	27 (13.4)	69 (17.1)
Lymph nodes	64 (31.5)	65 (32.3)	129 (31.9)
Other	27 (13.3)	17 (8.5)	44 (10.9)
Time since diagnosis (days)*			
Mean (SD)	91.7 (224.5)	102.3 (343.4)	97.0 (289.5)
Median	34.0	32.0	33.0
Q1, Q3	19, 56	18, 61	19, 57
Min, Max	6, 2204	2, 3287	2, 3287

(Source – NEPA 15-18 Study Report Page 81)

Chemotherapy

Reference Chemotherapy

Reference HEC administered to patients on Day 1 of each cycle is summarized for the FAS in the table below. Overall on Day 1 of Cycle 1, 387 (95.8%) patients received cisplatin (overall mean [SD] dose was 144.86 [22.98] mg). Fourteen (3.5%) patients received dacarbazine (overall mean [SD] dose was 1757.52 [391.67] mg) and 3 (0.74%) patients received cyclophosphamide (overall mean [SD] dose was 3003.33 [332.65] mg). In general, the mean (SD) doses of cisplatin, dacarbazine, and cyclophosphamide received on Day 1 of Cycles 2, 3, and 4 were similar to those on Day 1 of Cycle 1 for both overall and for each treatment group. No patient was treated with cyclophosphamide in the IV NEPA FDC group on Day 1 of Cycle 4 compared with 1 patient in the Oral NEPA FDC group, and no patient was treated with any of the remaining pre-defined reference HEC (carmustine or mechlorethamine).

Table 31 – Reference Chemotherapy NEPA 15-18

Reference Chemotherapy		IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Patients in Cycle 1		203	201	404
Cisplatin, mg	n	196 (96.6)	191 (95.0)	387 (95.8)
	Mean (SD)	145.49 (23.04)	144.22 (22.95)	144.86 (22.98)
Cyclophosphamide, mg	n	1 (0.5)	2 (1.0)	3 (0.7)
	Mean (SD)	2625.00 (NC)	3192.50 (81.31)	3003.33 (332.65)
Dacarbazine, mg	n	6 (3.0)	8 (4.0)	14 (3.5)
	Mean (SD)	1978.38 (207.62)	1591.87 (425.37)	1757.52 (391.67)
Patients in Cycle 2		179	176*	355
Cisplatin, mg	n	172 (96.1)	167 (94.9)	339 (95.5)
	Mean (SD)	145.53 (22.37)	144.09 (22.91)	144.82 (22.62)
Cyclophosphamide, mg	n	1 (0.6)	2 (1.1)	3 (0.8)
	Mean (SD)	2610.00 (NC)	3192.50 (81.31)	2998.33 (341.18)
Dacarbazine, mg	n	6 (3.4)	7 (4.0)	13 (3.7)
	Mean (SD)	1977.40 (208.21)	1728.92 (180.24)	1843.60 (225.67)
Patients in Cycle 3		163	150	313
Cisplatin, mg	n	156 (95.7)	143 (95.3)	299 (95.5)
	Mean (SD)	144.87 (23.02)	143.96 (23.05)	144.44 (23.00)
Cyclophosphamide, mg	n	1 (0.6)	1 (0.7)	2 (0.6)
	Mean (SD)	2610.00 (NC)	3250.00 (NC)	2930.00 (452.54)
Dacarbazine, mg	n	6 (3.7)	6 (4.0)	12 (3.8)
	Mean (SD)	1912.95 (301.16)	1705.91 (274.36)	1809.43 (295.18)
Patients in Cycle 4		122	117	239
Cisplatin, mg	n	117 (95.9)	111 (94.9)	228 (95.4)
	Mean (SD)	146.70 (23.69)	142.51 (22.13)	144.66 (22.99)
Cyclophosphamide, mg	n	0	1 (0.9)	1 (0.4)
	Mean (SD)	-	3250.00 (NC)	3250.00 (NC)
Dacarbazine, mg	n	5 (4.1)	5 (4.3)	10 (4.2)
	Mean (SD)	1734.36 (250.52)	1659.50 (279.17)	1696.92 (253.16)

(Source - NEPA 15-18 Study Report Page 84)

Concomitant Chemotherapy

Similar proportions of patients in each treatment group received chemotherapy concomitantly with their reference HEC up to Day 5 (inclusive) during each cycle (overall, 92.6% of patients during Cycle 1, 89.6% during Cycle 2, 88.2% during Cycle 3 and 89.5% during Cycle 4), mostly on Day 1 only (overall, 67.1% of patients during Cycle 1, 62.5% during Cycle 2, 62.3% during Cycle 3, and 65.3% during Cycle 4), with between 24.3% and 27.0% of patients overall receiving it on Days 1-5. Overall, between 22.6% and 30.4% of patients overall received chemotherapy after Day 5.

Overall, the most commonly administered concomitant chemotherapy agents up to Day 5 (inclusive) in each cycle were etoposide (between 24.9% and 25.7% of patients), cyclophosphamide (between 15.1% and 19.7%), fluorouracil (between 11.1% and 11.8%), gemcitabine (between 9.2% and 10.9%), vinorelbine (between 7.0% and 8.4%), vinorelbine tartrate (between 5.9% and 7.9%), doxorubicin (between 5.0% and 7.1%), and gemcitabine hydrochloride (between 4.6% and 5.7%) See table below.

Overall, the most commonly administered concomitant chemotherapy agents after Day 5 in each

cycle were gemcitabine (between 8.2% and 10.1% of patients) and gemcitabine hydrochloride (between 3.8% and 5.2%); and vinorelbine (between 5.8% and 7.0%) and vinorelbine tartrate (between 3.3% and 6.4%) See table below.

Table 32 – Concomitant Chemotherapy NEPA 15-18

Concomitant Chemotherapy	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Patients in Cycle 1	203	201	404
Any concomitant chemotherapy up to Day 5	189 (93.1)	185 (92.0)	374 (92.6)
No concomitant chemotherapy	14 (6.9)	16 (8.0)	30 (7.4)
Concomitant chemotherapy on Day 1 only	138 (68.0)	133 (66.2)	271 (67.1)
Concomitant chemotherapy on Days 1-5	51 (25.1)	52 (25.9)	103 (25.5)
Any chemotherapy after Cycle 1 Day 5	62 (30.5)	61 (30.3)	123 (30.4)
Patients in Cycle 2	179	176*	355
Any concomitant chemotherapy up to Day 5	161 (89.9)	157 (89.2)	318 (89.6)
No concomitant chemotherapy	18 (10.1)	19 (10.8)	37 (10.4)
Concomitant chemotherapy on Day 1 only	114 (63.7)	108 (61.4)	222 (62.5)
Concomitant chemotherapy on Days 1-5	47 (26.3)	49 (27.8)	96 (27.0)
Any chemotherapy after Cycle 2 Day 5	53 (29.6)	44 (25.0)	97 (27.3)
Patients in Cycle 3	163	150	313
Any concomitant chemotherapy up to Day 5	142 (87.1)	134 (89.3)	276 (88.2)
No concomitant chemotherapy	21 (12.9)	16 (10.7)	37 (11.8)
Concomitant chemotherapy on Day 1 only	103 (63.2)	92 (61.3)	195 (62.3)
Concomitant chemotherapy on Days 1-5	39 (23.9)	42 (28.0)	81 (25.9)
Any chemotherapy after Cycle 3 Day 5	45 (27.6)	34 (22.7)	79 (25.2)
Patients in Cycle 4	122	117	239
Any concomitant chemotherapy up to Day 5	109 (89.3)	105 (89.7)	214 (89.5)
No concomitant chemotherapy	13 (10.7)	12 (10.3)	25 (10.5)
Concomitant chemotherapy on Day 1 only	80 (65.6)	76 (65.0)	156 (65.3)
Concomitant chemotherapy on Days 1-5	29 (23.8)	29 (24.8)	58 (24.3)
Any chemotherapy after Cycle 4 Day 5	33 (27.0)	21 (17.9)	54 (22.6)

(Source - NEPA 15-18 Study Report Pages 85-86)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance is summarized in the table below. A patient was considered to be compliant with therapy if he/she took all study drugs (including dexamethasone) provided in the clinical study medication kit. Overall, the majority (95.8%) of patients were compliant with their study treatment throughout the study (96.1% in the IV NEPA FDC group and 95.5% in the Oral NEPA FDC group). The cases of non-compliance were exclusively due to missing doses of dexamethasone on any of the dosing days (Days 1-4), during one or more cycles.

Table 33– Treatment Compliance NEPA 15-18

	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Number of compliant patients throughout the study	195 (96.1)	192 (95.5)	387 (95.8)
Number of evaluable patients in cycle 1	203	201	404
Number of compliant patients in cycle 1	198 (97.5)	200 (99.5)	398 (98.5)
Number of evaluable patients in cycle 2	179	176	355
Number of compliant patients in cycle 2	174 (97.2)	172 (97.7)	346 (97.5)
Number of evaluable patients in cycle 3	163	150	313
Number of compliant patients in cycle 3	160 (98.2)	146 (97.3)	306 (97.8)
Number of evaluable patients in cycle 4	122	117	239
Number of compliant patients in cycle 4	121 (99.2)	116 (99.1)	237 (99.2)

(Source – NEPA 15-18 Study Report Page 313)

Prior Medications

Use of prior medications was recorded for 47.8% of patients in the study. The most commonly reported classes of medications ($\geq 5\%$ of patients overall; ATC level 4 headings) used prior to study entry were heparin group (9.7%), proton pump inhibitors (8.7%), selective beta blocking agents (6.4%), and platelet aggregation inhibitors excluding heparin (5.4%).

Concomitant Medications

Use of concomitant medications was recorded for 97.0% of patients in the study. As expected due to the specific patient population and administration of cytotoxic cancer chemotherapy, solutions producing osmotic diuresis such as mannitol (45.3%); solutions affecting electrolyte balance (39.6%) and electrolyte solutions (20.5%); and solutions for parenteral nutrition (21.0%) were very commonly reported classes of medications (ATC level 4 headings) during the present study.

In addition, other commonly reported classes of medications ($>10\%$ of patients overall; ATC level 4 headings) used concomitantly during the study were plain sulfonamides (45.3%, mainly furosemide), proton pump inhibitors (21.8%), heparin group (21.5%), H₂-receptor antagonists (20.8%), selective beta blocking agents (20.5%), plain ACE inhibitors (18.8%), colony stimulating factors (16.8%), propulsives (15.1%), anilides (14.9%, mainly paracetamol), and glucocorticoids (14.6%).

Rescue Medication Use

Please see table below for a summary of the patients who took rescue medication.

Table 34 – Anti-Emetic Rescue Medications NEPA 15-18

WHO ATC terms WHO Preferred Term	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Number of evaluable patients in cycle 1	203 (100.0)	201 (100.0)	404 (100.0)
Number of patients with at least one rescue medication intake in Cycle 1	34 (16.7)	21 (10.4)	55 (13.6)
Glucocorticoids	1 (0.5)	0 (0.0)	1 (0.2)
Dexamethasone	1 (0.5)	0 (0.0)	1 (0.2)
Other Antiemetics	2 (1.0)	0 (0.0)	2 (0.5)
Prochlorperazine	1 (0.5)	0 (0.0)	1 (0.2)
Prochlorperazine Maleate	1 (0.5)	0 (0.0)	1 (0.2)
Propulsives	33 (16.3)	21 (10.4)	54 (13.4)
Metoclopramide	19 (9.4)	17 (8.5)	36 (8.9)
Metoclopramide Hydrochloride	14 (6.9)	4 (2.0)	18 (4.5)
Serotonin (5ht3) Antagonists	1 (0.5)	0 (0.0)	1 (0.2)
Ondansetron	1 (0.5)	0 (0.0)	1 (0.2)

WHO ATC terms WHO Preferred Term	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Number of evaluable patients in cycle 2	179 (88.2)	176 (87.6)	355 (87.9)
Number of patients with at least one rescue medication intake in Cycle 2	25 (14.0)	21 (11.9)	46 (13.0)
Other Antiemetics	2 (1.1)	0 (0.0)	2 (0.6)
Prochlorperazine Maleate	1 (0.6)	0 (0.0)	1 (0.3)
Promethazine	1 (0.6)	0 (0.0)	1 (0.3)
Propulsives	23 (12.8)	21 (11.9)	44 (12.4)
Metoclopramide	16 (8.9)	12 (6.8)	28 (7.9)
Metoclopramide Hydrochloride	7 (3.9)	9 (5.1)	16 (4.5)

WHO ATC terms WHO Preferred Term	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Number of evaluable patients in cycle 3	163 (80.3)	150 (74.6)	313 (77.5)
Number of patients with at least one rescue medication intake in Cycle 3	16 (9.8)	11 (7.3)	27 (8.6)
Other Antiemetics	1 (0.6)	0 (0.0)	1 (0.3)
Prochlorperazine Maleate	1 (0.6)	0 (0.0)	1 (0.3)
Other Drugs For Peptic Ulcer And Gastro-Oesophageal Reflux Disease (Gord)	1 (0.6)	0 (0.0)	1 (0.3)
Gaviscon	1 (0.6)	0 (0.0)	1 (0.3)
Propulsives	16 (9.8)	11 (7.3)	27 (8.6)
Metoclopramide	11 (6.7)	6 (4.0)	17 (5.4)
Metoclopramide Hydrochloride	5 (3.1)	5 (3.3)	10 (3.2)

WHO ATC terms WHO Preferred Term	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Number of evaluable patients in cycle 4	122 (60.1)	117 (58.2)	239 (59.2)
Number of patients with at least one rescue medication intake in Cycle 4	13 (10.7)	3 (2.6)	16 (6.7)
Propulsives	13 (10.7)	3 (2.6)	16 (6.7)
Metoclopramide	10 (8.2)	1 (0.9)	11 (4.6)
Metoclopramide Hydrochloride	3 (2.5)	2 (1.7)	5 (2.1)

(NEPA 15-18 Study Report Pages 309-312)

Efficacy Results

Complete Response

Complete Response (CR) results in each cycle during the Acute, Delayed, and Overall phases are summarized in the table below. The treatment differences between arms in the acute, delayed, and overall phases were small (see table below).

However, the observed difference in CR in the delayed phase was noted to be higher in the oral NEPA FDC arm compared to the IV NEPA FDC arm occurring in all 4 cycles. This will be further discussed in the Additional Analyses Conducted on the Individual Trial section.

Table 35 – Complete Response in Each Cycle During the Acute, Delayed, and Overall Phases (FAS) - NEPA 15-18

Cycle Phase	IV NEPA FDC (N=203) n (%) [95%CI] ^a	Oral NEPA FDC (N=201) n (%) [95%CI] ^a	Treatment Difference % [95%CI]	
			Without strata adjustment ^b	With strata adjustment ^c
Patients with a Complete Response				
Number of evaluable patients in Cycle 1	203	201		
Acute Phase (0-24 h)	188 (92.6) [88.2;95.5]	182 (90.5) [85.7;93.9]	2.1 [-3.5;7.7]	2.3 [-2.7;7.2]
Delayed Phase (>24-120 h)	159 (78.3) [72.2;83.4]	176 (87.6) [82.3;91.4]	-9.2 [-16.5;-1.9]	-9.0 [-15.8;-2.2]
Overall (0-120 h)	156 (76.8) [70.6;82.1]	169 (84.1) [78.4;88.5]	-7.2 [-14.9;0.5]	-7.1 [-14.2;-0.1]
Number of evaluable patients in Cycle 2	179	176		
Acute Phase (0-24 h)	161 (89.9) [84.7;93.5]	159 (90.3) [85.1;93.9]	-0.4 [-6.8;6.0]	0.4 [-5.4;6.3]
Delayed Phase (>24-120 h)	147 (82.1) [75.9;87.0]	157 (89.2) [83.8;93.0]	-7.1 [-14.4;0.3]	-6.4 [-13.1;0.4]
Overall (0-120 h)	143 (79.9) [73.4;85.1]	151 (85.8) [79.9;90.2]	-5.9 [-13.7;2.0]	-5.3 [-12.7;2.0]
Number of evaluable patients in Cycle 3	163	150		
Acute Phase (0-24 h)	151 (92.6) [87.6;95.7]	144 (96.0) [91.5;98.2]	-3.4 [-8.9;2.1]	-2.4 [-7.3;2.4]
Delayed Phase (>24-120 h)	140 (85.9) [79.7;90.4]	135 (90.0) [84.2;93.8]	-4.1 [-11.4;3.3]	-2.2 [-8.5;4.0]
Overall (0-120 h)	137 (84.0) [77.7;88.9]	133 (88.7) [82.6;92.8]	-4.6 [-12.2;3.1]	-2.5 [-9.1;4.2]
Number of evaluable patients in Cycle 4	122	117		
Acute Phase (0-24 h)	110 (90.2) [83.6;94.3]	116 (99.1) [95.3;99.8]	-9.0 [-15.6;-3.4]	-7.0 [-11.9;-2.2]
Delayed Phase (>24-120 h)	105 (86.1) [78.8;91.1]	115 (98.3) [94.0;99.5]	-12.2 [-19.6;-5.6]	-9.6 [-15.4;-3.8]
Overall (0-120 h)	102 (83.6) [76.0;89.1]	114 (97.4) [92.7;99.1]	-13.8 [-21.6;-6.6]	-11.1 [-17.6;-4.6]

(Source - NEPA 15-18 Study Report Page 88)

Other Efficacy Results

Other exploratory efficacy results (absence of emetic episodes, absence of rescue medication, absence of significant nausea) are provided below for reference. These data did not contribute to the overall efficacy analysis.

Absence of Emetic Episodes

Absence of emetic episodes in each cycle during the Acute, Delayed, and Overall phases are summarized in the table below. The treatment differences between arms in the acute, delayed, and overall phases were small (see table below).

Table 36 – Absence of Emetic Episodes in Each Cycle During the Acute, Delayed, and Overall Phases in FAS - NEPA 15-18

Cycle Phase	IV NEPA FDC (N=203) n (%) [95%CI] ^a	Oral NEPA FDC (N=201) n (%) [95%CI] ^a	Treatment Difference % [95%CI]	
			Without strata adjustment ^b	With strata adjustment ^c
Patients with absence of emetic episodes				
Number of evaluable patients in Cycle 1	203	201		
Acute Phase (0-24 h)	193 (95.1) [91.2;97.3]	187 (93.0) [88.6;95.8]	2.0 [-2.7;7.0]	2.4 [-1.8;6.5]
Delayed Phase (>24-120 h)	173 (85.2) [79.7;89.4]	184 (91.5) [86.9;94.7]	-6.3 [-12.7;0.0]	-6.2 [-12.0;-0.4]
Overall (0-120 h)	171 (84.2) [78.6;88.6]	178 (88.6) [83.4;92.3]	-4.3 [-11.1;2.4]	-4.3 [-10.4;1.8]
Number of evaluable patients in Cycle 2	179	176		
Acute Phase (0-24 h)	164 (91.6) [86.6;94.9]	165 (93.8) [89.2;96.5]	-2.1 [-7.8;3.5]	-1.9 [-7.0;3.2]
Delayed Phase (>24-120 h)	156 (87.2) [81.5;91.3]	167 (94.9) [90.6;97.3]	-7.7 [-13.9;-1.8]	-7.6 [-13.2;-2.0]
Overall (0-120 h)	153 (85.5) [79.6;89.9]	164 (93.2) [88.5;96.1]	-7.7 [-14.3;-1.2]	-7.7 [-13.8;-1.7]
Number of evaluable patients in Cycle 3	163	150		
Acute Phase (0-24 h)	154 (94.5) [89.8;97.1]	145 (96.7) [92.4;98.6]	-2.2 [-7.2;2.8]	-1.4 [-5.7;3.0]
Delayed Phase (>24-120 h)	150 (92.0) [86.8;95.3]	140 (93.3) [88.2;96.3]	-1.3 [-7.3;4.8]	-0.3 [-5.4;4.8]
Overall (0-120 h)	147 (90.2) [84.7;93.9]	139 (92.7) [87.3;95.9]	-2.5 [-8.9;4.0]	-1.2 [-6.7;4.4]
Cycle Phase	IV NEPA FDC (N=203) n (%) [95%CI]^a	Oral NEPA FDC (N=201) n (%) [95%CI]^a	Treatment Difference % [95%CI]	
			Without strata adjustment^b	With strata adjustment^c
Number of evaluable patients in Cycle 4	122	117		
Acute Phase (0-24 h)	113 (92.6) [86.6;96.1]	117 (100) [96.8; 100]	-7.4 [-13.4;-2.7]	-6.4 [-10.6;-2.3]
Delayed Phase (>24-120 h)	110 (90.2) [83.6;94.3]	116 (99.1) [95.3;99.8]	-9.0 [-15.6;-3.4]	-7.5 [-12.7;-2.4]
Overall (0-120 h)	108 (88.5) [81.7;93.0]	116 (99.1) [95.3;99.8]	-10.6 [-17.5;-4.7]	-9.2 [-14.7;-3.7]

(Source – NEPA 15-18 Study Report Page 90)

Absence of Rescue Medication

Absence of rescue medication in each cycle during the acute, delayed, and overall phases are summarized in the table below. The treatment differences between arms in the acute, delayed, and overall phases were small (see table below).

Table 37 – Absence of Rescue Medication in Each Cycle During the Acute, Delayed, and Overall Phases for FAS - NEPA 15-18

Cycle Phase	IV NEPA FDC (N=203) n (%) [95%CI] ^a	Oral NEPA FDC (N=201) n (%) [95%CI] ^a	Treatment Difference % [95%CI]	
			Without strata adjustment ^b	With strata adjustment ^c
Patients with absence of rescue medication intake				
Number of evaluable patients in Cycle 1	203	201		
Acute Phase (0-24 h)	195 (96.1) [92.4;98.0]	187 (93.0) [88.6;95.8]	3.0 [-1.6;7.8]	3.3 [-0.6;7.3]
Delayed Phase (>24-120 h)	172 (84.7) [79.1;89.0]	184 (91.5) [86.9;94.7]	-6.8 [-13.2;-0.5]	-6.9 [-12.9;-1.0]
Overall (0-120 h)	168 (82.8) [77.0;87.3]	179 (89.1) [84.0;92.7]	-6.3 [-13.1;0.5]	-6.0 [-12.3;0.2]
Number of evaluable patients in Cycle 2	179	176		
Acute Phase (0-24 h)	169 (94.4) [90.0;96.9]	161 (91.5) [86.4;94.8]	2.9 [-2.6;8.6]	3.9 [-1.1;8.9]
Delayed Phase (>24-120 h)	156 (87.2) [81.5;91.3]	158 (89.8) [84.4;93.4]	-2.6 [-9.4;4.1]	-2.2 [-8.4;4.0]
Overall (0-120 h)	153 (85.5) [79.6;89.9]	153 (86.9) [81.2;91.1]	-1.5 [-8.7;5.8]	-0.6 [-7.4;6.1]
Number of evaluable patients in Cycle 3	163	150		
Acute Phase (0-24 h)	156 (95.7) [91.4;97.9]	145 (96.7) [92.4;98.6]	-1.0 [-5.7;3.8]	-0.6 [-4.7;3.5]
Cycle Phase	IV NEPA FDC (N=203) n (%) [95%CI]^a	Oral NEPA FDC (N=201) n (%) [95%CI]^a	Treatment Difference % [95%CI]	
			Without strata adjustment^b	With strata adjustment^c
Delayed Phase (>24-120 h)	148 (90.8) [85.4;94.3]	136 (90.7) [84.9;94.4]	0.1 [-6.4;6.9]	1.3 [-4.4;6.9]
Overall (0-120 h)	146 (89.6) [83.9;93.4]	135 (90.0) [84.2;93.8]	-0.4 [-7.3;6.5]	1.0 [-4.8;6.9]
Number of evaluable patients in Cycle 4	122	117		
Acute Phase (0-24 h)	114 (93.4) [87.6;96.6]	116 (99.1) [95.3;99.8]	-5.7 [-11.6;-0.7]	-4.5 [-8.6;-0.4]
Delayed Phase (>24-120 h)	110 (90.2) [83.6;94.3]	115 (98.3) [94.0;99.5]	-8.1 [-14.8;-2.2]	-6.0 [-10.8;-1.1]
Overall (0-120 h)	108 (88.5) [81.7;93.0]	114 (97.4) [92.7;99.1]	-8.9 [-16.0;-2.4]	-6.7 [-12.3;-1.1]

(Source – Study Report NEPA 15-18 page 92)

Absence of Significant Nausea

Absence of significant nausea in each cycle during the acute, delayed, and overall phases are summarized in the table below. The treatment differences between arms in the acute, delayed, and overall phases were small (see table below).

Table 38 – Absence of Significant Nausea in Each Cycle During the Acute, Delayed, and Overall Phases for FAS - NEPA 15-18

Cycle Phase	IV NEPA FDC (N=203) n (%) [95%CI] ^a	Oral NEPA FDC (N=201) n (%) [95%CI] ^a	Treatment Difference % [95%CI]	
			Without strata adjustment ^b	With strata adjustment ^c
Patients with absence of significant nausea				
Number of evaluable patients in Cycle 1	203	201		
Acute Phase (0-24 h)	183 (90.1) [85.3;93.5]	187 (93.0) [88.6;95.8]	-2.9 [-8.5;2.7]	-2.6 [-7.6;2.3]
Delayed Phase (>24-120 h)	165 (81.3) [75.4;86.0]	179 (89.1) [84.0;92.7]	-7.8 [-14.7;-0.8]	-7.3 [-13.7;-0.8]
Overall (0-120 h)	161 (79.3) [73.2;84.3]	174 (86.6) [81.2;90.6]	-7.3 [-14.6;0.1]	-7.0 [-13.8;-0.2]
Number of evaluable patients in Cycle 2	179	176		
Acute Phase (0-24 h)	163 (91.1) [86.0;94.4]	165 (93.8) [89.2;96.5]	-2.7 [-8.5;3.0]	-1.8 [-7.0;3.4]
Delayed Phase (>24-120 h)	145 (81.0) [74.6;86.1]	157 (89.2) [83.8;93.0]	-8.2 [-15.6;-0.8]	-8.4 [-15.1;-1.7]
Overall (0-120 h)	143 (79.9) [73.4;85.1]	153 (86.9) [81.2;91.1]	-7.0 [-14.8;0.7]	-7.3 [-14.4;-0.3]
Number of evaluable patients in Cycle 3	163	150		
Acute Phase (0-24 h)	151 (92.6) [87.6;95.7]	143 (95.3) [90.7;97.7]	-2.7 [-8.3;2.9]	-1.5 [-6.3;3.2]
Delayed Phase (>24-120 h)	141 (86.5) [80.4;90.9]	135 (90.0) [84.2;93.8]	-3.5 [-10.7;3.8]	-2.2 [-8.5;4.2]
Overall (0-120 h)	137 (84.0) [77.7;88.9]	135 (90.0) [84.2;93.8]	-6.0 [-13.4;1.6]	-4.3 [-10.8;2.3]
Number of evaluable patients in Cycle 4	122	117		
Acute Phase (0-24 h)	110 (90.2) [83.6;94.3]	111 (94.9) [89.3;97.6]	-4.7 [-11.8;2.3]	-3.0 [-9.2;3.3]
Delayed Phase (>24-120 h)	107 (87.7) [80.7;92.4]	111 (94.9) [89.3;97.6]	-7.2 [-14.7;0.2]	-5.2 [-11.5;1.1]
Overall (0-120 h)	103 (84.4) [77.0;89.8]	110 (94.0) [88.2;97.1]	-9.6 [-17.7;-1.6]	-7.0 [-14.0;0.1]

(Source – Study Report NEPA 15-18 page 95)

Subgroup Analyses

Sex

The proportion of female patients with CR was numerically lower compared with male patients in each phase and in each cycle for both treatment group (IV NEPA FDC and Oral NEPA FDC). See the tables below.

Table 39 - Subgroup analysis: Complete Response in each phase by Cycle – Males (FAS)

Cycle	Phase	IV NEPA FDC (N=203) n (%) [95%CI]	Oral NEPA FDC (N=201) n (%) [95%CI]	Treatment Difference % [95%CI]	
				Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	107	107		
	Acute Phase (0-24 hours)	106 (99.1) [94.9;99.8]	103 (96.3) [90.8;98.5]	2.8 [-1.9; 8.3]	2.8 [-1.1; 6.7]
	Delayed Phase (>24-120 hours)	91 (85.0) [77.1;90.6]	99 (92.5) [85.9;96.2]	-7.5 [-16.2; 1.1]	-7.5 [-15.5; 0.5]
	Overall (0-120 hours)	90 (84.1) [76.0;89.8]	98 (91.6) [84.8;95.5]	-7.5 [-16.5; 1.4]	-7.5 [-15.8; 0.8]
Cycle 2	Number of evaluable patients in cycle	92	96		
	Acute Phase (0-24 hours)	88 (95.7) [89.3;98.3]	91 (94.8) [88.4;97.8]	0.9 [-6.1; 7.8]	0.7 [-5.2; 6.7]
	Delayed Phase (>24-120 hours)	79 (85.9) [77.3;91.6]	89 (92.7) [85.7;96.4]	-6.8 [-16.2; 2.2]	-6.3 [-14.4; 1.8]
	Overall (0-120 hours)	77 (83.7) [74.8;89.9]	87 (90.6) [83.1;95.0]	-6.9 [-16.8; 2.8]	-6.4 [-15.3; 2.6]
Cycle 3	Number of evaluable patients in cycle	80	80		
	Acute Phase (0-24 hours)	79 (98.8) [93.3;99.8]	78 (97.5) [91.3;99.3]	1.3 [-4.5; 7.5]	1.4 [-2.9; 5.7]
	Delayed Phase (>24-120 hours)	74 (92.5) [84.6;96.5]	74 (92.5) [84.6;96.5]	0.0 [-8.9; 8.9]	1.4 [-5.6; 8.3]
	Overall (0-120 hours)	73 (91.3) [83.0;95.7]	74 (92.5) [84.6;96.5]	-1.3 [-10.4; 7.8]	0.1 [-7.1; 7.4]
Cycle 4	Number of evaluable patients in cycle	57	62		
	Acute Phase (0-24 hours)	53 (93.0) [83.3;97.2]	62 (100) [94.2; 100]	-7.0 [-16.7; 0.2]	-6.5 [-12.4; -0.6]
	Delayed Phase (>24-120 hours)	51 (89.5) [78.9;95.1]	62 (100) [94.2; 100]	-10.5 [-21.1; -2.4]	-8.5 [-15.3; -1.6]
	Overall (0-120 hours)	50 (87.7) [76.8;93.9]	62 (100) [94.2; 100]	-12.3 [-23.2; -3.8]	-10.0 [-17.2; -2.8]

Table above is taken from Page 293 of the NEPA 15-18 CSR

Table 40 - Subgroup analysis: Complete Response in each phase by Cycle – Females (FAS)

Cycle	Phase	IV NEPA FDC (N=203) n (%) [95%CI]	Oral NEPA FDC (N=201) n (%) [95%CI]	Treatment Difference % [95%CI]	
				Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	96	94		
	Acute Phase (0-24 hours)	82 (85.4) [77.0;91.1]	79 (84.0) [75.3;90.1]	1.4 [-9.0; 11.8]	1.7 [-8.0; 11.4]
	Delayed Phase (>24-120 hours)	68 (70.8) [61.1;79.0]	77 (81.9) [72.9;88.4]	-11.1 [-22.8; 1.0]	-10.7 [-22.1; 0.6]
	Overall (0-120 hours)	66 (68.8) [58.9;77.1]	71 (75.5) [66.0;82.1]	-6.8 [-19.2; 6.0]	-6.7 [-18.5; 5.0]
Cycle 2	Number of evaluable patients in cycle	87	80		
	Acute Phase (0-24 hours)	73 (83.9) [74.8;90.2]	68 (85.0) [75.6;91.2]	-1.1 [-12.1; 10.2]	0.1 [-10.5; 10.7]
	Delayed Phase (>24-120 hours)	68 (78.2) [68.4;85.5]	68 (85.0) [75.6;91.2]	-6.8 [-18.4; 5.1]	-6.4 [-17.5; 4.6]
	Overall (0-120 hours)	66 (75.9) [65.9;83.6]	64 (80.0) [70.0;87.3]	-4.1 [-16.3; 8.6]	-4.1 [-16.1; 7.8]
Cycle 3	Number of evaluable patients in cycle	83	70		
	Acute Phase (0-24 hours)	72 (86.7) [77.8;92.4]	66 (94.3) [86.2;97.8]	-7.5 [-17.1; 2.3]	-6.6 [-15.4; 2.3]
	Delayed Phase (>24-120 hours)	66 (79.5) [69.6;86.8]	61 (87.1) [77.3;92.1]	-7.6 [-19.2; 4.6]	-6.1 [-16.7; 4.4]
	Overall (0-120 hours)	64 (77.1) [67.0;84.8]	59 (84.3) [74.0;91.0]	-7.2 [-19.3; 5.7]	-5.2 [-16.5; 6.0]
Cycle 4	Number of evaluable patients in cycle	65	55		
	Acute Phase (0-24 hours)	57 (87.7) [77.5;93.6]	54 (98.2) [90.4;99.7]	-10.5 [-20.7; -0.7]	-7.6 [-15.4; 0.2]
	Delayed Phase (>24-120 hours)	54 (83.1) [72.2;90.3]	53 (96.4) [87.7;99.0]	-13.3 [-24.5; -2.0]	-10.7 [-20.1; -1.3]
	Overall (0-120 hours)	52 (80.0) [68.7;87.9]	52 (94.5) [85.1;98.1]	-14.5 [-26.4; -2.3]	-12.2 [-22.9; -1.4]

Table above is taken from Page 294 of the NEPA 15-18 CSR

Country

The results for the countries with the largest enrollment, Ukraine (162 patients), Poland (112 patients), and Serbia (55 patients) are summarized below. There was a numerically higher treatment difference for CR (CR in IV group minus CR in PO group) for the highest enrolling country (Ukraine) in Cycle 1 particularly in the delayed phase compared to the second and third highest enrolling country (Poland and Serbia). The Ukraine treatment difference for CR in the delayed phase appeared to drive the overall treatment difference for CR in the delayed phase. No clear conclusion can be drawn from this observation.

Table 41 – Ukraine

Cycle	Phase	IV NEPA FDC (N=203) n (%) [95%CI]	Oral NEPA FDC (N=201) n (%) [95%CI]	Treatment Difference # [95%CI]	
				Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	81	81		
	Acute Phase (0-24 hours)	73 (90.1) [81.7;94.9]	75 (92.6) [84.8;96.6]	-2.5 [-11.8; 6.7]	-2.5 [-10.8; 5.9]
	Delayed Phase (>24-120 hours)	59 (72.8) [62.3;81.3]	73 (90.1) [81.7;94.9]	-17.3 [-28.9; -5.3]	-17.3 [-28.8; -5.8]
	Overall (0-120 hours)	57 (70.4) [59.7;79.2]	71 (87.7) [78.7;93.2]	-17.3 [-29.3; -4.7]	-17.3 [-29.3; -5.3]
Cycle 2	Number of evaluable patients in cycle	72	74		
	Acute Phase (0-24 hours)	66 (91.7) [83.0;96.1]	67 (90.5) [81.7;95.2]	1.1 [-8.8; 11.0]	1.1 [-7.9; 10.2]
	Delayed Phase (>24-120 hours)	60 (83.3) [73.1;90.2]	68 (91.9) [83.4;96.2]	-8.6 [-19.7; 2.3]	-8.5 [-19.1; 2.0]
	Overall (0-120 hours)	58 (80.6) [70.0;88.0]	64 (86.5) [76.9;92.5]	-5.9 [-18.1; 6.3]	-5.9 [-17.8; 6.0]
Cycle 3	Number of evaluable patients in cycle	66	67		
	Acute Phase (0-24 hours)	59 (89.4) [79.7;94.8]	65 (97.0) [89.8;99.2]	-7.6 [-17.6; 1.4]	-7.4 [-15.5; 0.8]
	Delayed Phase (>24-120 hours)	57 (86.4) [76.1;92.7]	63 (94.0) [85.6;97.7]	-7.7 [-18.6; 2.8]	-7.4 [-17.0; 2.2]
	Overall (0-120 hours)	56 (84.8) [74.3;91.6]	61 (91.0) [81.8;95.8]	-6.2 [-17.8; 5.2]	-5.8 [-16.3; 4.7]
Cycle 4	Number of evaluable patients in cycle	56	57		
	Acute Phase (0-24 hours)	53 (94.6) [85.4;98.2]	56 (98.2) [90.7;99.7]	-3.6 [-13.0; 4.7]	-3.4 [-10.1; 3.2]
	Delayed Phase (>24-120 hours)	51 (91.1) [80.7;96.1]	55 (96.5) [88.1;99.0]	-5.4 [-16.1; 4.4]	-5.1 [-13.7; 3.5]
	Overall (0-120 hours)	50 (89.3) [78.5;95.0]	54 (94.7) [85.6;98.2]	-5.5 [-16.7; 5.3]	-5.1 [-14.7; 4.5]

Table above is taken from Page 304 of the NEPA 15-18 CSR

Table 42 – Poland

Cycle	Phase	IV NEPA FDC (N=203) n (%) [95%CI]	Oral NEPA FDC (N=201) n (%) [95%CI]	Treatment Difference # [95%CI]	
				Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	56	56		
	Acute Phase (0-24 hours)	54 (96.4) [87.9;99.0]	54 (96.4) [87.9;99.0]	0.0 [-8.9; 8.9]	-0.0 [-6.8; 6.8]
	Delayed Phase (>24-120 hours)	51 (91.1) [80.7;96.1]	51 (91.1) [80.7;96.1]	0.0 [-11.5; 11.5]	0.0 [-10.5; 10.5]
	Overall (0-120 hours)	51 (91.1) [80.7;96.1]	51 (91.1) [80.7;96.1]	0.0 [-11.5; 11.5]	0.0 [-10.5; 10.5]
Cycle 2	Number of evaluable patients in cycle	49	45		
	Acute Phase (0-24 hours)	45 (91.8) [80.8;96.8]	43 (95.6) [85.2;98.8]	-3.7 [-15.2; 7.8]	-3.3 [-13.1; 6.5]
	Delayed Phase (>24-120 hours)	44 (89.8) [78.2;95.6]	41 (91.1) [79.3;96.5]	-1.3 [-14.1; 11.9]	-1.2 [-13.1; 10.8]
	Overall (0-120 hours)	43 (87.8) [75.8;94.3]	41 (91.1) [79.3;96.5]	-3.4 [-16.5; 10.2]	-3.3 [-15.8; 9.2]
Cycle 3	Number of evaluable patients in cycle	42	36		
	Acute Phase (0-24 hours)	41 (97.6) [87.7;99.6]	34 (94.4) [81.9;98.5]	3.2 [-7.5; 15.9]	3.5 [-5.2; 12.1]
	Delayed Phase (>24-120 hours)	40 (95.2) [84.2;98.7]	33 (91.7) [78.2;97.1]	3.6 [-8.7; 17.5]	4.0 [-7.2; 15.2]
	Overall (0-120 hours)	40 (95.2) [84.2;98.7]	33 (91.7) [78.2;97.1]	3.6 [-8.7; 17.5]	4.0 [-7.2; 15.2]
Cycle 4	Number of evaluable patients in cycle	29	30		
	Acute Phase (0-24 hours)	27 (93.1) [78.0;98.1]	30 (100) [88.6; 100]	-6.9 [-22.0; 5.5]	-6.9 [-16.1; 2.4]
	Delayed Phase (>24-120 hours)	27 (93.1) [78.0;98.1]	30 (100) [88.6; 100]	-6.9 [-22.0; 5.5]	-7.7 [-17.6; 2.2]
	Overall (0-120 hours)	26 (89.7) [73.6;96.4]	30 (100) [88.6; 100]	-10.3 [-26.4; 2.9]	-10.7 [-22.2; 0.7]

Table above is taken from Page 301 of the NEPA 15-18 CSR

Table 43 -Serbia

Cycle	Phase	IV NEPA FDC	Oral NEPA FDC	Treatment Difference	
		(N=203) n (%) [95%CI]	(N=201) n (%) [95%CI]	Without strata adjustment	With strata adjustment
Patients with a Complete Response					
Cycle 1	Number of evaluable patients in cycle	27	28		
	Acute Phase (0-24 hours)	25 (92.6) [76.6;97.9]	21 (75.0) [56.6;87.3]	17.6 [-2.6; 36.7]	17.2 [-0.6; 34.9]
	Delayed Phase (>24-120 hours)	22 (81.5) [63.3;91.8]	22 (78.6) [60.5;89.8]	2.9 [-18.5; 23.8]	2.3 [-17.3; 21.8]
	Overall (0-120 hours)	21 (77.8) [59.2;89.4]	18 (64.3) [45.8;79.3]	13.5 [-10.4; 35.3]	12.7 [-8.2; 33.5]
Cycle 2	Number of evaluable patients in cycle	24	27		
	Acute Phase (0-24 hours)	21 (87.5) [69.0;96.7]	22 (81.5) [63.3;91.8]	6.0 [-15.2; 25.9]	5.8 [-13.9; 25.5]
	Delayed Phase (>24-120 hours)	20 (83.3) [64.1;93.3]	23 (85.2) [67.5;94.1]	-1.9 [-23.0; 18.4]	-2.6 [-21.0; 15.7]
	Overall (0-120 hours)	19 (79.2) [59.5;90.8]	21 (77.8) [59.2;89.4]	1.4 [-21.4; 23.2]	0.7 [-20.8; 22.1]
Cycle 3	Number of evaluable patients in cycle	23	24		
	Acute Phase (0-24 hours)	22 (95.7) [79.0;99.2]	22 (91.7) [74.2;97.7]	4.0 [-13.7; 21.9]	4.1 [-9.4; 17.6]
	Delayed Phase (>24-120 hours)	22 (95.7) [79.0;99.2]	18 (75.0) [55.1;88.0]	20.7 [-0.5; 40.9]	20.6 [1.7; 39.4]
	Overall (0-120 hours)	21 (91.3) [73.2;97.6]	18 (75.0) [55.1;88.0]	16.3 [-6.0; 37.2]	16.4 [-3.8; 36.6]
Cycle 4	Number of evaluable patients in cycle	18	15		
	Acute Phase (0-24 hours)	16 (88.9) [67.2;96.9]	15 (100) [79.6; 100]	-11.1 [-32.8; 10.8]	-10.7 [-24.3; 2.9]
	Delayed Phase (>24-120 hours)	15 (83.3) [60.8;94.2]	15 (100) [79.6; 100]	-16.7 [-39.2; 6.4]	-16.8 [-34.1; 0.5]
	Overall (0-120 hours)	14 (77.8) [54.8;91.0]	15 (100) [79.6; 100]	-22.2 [-45.2; 2.1]	-22.1 [-41.3; -3.0]

Table above is taken from Page 302 of the NEPA 15-18 CSR

Data Quality and Integrity – Reviewers’ Assessment

Please refer to OSI analysis in Section 4.1. There were no anomalies in the results with respect to different study sites. No other concerns with the study results were identified.

Dose/Dose Response

Dose/Dose response was not specifically addressed in this trial.

Durability of Response

Efficacy was not the primary endpoint of this study; thus, durability of response is not relevant.

Persistence of Effect

Efficacy was not the primary endpoint of this study; thus, persistence of effect is not relevant.

Additional Analyses Conducted on the Individual Trial

Initial Request for Explanation by Applicant of 9 Percent Lower Observed CR in Delayed Phase (IV Akynzeo vs. PO Akynzeo)

An IR was sent to the applicant on 07/10/2017 requesting what they thought accounted for the observed 9 percent lower delayed phase CR in the IV Akynzeo® (NEPA FDC) arm compared to the oral Akynzeo® arm in Cycle 1, given that fosnetupitant and oral netupitant had been shown to be associated with comparable netupitant exposures in the dedicated relative bioavailability study. On 07/19/2017, the applicant responded, and reported that 9 patients in Cycle 1 took rescue medications “in the absence of emetic episodes and significant nausea” (absence of

significant nausea was defined as VAS < 25 mm)₂^{14,15}. As per the applicant, 7 of these patients were enrolled in the IV NEPA FDC arm, and 5 of them were enrolled at site 3107 (Ukraine). The applicant asserted that this uneven distribution explained the observed treatment distribution as a higher number of patients would have been disqualified as being complete responders in the IV arm.

Cycle 1 Results - Listing of Sites with Patients Reported to have Taken Rescue Medications Inappropriately

On 07/31/2017, an IR was sent to the applicant requesting a listing of the patients by site and phase who were reported to have taken rescue medications inappropriately. The applicant responded on 08/16/2017; see the table below.

¹⁴ “No significant nausea” was defined as VAS < 25 mm (see Section 6.2.1).

¹⁵ In another response to Information request (received 9/26/17), the Applicant provided (for patients identified by the Applicant as having taken rescue medications inappropriately in a given phase and cycle) the following: pertinent portions of the CRF’s documenting (by phase and cycle) absence of emetic episodes, absence of significant nausea (i.e., VAS < 25 mm), and administration of rescue medication.

Table 44 – Listing of Sites with Patients Reported to have Taken Rescue Medications Inappropriately by Phase, Cycle 1 - NEPA 15-18

Cycle 1
Acute Phase

	IV NEPA FDC		Oral NEPA FDC	
	Inappropriately took rescue medication	Total number of patients enrolled	Inappropriately took rescue medication	Total number of patients enrolled
Site 2702	1	3	0	1
Site 3102	1	9	0	7
Site 3104	0	2	1	5
Site 3114	0	7	1	9

Cycle 1
Delayed Phase

	IV NEPA FDC		Oral NEPA FDC	
	Inappropriately took rescue medication	Total number of patients enrolled	Inappropriately took rescue medication	Total number of patients enrolled
Site 2806	0	4	1	6
Site 3107	5	15	0	8
Site 3114	0	7	1	9
Site 3206	1	5	0	5

Cycle 1
Overall Phase

	IV NEPA FDC		Oral NEPA FDC	
	Inappropriately took rescue medication	Total number of patients enrolled	Inappropriately took rescue medication	Total number of patients enrolled
Site 2806	0	4	1	6
Site 3102	1	9	0	7
Site 3107	5	15	0	8
Site 3114	0	7	1	9
Site 3206	1	5	0	5

(Source – Response to IR Received 08/16/2017)

Reanalysis of Cycles 1 through 4 Results after Excluding Patients Reported to have Taken Rescue Medication Inappropriately

On 09/21/2017, another IR was sent to the applicant requesting re-analysis of Cycles 1 through 4 results (Delayed Phase CR) after excluding patients reported to have taken rescue medications inappropriately. The response was received on 09/26/2017. The data are summarized in the table below.

Table 45 – Reanalysis of Delayed Phase CR for all 4 Cycles Excluding Patients Reported to Have Taken Rescue Medication Inappropriately - NEPA 15-18

NEPA-15-18 Delayed phase cycle 1					
Endpoint	Population	IV NEPA FDC n (%)	Oral NEPA FDC n (%)	Treatment Difference % [95%CI]	
				Without strata adjustment	With strata adjustment
CR	FAS	159/203 (78.3)	176/201 (87.6)	-9.2 [-16.5; -1.9]	-9.0 [-15.8; -2.2]
	FAS excluding pts that inappropriately took rescue at site 3107	159/198 (80.3)	176/201 (87.6)	-7.3 [-14.5; 0.0]	-6.9 [-13.6; -0.2]
	FAS excluding pts that inappropriately took rescue at site 2702, 3102, 3104, 3107, 3114	159/197 (80.7)	176/199 (88.4)	-7.7 [-14.9; -0.6]	-7.4 [-14.1; -0.7]
	"PP"	151/190 (79.5)	165/187 (88.2)	-8.8 [-16.2; -1.3]	-8.8 [-15.8; -1.8]
	"PP" excluding pts that inappropriately took rescue at site 3107	151/185 (81.6)	165/187 (88.2)	-6.6 [-13.9; 0.7]	-6.5 [-13.4; 0.3]
	"PP" excluding pts that inappropriately took rescue at site 2702, 3102, 3104, 3107, 3114	151/184 (82.1)	165/185 (89.2)	-7.1 [-14.3; 0.1]	-7.0 [-13.8; -0.2]
NEPA-15-18 Delayed phase cycle 2					
Endpoint	Population	IV NEPA FDC n (%)	Oral NEPA FDC n (%)	Treatment Difference % [95%CI]	
				Without strata adjustment	With strata adjustment
CR	FAS	147/179 (82.1)	157/176 (89.2)	-7.1 [-14.4; 0.3]	-6.4 [-13.1; 0.4]
	FAS excluding pts that inappropriately took rescue at sites 2502, 2602, 2707, 3104, 3113, 3114, 3206	147/176 (83.5)	157/170 (92.4)	-8.8 [-15.8; -1.9]	-8.8 [-15.0; -2.6]
	"PP"	142/170 (83.5)	149/166 (89.8)	-6.2 [-13.6; 1.1]	-5.8 [-12.4; 0.8]
	"PP" excluding pts that inappropriately took rescue at sites 2502, 2602, 2707, 3104, 3113, 3114, 3206	142/167 (85.0)	149/161 (92.5)	-7.5 [-14.5; -0.6]	-7.7 [-13.8; -1.5]
NEPA-15-18 Delayed phase cycle 3					
Endpoint	Population	IV NEPA FDC n (%)	Oral NEPA FDC n (%)	Treatment Difference % [95%CI]	
				Without strata adjustment	With strata adjustment
CR	FAS	140/163 (85.9)	135/150 (90.0)	-4.1 [-11.4; 3.3]	-2.2 [-8.5; 4.0]
	FAS excluding pts that inappropriately took rescue at sites 2602, 2605, 2806, 3104, 3107, 3113	140/159 (88.1)	135/148 (91.2)	-3.2 [-10.1; 3.9]	-1.6 [-7.6; 4.5]
	"PP"	136/155 (87.7)	130/145 (89.7)	-1.9 [-9.2; 5.5]	-1.1 [-7.5; 5.3]
	"PP" excluding pts that inappropriately took rescue at sites 2602, 2605, 2806, 3104, 3107, 3113	136/152 (89.5)	130/143 (90.9)	-1.4 [-8.4; 5.6]	-0.6 [-6.8; 5.5]

NEPA-15-18
Delayed phase cycle 4

Endpoint	Population	IV NEPA FDC n (%)	Oral NEPA FDC n (%)	Treatment Difference % [95%CI]	
				Without strata adjustment	With strata adjustment
CR					
	FAS	105/122 (86.1)	115/117 (98.3)	-12.2 [-19.6; -5.6]	-9.6 [-15.4; -3.8]
	FAS excluding pts that inappropriately took rescue at sites 2212, 3107, 3206	105/119 (88.2)	115/117 (98.3)	-10.1 [-17.2; -3.7]	-8.5 [-14.2; -2.9]
	"pp"	102/118 (86.4)	112/114 (98.2)	-11.8 [-19.2; -5.1]	-9.9 [-15.9; -4.0]
	"PP" excluding pts that inappropriately took rescue at sites 2212, 3107, 3206	102/115 (88.7)	112/114 (98.2)	-9.5 [-16.7; -3.2]	-8.9 [-14.7; -3.1]

(Source – Response to IR received 09/26/2017)

This analysis did not reveal consistent results across cycles. The treatment difference became slightly less negative in Cycles 1, 3, and 4 in the FAS population; however, it became more negative in Cycle 2.

Discussion of Study NEPA 15-18

The efficacy data from this trial were included and discussed for completeness, and there were many post hoc analyses performed to explore the observed difference in CR in the delayed phase between the oral and IV NEPA FDC arms. However, the study was conducted to evaluate safety of fosnetupitant in a controlled trial setting; it was neither designed nor powered to be a non-inferiority trial to evaluate efficacy. The Statistical reviewers noted in their review of this trial that the noninferiority margin for the oral combination product (containing 300 mg of netupitant) for the delayed phase is very small, i.e., 1%; therefore, Study NEPA 15-18 had only 4% power to establish noninferiority of the IV combination product to the oral combination. In this NDA, fosnetupitant's efficacy was established by demonstrating that the netupitant exposures ($AUC_{0-120hr}$ and $AUC_{0-\infty}$) associated with fosnetupitant and oral netupitant met bioequivalence criteria in a relative bioavailability study (Study PNET-12-23). As described in Section 4.5.3 above, the reviewers concluded that the observed differences in Study NEPA 15-18 could not be attributed to differences in metabolite exposures between the products.

This reviewer, in conjunction with the other members of the review team, concluded that the observed differences in Study NEPA 15-18 were not interpretable because the study was not designed and adequately powered to evaluate noninferiority, and should not alter the efficacy conclusion supported by the results of the relative bioavailability study (Study PNET-12-23), i.e., the efficacy associated with fosnetupitant in the setting HEC (excluding AC combination chemotherapy) is comparable to that associated with oral netupitant. The CDTL, Division Director, and ODE III Director concur with that conclusion.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Fosnetupitant:

Study PNET 12-23 was a relative bioavailability study in healthy subjects which included a comparison of 260 mg of IV fosnetupitant (a prodrug of netupitant) with 300 mg of oral netupitant (the dose of netupitant in the approved Akynzeo capsules). The fosnetupitant dose selected was shown to meet bioequivalence criteria (for AUC_{0-120} and $AUC_{0-\infty}$) in a comparison of relative bioavailability with the netupitant dose in Akynzeo capsules. The oral netupitant dose selection was from a dose-ranging study (Study NETU-07-07) submitted for Akynzeo capsules [see reviews from Akynzeo capsules NDA (NDA 205718) particularly the Clinical Pharmacology and Statistics Reviews]. The study showed that for the delayed phase, there was a flat dose-response relationship over the range of 100 to 300 mg netupitant when netupitant + palonosetron 0.5 mg was compared to palonosetron 0.5 mg alone; each of the doses showed statistical significance over placebo. However, for the acute phase, only netupitant 300 mg was shown to be statistically significantly higher than placebo for the Complete Response endpoint. Because bioequivalence criteria were met, a bridging argument for efficacy of fosnetupitant can be supported for Akynzeo IV based on the oral Akynzeo efficacy data.

Palonosetron:

Study PALO 15-17 was a non-inferiority (NI) study in the acute phase conducted in a HEC population that did not include patients treated with AC comparing palonosetron infused over 30 minutes (as in the proposed product) to palonosetron infused over 30 seconds (as approved for Aloxi IV).

7.1.1. Primary Endpoints

PALO 15-17

Non-inferiority of a 30-minute infusion of IV palonosetron 0.25 mg to a 30-second bolus injection of palonosetron 0.25 mg (the approved posology for Aloxi IV) was established for CR in the acute phase of CINV in a single cycle of HEC (not including AC combination chemotherapy).

7.1.2. Secondary and Other Endpoints

PALO 15-17

No adjustment for multiplicity was made in this study. Results for the secondary and other endpoints from this study are included for completeness only (see Section 6.1.2).

NEPA 15-18

Analyses of all efficacy endpoints in this study were descriptive. Results for these endpoints are included for completeness only (see Section 6.2.2).

7.1.3. Subpopulations

A summary of the applicant's subgroup analyses is provided below. In both PALO 15-17 and NEPA 15-18, the applicant conducted subgroup analyses of CR based on sex and country.

PALO 15-17

Sex: No treatment by sex interaction was detected (see Section 6.1.2).

Country: No treatment-by country interaction was detected (see Section 6.1.2).

NEPA 15-18

Sex: The proportion of female patients with CR was numerically lower compared with male patients in each phase and in each cycle for both treatment groups (IV NEPA FDC and Oral NEPA FDC). These results were expected as female sex is one of the risk factors for CINV (see Section 2.1). See Section 6.2.2.

Country: No clear relation between CR across phases and cycles and country was appreciated. See Section 6.2.2.

7.1.4. Dose and Dose-Response

Dose and Dose response was not specifically addressed by either PALO 15-17 or NEPA 15-18.

Palonosetron: The approved dose of Aloxi (palonosetron) IV was used.

Fosnetupitant: The fosnetupitant dose was determined from Study PNET 12-23.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Onset, duration, and durability of efficacy effects were not specifically addressed by either PALO 15-17 or NEPA 15-18. A discussion of these issues can be found in the oral Akynzeo review written by Dr. Nancy Snow.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No potential efficacy issues in the postmarket setting have been identified.

7.2.2. Other Relevant Benefits

Akynzeo® for injection has some additional benefits. It can be reasonably expected to prevent/treat CINV in patients receiving non-AC HEC chemotherapy who cannot tolerate oral medication. Though the indication is more narrow for Akynzeo® for injection, its route of administration will still likely be of benefit to patients receiving the most emetogenic of chemotherapy regimens. The fact that it is a combination product (5HT₃ and NK₁ antagonists) is also of benefit as both medication classes are recommended for the treatment of CINV in HEC per the most recent ASCO guidelines. As such, one medication could be administered to the patient as opposed to two.

7.3. Integrated Assessment of Effectiveness

Akynzeo® for injection has met the statutory evidentiary standard. The evidence for the effectiveness of Akynzeo for Injection, an intravenous fixed combination product (of fosnetupitant and palonosetron) is based on bridging to the approved fixed combination oral Akynzeo product (netupitant and palonosetron) and the currently approved intravenous product.

- (i) Trials that supported the approval of oral Akynzeo capsules established the efficacy of the netupitant component for prevention of acute and delayed phases of HEC CINV and the efficacy of palonosetron for acute phase of HEC CINV. (The NDA also included trials that established the oral netupitant's efficacy for prevention of acute and delayed phase CINV associated with AC combination chemotherapy, when it was combined with oral palonosetron.)
- (ii) Trials that supported the approval of intravenous Aloxi (**palonosetron, IV**) established its efficacy for prevention of acute phase of HEC CINV. (The NDA also included trials that established the efficacy of intravenous palonosetron for prevention of CINV, associated with AC combination chemotherapy, in both the acute and delayed phases.
- (iii) Studies submitted in the current NDA to bridge to the approved products are:
 - **Non-Inferiority Trial (Palonosetron 30 minute vs. 30 second infusion; Study PALO 15-17):** This was a non-inferiority (NI) study of prevention of **acute phase CINV** in HEC (not including AC population). It compared **palonosetron infused over 30 minutes** (as in the proposed product) to palonosetron infused over 30 seconds (as approved for Aloxi IV). Non-inferiority was demonstrated for the Complete Response endpoint in the acute phase.
 - **Relative Bioavailability Study (IV fosnetupitant vs. oral netupitant; Study PNET 12-23):** This was a relative bioavailability study in healthy subjects which included a comparison of 260 mg of **IV fosnetupitant** (a prodrug of netupitant) with 300 mg of oral netupitant (the dose of netupitant in the approved Akynzeo capsules). Bioequivalence criteria were met (for AUC_{0-120h} and AUC_{0-∞}). Cmax was approximately 50% higher with fosnetupitant 260 mg IV than with netupitant 300 mg PO (see Clinical Pharmacology Review); thus, fosnetupitant 260 mg IV is expected to be at least as efficacious as netupitant 300 mg PO.

The effect of **palonosetron infused over 30 minutes** was demonstrated in the **acute phase** in the population of **HEC not including AC**, and the effect of **IV fosnetupitant** was demonstrated in the **acute and delayed phases** in the population of **HEC not including AC**. It should be

noted that because palonosetron IV has a delayed phase indication in the AC population but palonosetron PO does not, **demonstration of the contribution of fosnetupitant IV in the delayed phase in the AC population would be needed for an Akynzeo IV indication in the delayed phase in the AC population.**

A description and results of Study Palo-15-17 should be included in the Clinical Studies section of the label. A description and results of Study NEPA 15-18 should not be included in the Clinical Studies section of the label because only descriptive efficacy analyses were performed in this study, which was intended to evaluate safety in a controlled trial setting, to assess the safety of fosnetupitant and the higher Cmax of netupitant associated with intravenous Akynzeo.

8 Review of Safety

8.1. Safety Review Approach

The safety review involved analysis of three trials, PNET 12-23 (Phase 1 ascending dose and relative bioavailability study), PALO 15-17, and NEPA 15-18. PNET 12-23 involved healthy volunteers. In addition, PALO 15-17 only studied the infusion duration of palonosetron. NEPA 15-18 was the primary safety study as it involved cancer patients receiving HEC who were also given Akynzeo® for injection or oral Akynzeo capsules. Because of these key differences in these study populations, each trial was considered separately. The safety data were analyzed by evaluating the applicant's data in the study reports, reviewing patient narratives where appropriate, reviewing safety data from the oral Akynzeo® program, and using J-Review.

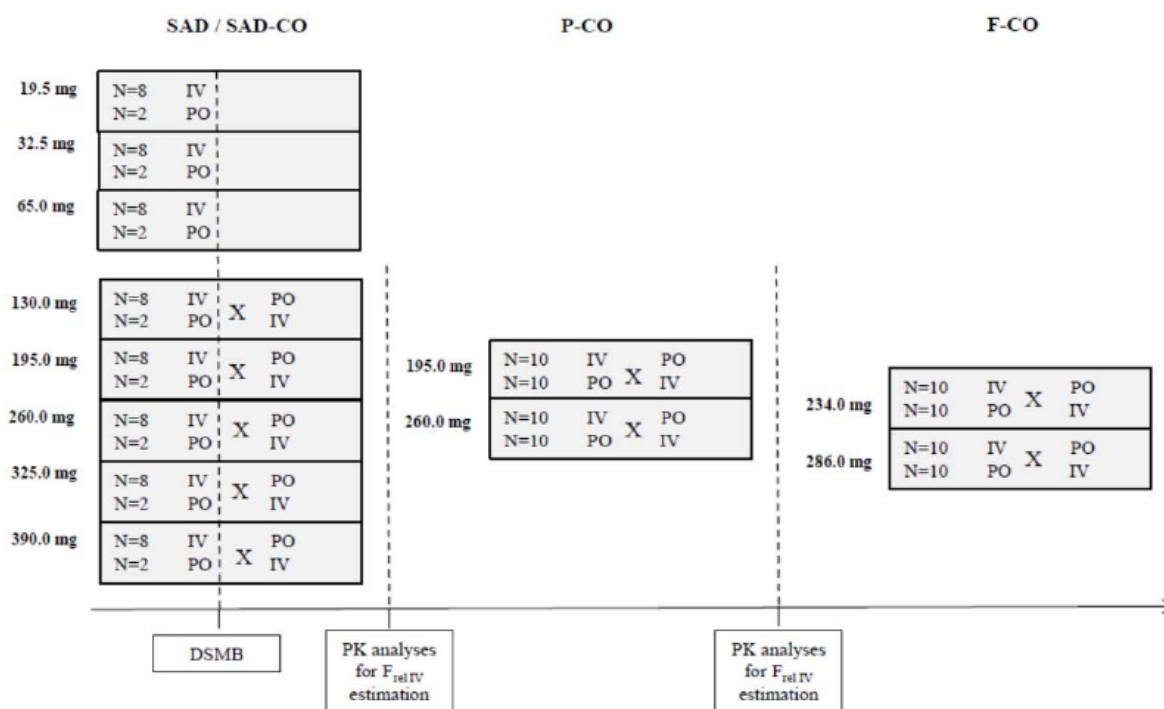
8.2. Review of the Safety Database

8.2.1. Overall Exposure

PNET 12-23

The study was conducted with 8 single ascending pro-netupitant dose levels from 19.5 mg up to a maximum dose of 390 mg, with a crossover arm from 130 mg up to 390 mg pro-netupitant. A total of 10 subjects were planned to be treated per dose cohort. Two additional crossover parts, each with 2 dose cohorts and with 20 subjects per dose cohort, were also performed. See the figure below.

Figure 3. Study PNET-12-23: Overview of Design



DSMB: Drug Safety Monitoring Board, F-CO: final crossover, IV: intravenous, N: number of subjects, P-CO: pilot crossover, PK: pharmacokinetics, PO: per os, SAD: single ascending dose, SAD-CO: single ascending dose crossover

The figure above is taken from Page 30 of the Study Report.

One hundred and sixty (160) subjects were randomized in the study. Two (2) randomized subjects were not treated due to premature discontinuation of the study prior to the first drug administration. All other 158 randomized subjects were treated during the study. In the ascending dose part, 30 subjects received only 1 dose as planned, either 1 IV dose of 19.5, 32.5, or 65 mg pro-netupitant (8 subjects each, 24 subjects overall) or 1 oral dose of 300 mg netupitant/0.5 mg palonosetron (6 subjects overall).

In the crossover parts, 3 subjects received only 1 oral dose of 300 mg netupitant and 0.5 mg palonosetron (together with placebo infusion) due to premature discontinuation of the study prior to administration of the IV dose (together with a placebo capsule).

All other 125 subjects of the crossover parts received 2 doses as planned, 1 IV dose of 130 mg to 390 mg pro-netupitant (together with a placebo capsule) and 1 oral dose of 300 mg netupitant/0.5 mg palonosetron (together with a placebo infusion).

In total, 149 subjects received 1 dose of the IV pro-netupitant treatment and 134 subjects received 1 dose of the oral 300 mg netupitant/0.5 mg palonosetron treatment. One (1) subject of the 286 mg dose cohort received, however, the wrong oral treatment during the second period of the crossover part. Thus, this subject received both, 1 oral dose of 300 mg netupitant/0.5 mg palonosetron (instead of the oral placebo assigned according to randomization) together with the IV infusion of 286 mg pro-netupitant. The planned IV dose was not completely administered due to infusion interruption following the discovery of the erroneous oral medication administration; 80.1 mL instead of 110 mL of the infusion solution were administered, resulting in an administered dose of 208.26 mg IV pro-netupitant.

Furthermore, 1 subject of the 325 mg dose cohort probably did not receive the complete IV dose of 325 mg pro-netupitant in the first period of the crossover part due to a probable extravasation of the IV study drug. In fact, during the infusion the subject experienced swelling at the infusion site. Infusion was immediately interrupted and restarted in another vein, where the entire remaining volume of the infusion solution was administered. Extravasation of part of the volume infused prior to interruption (32.5 mL of the 125 mL corresponding to a dose of 84.5 mg pro-netupitant) could not be excluded.

PALO 15-17

Treatment exposure to palonosetron is summarized in the table below. All patients treated in the infusion group except one received the planned dose of palonosetron 0.25 mg IV in 50 mL solution, and all patients treated in the bolus group received the planned dose of palonosetron 0.25 mg IV in 5 mL solution. The exception in the infusion group was patient 1907-02, who received the correct dose of 0.25 mg palonosetron in 55 mL due to erroneous preparation of the infusion solution. No patients in the infusion group had interruptions of the study treatment infusion.

Table 46 – Treatment Exposure PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
Total IMP administered (mL)		
Mean (SD)	50.0 (0.3)	5.0 (0.0)
Median	50.0	5.0
Min, Max	50, 55	5, 5
Total dexamethasone administered on Day 1 (mg)		
Mean (SD)	20.0 (0.0)	20.0 (0.0)
Median	20.0	20.0
Min, Max	20, 20	20, 20
Total dexamethasone administered on Days 2 to 4 (mg)		
Mean (SD)	47.9 (1.3)	47.6 (3.9)
Median	48.0	48.0
Min, Max	32, 48	8, 48

(Source – PALO 15-17 Study Report Page 101)

NEPA 15-18

Treatment exposure to IV or Oral NEPA FDC throughout the study is summarized in the table below. All patients treated in the IV NEPA FDC treatment group received at least one infusion of the planned dose of 260 mg fosnetupitant/0.25 mg palonosetron in 50 mL 5% glucose solution, and all patients treated in the Oral NEPA FDC group received at least one oral capsule of the planned dose of 300 mg netupitant/0.50 mg palonosetron. The mean (SD) number of infusions administered in the IV NEPA FDC group during the study was 3.3 (1.0). The mean (SD) number of capsules administered in the Oral NEPA FDC group during the study was 3.2 (1.1).

Table 47 – Treatment Exposure NEPA 15-18

Treatment		IV NEPA FDC (N=203)	Oral NEPA FDC (N=201)
Fosnetupitant/palonosetron			
Patients who received at least 1 dose of IMP	N	203	201
Number of infusions per patient	Mean (SD)	3.3 (1.0)	3.2 (1.1)
	Median	4.0	4.0
	Min, Max	1, 4	1, 4
Infusion total volume administered (mL) ^a	Mean (SD)	164.3 (51.9)	0
	Median	200.0	0
	Min, Max	50, 200	0
Number of capsules per patient	Mean (SD)	3.3 (1.0)	3.2 (1.1)
	Median	4.0	4.0
	Min, Max	1, 4	1, 4
Capsule total dose administered (mg) ^b	Mean (SD)	0	962.7 (322.6)
	Median	0	1200.0
	Min, Max	0	300, 1200

(Source - NEPA 15-18 Study Report Page 102)

8.2.2. Relevant characteristics of the safety population:

For the purposes of the safety populations, PNET 12-23 was conducted in healthy volunteers. NEPA 15-18 and PALO 15-17 were conducted in cancer patients that were receiving cisplatin based HEC. The specifics of each population were discussed in section 6.1.1 and 6.2.1.

8.2.3. Adequacy of the safety database:

The study data base for the Akynzeo[®] for injection development program was adequate. The

safety data from the oral development program was considered along with the safety data from the populations studied in PNET 12-23, NEPA 15-18, and PALO 15-17. In addition, the studies (excluding PNET 12-23) were conducted in cancer patients receiving HEC chemotherapy. Safety was assessed in the 120 hours following drug administration, including with repeat dosing in NEPA 15-18.

NEPA 15-18 was the only dedicated safety study that was conducted during the Akynzeo® for injection development program. These results will be emphasized given that this was the study where cancer patients receiving HEC received both components of the drug (palonosetron and fosnetupitant).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality and integrity of the safety data was adequate for this review. No concerns were identified with any study sites. Though there was a minimal amount of missing data in the data sets, quality of the data was acceptable. An Office of Computational Science (OCS) consultation was not required. The submission documents were reasonably well organized. A review of the diary modules and VAS identified no concerns. Multiple information requests were sent to the applicant for additional information and data analysis, and there were no issues with the responses that were received.

8.3.2. Categorization of Adverse Events

For all three studies, AEs and serious adverse events (SAEs) were adequately defined per the regulations in 21 CFR 312.32.

Planned surgical interventions or planned hospitalizations scheduled prior to the informed consent but performed during the study (study procedures, chemotherapy cycles, etc.) were not considered (serious) AEs.

Signs and symptoms considered as lack of efficacy (nausea and vomiting) and occurring during the studies up to 5 days after the study drugs administration were to be recorded on the AEs section of the eCRF, except on the condition that, in the Investigator's opinion, nausea and vomiting was caused by any reason different from lack of efficacy of study treatment or meet the definition of a serious AE.

An Unexpected Adverse Event was any experience not previously reported (in nature, severity or incidence) in the current Investigator's Brochures for palonosetron, oral NEPA FDC, and/ or IV NEPA FDC.

A pre-existing condition was one that is present at the start of the study. A pre-existing condition was recorded as an adverse event if the frequency, intensity, or the character of the condition worsened during the study period.

The Investigator classified AEs based on their severity and relationship to IMP. Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship.

The severity of an AE was rated by the Investigator according to the descriptions and grading scales of the Common Terminology Criteria for Adverse Events (CTCAE) (for details please refer to the integral document Terminology Criteria for Adverse Events (CTCAE, Version 4.03: June 14, 2010); U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute).

For these trials, an AE cause and effect relationship to the study drug was classified by the Investigator as reported as definitely related, probably related, possibly related, unlikely related, not related/ none, and un-assessable.

Adverse events were coded using the MedDRA dictionary to give a preferred term (PT) and a system/organ class term (SOC) for each event. The number and percentage of patients who experienced at least one treatment emergent adverse event (TEAE), drug related TEAE (defined as adverse events with relationship classified as definitely, probably, possibly, un-assessable or missing), serious TEAE, serious related, severe TEAE (i.e. TEAE with CTCAE grade ≥ 3), and the number and percentage of patients withdrawn due to TEAE were summarized by treatment arm.

For each SOC and preferred term, summaries were made with respect to the proportion of patients having at least one occurrence of that event during the study and the total number of events. The incidence of TEAEs in each treatment arm were presented overall, by SOC and preferred term, and additional grouping by severity according to the CTCAE grade and relationship to the study treatment. Tables by drug relationship were presented by relationship to study drugs and relationship to additional study drug (dexamethasone) separately. Additional tables including any relationship were presented.

No formal test was used for “between groups” comparison. All adverse events were listed.

AE reporting was in accordance with the ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management.

During the course of the study, all AEs (including SAEs), irrespective of the relatedness to the study drugs, were recorded in detail in the source records and transcribed onto the AEs pages of the eCRF. During each monitoring visit, the Investigator and the site monitor reviewed all AEs and perform Source Data Verification (SDV). The Investigator was responsible for ensuring that the correct information concerning all AEs is entered on the appropriate eCRF pages.

The reporting period for AEs was the period starting from the time of Informed Consent signature and lasting until Day 21 (20 [± 2] days post study drug administration on Day 1). All unresolved AEs (including SAEs) were documented on the eCRF as “ongoing”.

All SAEs occurring from the time of signing of the informed consent until Day 21 (20 [± 2] days

post study drug administration on Day 1) were reported immediately to the CRO pharmacovigilance. Information on the actual fax and phone numbers were provided in the Investigator file as well as at Section General Information of the present protocol. The Investigator or designated study coordinator completed the Investigational Serious AE Form and sent it to the CRO within 24 hours of observation or notification of a serious AE. All of these events were recorded on the appropriate eCRF pages.

It was the responsibility of the Investigator to inform his or her local Institutional Review Board (IRB)/Ethics Committee (EC) about SAEs according to the local IRB/EC requirements. It was the responsibility of the Sponsor (or Sponsor's designee) to submit applicable SAE Reports to the Competent Authorities. Reporting of suspected unexpected serious adverse reactions (SUSARs) to the relevant IRB/EC, in accordance with the EU Clinical Trial Directive 2001/20/EC, the US Code of Federal Regulations 313.32 and ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management, was also be the responsibility of the Sponsor (or Sponsor's designee).

A safety contact sheet was provided to the Investigator and was maintained in the Investigator file at the site.

SAEs were followed by the Investigator until the outcome was resolved, had reached a stable condition in the Investigator's opinion, or until the patient was lost to follow-up. When the investigational site received any information about a serious adverse event which changed or added to the information on the initial investigational SAE form, the site filled out a new investigational SAE form and ticked the "follow-up" box of the SAE form and faxed it within 24 hours to the CRO, especially if this new information had an effect on the seriousness, relatedness or expectedness of an adverse event.

Analysis of reported term and dictionary derived term did not reveal any issues with coding for each of the study. Furthermore, there was no indication of lumping or splitting of the terms. All of the AEs were grouped and analyzed using the MedDRA hierarchy.

Considering that QT prolongation and constipation are known class effects of 5-HT₃ receptor antagonist, special attention was paid to both events, in particular on severe forms of constipation (CTCAE grade 3 or 4). In such cases, an accurate follow-up was to be performed by the Sponsor.

8.3.3. Routine Clinical Tests

Clinical evaluations for safety assessments included physical examinations, monitoring AEs, vital signs, ECGs, and laboratory tests. Laboratory tests consisted of blood chemistry, hematology, and urinalysis.

The following laboratory parameters were assessed:

- a) Hematology: hematocrit, hemoglobin, erythrocytes, platelets, leukocytes, neutrophils, lymphocytes, basophils, eosinophils, monocytes.
- b) Blood Chemistry: urea, creatinine, creatinine clearance (derived from blood creatinine

value by application of the Cockcroft formula), total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, chloride, bicarbonate, calcium, albumin, total protein, and blood glucose. A serum beta-hCG pregnancy test was also performed.

c) Urinalysis: protein, glucose, WBC, erythrocytes, and bacteria.

The laboratory data were analyzed and described as listings, descriptive statistics for observed values, and change from baseline. ECG data were summarized highlighting differences compared to the baseline values for quantitative variables and frequencies of treatment emergent abnormalities. Descriptive statistics were presented by treatment for the following parameters: heart rate, PR, QRS, QT, QTcB and QTcF. An outlier analysis depicting the number and proportion of patients who meet specific pre-defined criteria will be performed. The number of patients who had treatment emergent abnormalities in ECG results were summarized in frequency tables. All ECG data will be listed.

Vital signs were summarized by treatment using descriptive statistics for absolute values and change from baseline, in addition to being listed.

Physical examination results, apart from baseline, that were summaries in a frequency table (normal/abnormal), were listed.

Please refer to section 6.1.1 and 6.2.1 for a discussion of the timing of the testing for PALO 15-17 and NEPA 15-18.

Please see the table below for further information on the timing of the various tests conducted in PNET 12-23. Of note, in addition to the other testing that was done in the other studies, color Doppler ultrasound scanning was performed on the dosing and contralateral veins to detect any abnormality in the dosing vein that could indicate a thrombotic event. Any clinically significant changes during the study period (from the first study drug administration and up to the final study visit) were recorded in the CRF as AEs.

Table 48 – Schedule of Testing PNET 12-23

Days	SCREENING VISIT	1 st period							Washout Phase (at least 4 weeks between administrations)	2 nd period [#]							FINAL VISIT (telephone contact) ^{##}
	-14 to -2	-1	1	2	3	4	5	6		-1	1	2	3	4	5	6	14
Activity																	
Confinement to study center (X) or return to facility (R)		X	X	X	X	R	R	R		X	X	X	X	R	R	R	
Informed consent signature	X																
Inclusion / exclusion criteria	X ¹	X ¹								X ¹							
Demography, baseline characteristics	X ²																
Medical and surgical history	X																
Laboratory analysis – general safety evaluation (hematology, blood chemistry, urinalysis)	X	X						X		X						X	
Laboratory analysis (blood) – local tolerability evaluation (D-dimer, haptoglobin, total and direct bilirubin and direct and indirect Coombs test)		X ³		X ³						X ³		X ³					
Blood Coagulation test		X	X ⁴							X	X ⁴						
Blood sampling for CYP3A4 genotyping			X														
Serology	X																

Days	SCREENING VISIT	1 st period							Washout Phase (at least 4 weeks between administrations)	2 nd period [#]							FINAL VISIT (telephone contact) ^{##}
	-14 to -2	-1	1	2	3	4	5	6		-1	1	2	3	4	5	6	14
Pregnancy test (for females)	X ⁵	X ⁵						X ⁵		X ⁵						X ⁵	
Urine toxicology screening	X	X								X							
Alcohol breath test	X	X								X							
Prior and concomitant medication	X ⁶	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vital signs	X	X	X ⁷	X	X	X	X	X		X	X ⁷	X	X	X	X	X	
Complete (C)/ Limited (L) physical examination (PE)	C	C				L		L		C			L		L		
Color Doppler ultrasound scanning of the infusion vein and contralateral vein		X	X ^{8,9}	X				X ⁹		X	X ^{8,9}	X				X ⁹	
ECG assessment	X	X	X ¹⁰		X			X		X	X ¹⁰	X				X	
Randomization		X															
Continuous safety monitoring			X ¹¹								X ¹¹						
IMP administration			X								X						
PK sampling (*)			X	X	X	X	X	X			X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

(Source – PNET-12-23 Study Report Pages 56-57)

8.4. Safety Results

8.4.1. Deaths

PNET 12-23

No deaths occurred in this study.

PALO 15-17

TEAEs leading to death were reported for 13 patients: 6 (2.7%) patients in the infusion group and 7 (3.3%) patients in the bolus group. These results are summarized in the table below by SOC and Dictionary Derived Term.

Table 49 – TEAE Leading to Death by SOC and Dictionary Derived Term PALO 15-17

TEAE leading to Death Char	Analysis Primary System Organ Class	Dictionary Derived Term	Unique Subject Identifier	PALONOSETRON 0.25 MG IV BOLUS	PALONOSETRON 0.25 MG IV INFUSION	Subjects(filtered)
Y	Cardiac disorders	Atrial flutter	(b) (6)	0 (0.0%)	1 (0.4%)	1 (0.2%)
		Cardio-respiratory arrest		0 (0.0%)	1 (0.4%)	1 (0.2%)
				1 (0.5%)	0 (0.0%)	1 (0.2%)
	Gastrointestinal disorders	Mesenteric vein thrombosis		0 (0.0%)	1 (0.4%)	1 (0.2%)
	General disorders and administration site conditions	Death		1 (0.5%)	0 (0.0%)	1 (0.2%)
		Disease progression		1 (0.5%)	0 (0.0%)	1 (0.2%)
	Infections and infestations	Pneumonia		0 (0.0%)	1 (0.4%)	1 (0.2%)
		Sepsis		1 (0.5%)	0 (0.0%)	1 (0.2%)
				0 (0.0%)	1 (0.4%)	1 (0.2%)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression		1 (0.5%)	0 (0.0%)	1 (0.2%)
				0 (0.0%)	1 (0.4%)	1 (0.2%)
	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism		1 (0.5%)	0 (0.0%)	1 (0.2%)
		Respiratory failure		1 (0.5%)	0 (0.0%)	1 (0.2%)
		Subjects(filtered)		7 (3.3%)	6 (2.7%)	441 (100.0%)
		1stColItemSubjects		215 (100.0%)	225 (100.0%)	(Denom=1stColTot)

(Source – Reviewers Table)

One patient who died experienced two TEAEs, atrial flutter [Grade 5] (onset at Day 6) and dyspnea [Grade 4] (onset at Day 12) which were both classified as severe. According to the narrative, subject (b) (6) had history of atrial flutter, advanced small cell neuroendocrine carcinoma, myocardial ischemia, and diabetes. Though the dyspnea and atrial flutter were possibly attributed to the study drug, the subject died of respiratory failure and cardiac arrest which were not attributed to the study drug. Cardiac side effects will be discussed further in Sections 8.4.5 and 8.5.1. The narratives of the other patients were reviewed, and these deaths were not likely related to either the infusion time or the study drug itself.

NEPA 15-18

TEAEs leading to death were reported for 10 (4.9%) patients in the IV NEPA FDC group and 14 (7.0%) patients in the Oral NEPA FDC group. These results are summarized in the table below by SOC and Dictionary Derived Term.

Table 50 – TEAE Leading to Death by SOC and Dictionary Derived Term NEPA 15-18

TEAE leading to Death Char	Analysis Primary System Organ Class	Dictionary Derived Term	Unique Subject Identifier	IV PRO- NETUPITANT / PALONOSETRON 5.2 mg/mL / 5 ug/mL	ORAL NETUPITANT / PALONOSETRON 300 mg / 0.50 mg	Subjects(filtered)
Y	Blood and lymphatic system disorders	Febrile neutropenia	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Cardiac disorders	Cardiac failure	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Gastrointestinal disorders	Gastric ulcer haemorrhage	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
		Ileus	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	General disorders and administration site conditions	Intestinal obstruction	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
		Death	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
		Disease progression	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
		Oedema peripheral	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
		Sudden death	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
			(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	Infections and infestations	Pneumonia	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
			(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
		Pyopneumothorax	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
		Sepsis	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
			(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	Injury, poisoning and procedural complications	Accidental overdose	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
			(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	Renal and urinary disorders	Nephropathy	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
	Respiratory, thoracic and mediastinal disorders	Haemoptysis	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Vascular disorders	Haemorrhage	(b) (6)	1 (0.5%)	0 (0.0%)	1 (0.2%)
		Peripheral embolism	(b) (6)	0 (0.0%)	1 (0.5%)	1 (0.2%)
			Subjects(filtered)	10 (4.9%)	14 (7.0%)	405 (100.0%)
			1stColItemSubjects	203 (100.0%)	201 (100.0%)	(Denom=1stColTot)

Note: The accidental overdose case in the table above (b) (6) was an overdose of diazepam.

Note: The Sudden Death cases occurred on Day 13 (b) (6), Day 8 (b) (6), Day 62 (b) (6) and Day 52 (b) (6).

(Source – Reviewers Table)

None of the deaths that occurred were attributed to the study drug. The narratives of these subjects were reviewed and the Clinical Reviewer confirmed this determination.

8.4.2. Serious Adverse Events

PNET 12-23

TEAEs will be summarized in Section 8.4.5. There were no other serious adverse events that occurred in this study.

PALO 15-17

SAEs were reported for a total of 15 (6.7%) patients (34 events) in the infusion group and 12 (5.6%) patients (14 events) in the bolus group. Neutropenia was experienced by 2 (0.9%) patients in the infusion group and 3 (1.4%) patients in the bolus group, and asthenia by 2 (0.9%) patients in the infusion group and 1 (0.5%) patient in the bolus group. Two SAEs (atrial flutter [Grade 5] and dyspnea [Grade 4]), both in 1 patient (0.4%) in the infusion group were assessed as possibly related to study drug. Please see Section 8.4.1 for further discussion of this patient. In

general, there were more cardiac disorders in the 30-minute infusion arm. This will be discussed further in section 8.5.1 In general, there were no serious events not already listed as TEAEs that were attributable to the study drug or infusion time. TEAEs will be discussed further in section 8.4.5. Please see table below.

Table 51 – Serious Adverse Events by SOC and Dictionary Derived Term PALO 15-17

Serious Event	Analysis Primary System Organ Class	Dictionary Derived Term	PALONOSETRON 0.25 MG IV BOLUS	PALONOSETRON 0.25 MG IV INFUSION	Subjects(filtered)
Y	Blood and lymphatic system disorders	Leukopenia	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Neutropenia	3 (1.40%)	2 (0.89%)	5 (1.13%)
		Thrombocytopenia	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Cardiac disorders	Atrial fibrillation	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Atrial flutter	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Cardiac arrest	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Cardio-respiratory arrest	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Gastrointestinal disorders	Abdominal pain	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Constipation	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Mesenteric vein thrombosis	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Vomiting	1 (0.47%)	1 (0.44%)	2 (0.45%)
	General disorders and administration site conditions	Asthenia	1 (0.47%)	2 (0.89%)	3 (0.68%)
		Death	2 (0.93%)	0 (0.00%)	2 (0.45%)
		Disease progression	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Pain	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Infections and infestations	Pneumonia	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Sepsis	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Injury poisoning and procedural complications	Brain contusion	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Subdural haematoma	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Investigations	Blood creatinine increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Blood urea increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
		ECG signs of myocardial infarcti	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Metabolism and nutrition disorders	Dehydration	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Hypokalaemia	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Hyponatraemia	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Nervous system disorders	Epilepsy	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Transient ischaemic attack	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Respiratory, thoracic and mediastinal disorders	Dyspnoea	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Pulmonary embolism	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Respiratory failure	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Skin and subcutaneous tissue disorders	Angioedema	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Dermatitis allergic	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Vascular disorders	Hypotension	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Subjects(filtered)	12 (5.58%)	15 (6.67%)	441 (100.00%)
		1stColItemSubjects	215 (100.00%)	225 (100.00%)	(Denom=1stColTot)

(Source – Reviewers Table)

NEPA 15-18

The serious adverse events are summarized in the table below. In general, there were no serious events not already listed as TEAEs that were attributable to the study drug. TEAEs will be discussed further in section 8.4.5.

Table 52 – Serious Adverse Events by SOC and Dictionary Derived Term NEPA 15-18

Serious Event	Analysis Primary System Organ Class	Dictionary Derived Term	IV PRO- NETUPITANT / PALONOSETRON 5 2 mg/mL / 5 µg/mL	ORAL NETUPITANT / PALONOSETRON 300 mg / 0 50 mg	Subjects(filtered)
Y	Blood and lymphatic system disorders	Agranulocytosis	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Anaemia	0 (0 00%)	4 (1 99%)	4 (0 99%)
		Febrile neutropenia	3 (1 48%)	1 (0 50%)	4 (0 99%)
		Leukopenia	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Neutropenia	6 (2 96%)	8 (3 98%)	14 (3 46%)
		Thrombocytopenia	1 (0 49%)	4 (1 99%)	5 (1 23%)
	Cardiac disorders	Atrial fibrillation	1 (0 49%)	1 (0 50%)	2 (0 49%)
		Cardiac failure	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Extrasystoles	1 (0 49%)	0 (0 00%)	1 (0 25%)
	Eye disorders	Diplopia	1 (0 49%)	0 (0 00%)	1 (0 25%)
	Gastrointestinal disorders	Duodenal ulcer	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Gastric haemorrhage	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Gastric ulcer haemorrhage	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Gastritis	0 (0 00%)	2 (1 00%)	2 (0 49%)
		Gastrointestinal haemorrhage	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Ileus	0 (0 00%)	2 (1 00%)	2 (0 49%)
		Intestinal obstruction	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Nausea	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Oesophageal stenosis	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Pancreatitis	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Vomiting	1 (0 49%)	0 (0 00%)	1 (0 25%)
	General disorders and administration site conditions	Asthenia	1 (0 49%)	2 (1 00%)	3 (0 74%)
		Death	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Disease progression	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Fatigue	1 (0 49%)	0 (0 00%)	1 (0 25%)
		General physical health deterioration	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Oedema peripheral	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Pyrexia	3 (1 48%)	1 (0 50%)	4 (0 99%)
		Sudden death	1 (0 49%)	3 (1 49%)	4 (0 99%)
	Hepatobiliary disorders	Jaundice cholestatic	1 (0 49%)	0 (0 00%)	1 (0 25%)
	Infections and infestations	Bronchitis	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Infection	1 (0 49%)	1 (0 50%)	2 (0 49%)
		Perirectal abscess	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Pharyngitis	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Pneumonia	6 (2 96%)	4 (1 99%)	10 (2 47%)
		Pyopneumothorax	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Respiratory tract infection	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Sepsis	0 (0 00%)	3 (1 49%)	3 (0 74%)
		Urinary tract infection	0 (0 00%)	4 (1 99%)	4 (0 99%)
	Injury poisoning and procedural complications	Accidental overdose	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Femoral neck fracture	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Pneumothorax traumatic	1 (0 49%)	0 (0 00%)	1 (0 25%)
	Investigations	Blood creatinine increased	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Neutrophil count decreased	1 (0 49%)	0 (0 00%)	1 (0 25%)
	Metabolism and nutrition disorders	Diabetes mellitus	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Hypokalaemia	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Hyponatraemia	2 (0 98%)	0 (0 00%)	2 (0 49%)
		Malnutrition	0 (0 00%)	1 (0 50%)	1 (0 25%)
	Musculoskeletal and connective tissue disorders	Back pain	0 (0 00%)	1 (0 50%)	1 (0 25%)
	Neoplasms benign malignant and unspecified (incl cysts and polyps)	Lung carcinoma cell type unspecified recurrent	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Malignant neoplasm progression	0 (0 00%)	2 (1 00%)	2 (0 49%)
		Metastases to central nervous system	1 (0 49%)	0 (0 00%)	1 (0 25%)
	Nervous system disorders	Cerebrovascular accident	1 (0 49%)	1 (0 50%)	2 (0 49%)
		Syncope	0 (0 00%)	1 (0 50%)	1 (0 25%)
	Renal and urinary disorders	Acute kidney injury	1 (0 49%)	2 (1 00%)	3 (0 74%)
		Anuria	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Haematuria	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Nephropathy	0 (0 00%)	1 (0 50%)	1 (0 25%)
	Respiratory thoracic and mediastinal disorders	Renal failure	1 (0 49%)	1 (0 50%)	2 (0 49%)
		Dyspnoea	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Haemoptysis	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Pleural effusion	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Pneumothorax	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Pulmonary embolism	0 (0 00%)	2 (1 00%)	2 (0 49%)
	Vascular disorders	Haemorrhage	1 (0 49%)	0 (0 00%)	1 (0 25%)
		Peripheral embolism	0 (0 00%)	1 (0 50%)	1 (0 25%)
		Subjects(filtered)	41 (20 20%)	44 (21 89%)	405 (100 00%)
		1stColItemSubjects	203 (100 00%)	201 (100 00%)	(Denom=1stColTot)

Note: The atrial fibrillation cases day of onset was Day 2 (b) (6) and Day 6 (b) (6)

Note: The accidental overdose was reported as valium (b) (6)

Note: The day of onset of the pancreatitis case was Day 7 (b) (6). On (b) (6), the patient was hospitalized for administration of Cycle 1 chemotherapy. On (b) (6) she reported a stomach ache. An abdominal ultrasound and diagnostic gastroscopy with urease test were performed. Significant findings included low grade inflammation of gastric mucosa of pyloric area and a hiatal hernia on the gastroscopy. Serum amylase was 41 U/L (normal range up to 100 U/L). The patient was ultimately diagnosed with pancreatitis. (Source – Reviewers Table)

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

PNET 12-23

None of the subjects discontinued this study after drug administration due to an adverse event. Two subjects discontinued prior to first drug administration. In the crossover parts, three subjects

received only one oral dose of 300 mg netupitant and 0.5 g palonosetron (together with placebo infusion) due to premature discontinuation of the study prior to administration of the IV dose and placebo capsule. One subject (Subject No. (b) (6)) discontinued due to vasovagal syncope and dizziness which according to the narrative could have been attributed to insertion of the cannula. Infusion of the study drug was interrupted and restarted in two subjects (Subject No. (b) (6) and Subject No. (b) (6)) due to adverse events (swelling around the infusion site and strange sensation at infusion site). According to the narratives, the swelling was due to extravasation, and the sensation was mild, and interruption of the infusion resolved the event.

PALO 15-17

No patient withdrew from this study due to a TEAE.

NEPA 15-18

TEAEs leading to discontinuation from the study (the majority being not related to study drug) were reported for a total of 36 (8.9%) patients: 16 (7.9%) patients in the IV NEPA FDC group and 20 (10.0%) patients in the Oral NEPA FDC group. The most frequently reported TEAEs leading to discontinuation were disease progression (6 [3.0%] patients in each of the two treatment groups) and renal failure (3 [1.5%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group). Two patients (1.0%) in the Oral NEPA FDC group had TEAEs leading to discontinuation from the study that were serious not-related TEAEs leading to death (sudden death). Please see table below.

In all cases, the patients that developed renal failure did so after marked periods of time after drug exposure. Subject (b) (6) developed renal failure 21 days after drug exposure. Subject (b) (6) developed renal failure 29 days after drug exposure. Subject (b) (6) experienced renal failure 51 days after drug exposure. Finally, subject (b) (6) developed renal failure 8 days after drug exposure. It is unlikely, therefore, that the renal failure is attributable to the study drug. In addition, the applicant also included language in the draft labeling concerning slightly more patients having elevated creatinine levels IV NEPA FDC treatment group. This issue is addressed in section 8.5.2.

This Reviewer conducted further analyses (see Hy's Law plot in Section 8.5.2 of this review) which showed that none of the patients met Hy's Law criteria.

Table 53 – TEAEs Leading to Discontinuation by SOC and Preferred Term NEPA 15-18

MedDRA System Organ Class (SOC) MedDRA Preferred Term	IV NEPA FDC (N=203)		Oral NEPA FDC (N=201)		Overall (N=404)	
	n (%)	E	n (%)	E	n (%)	E
Number of patients with any TEAE leading to Discontinuation	16 (7.9)	17	20 (10.0)	20	36 (8.9)	37
Blood and lymphatic system disorders	1 (0.5)	1	1 (0.5)	1	2 (0.5)	2
Febrile neutropenia	1 (0.5)	1	0 (0.0)	0	1 (0.2)	1
Neutropenia	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Gastrointestinal disorders	0 (0.0)	0	2 (1.0)	2	2 (0.5)	2
Duodenal ulcer	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Ileus	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
General disorders and administration site conditions	7 (3.4)	7	8 (4.0)	8	15 (3.7)	15
Disease progression	6 (3.0)	6	6 (3.0)	6	12 (3.0)	12
Fatigue	1 (0.5)	1	0 (0.0)	0	1 (0.2)	1
Sudden death	0 (0.0)	0	2 (1.0)	2	2 (0.5)	2
Immune system disorders	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Hypersensitivity	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Infections and infestations	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Bronchitis	2 (1.0)	2	0 (0.0)	0	2 (0.5)	2
Perirectal abscess	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Sialoadenitis	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Investigations	3 (1.5)	4	0 (0.0)	0	3 (0.7)	4
Alanine aminotransferase increased	1 (0.5)	1	0 (0.0)	0	1 (0.2)	1
Aspartate aminotransferase increased	1 (0.5)	1	0 (0.0)	0	1 (0.2)	1
Blood creatinine increased	1 (0.5)	1	0 (0.0)	0	1 (0.2)	1
Hepatic enzyme increased	1 (0.5)	1	0 (0.0)	0	1 (0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0	3 (1.5)	3	3 (0.7)	3

MedDRA System Organ Class (SOC) MedDRA Preferred Term	IV NEPA FDC (N=203)		Oral NEPA FDC (N=201)		Overall (N=404)	
	n (%)	E	n (%)	E	n (%)	E
Lung carcinoma cell type unspecified recurrent	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Malignant neoplasm progression	0 (0.0)	0	2 (1.0)	2	2 (0.5)	2
Nervous system disorders	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Cerebrovascular accident	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Renal and urinary disorders	3 (1.5)	3	1 (0.5)	1	4 (1.0)	4
Renal failure	3 (1.5)	3	1 (0.5)	1	4 (1.0)	4
Vascular disorders	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1
Deep vein thrombosis	0 (0.0)	0	1 (0.5)	1	1 (0.2)	1

(Source – NEPA 15-18 Study Report Pages 1105-1106)

8.4.4. Significant Adverse Events

PNET 12-23

There were no serious or severe adverse events reported after drug administration. The safety evaluation after completion of the study showed a comparable safety profile after IV administration of pro-netupitant infusion solution at 2.6 mg/mL concentration and oral administration of netupitant 300 mg/palonosetron 0.5 mg. Most of the TEAEs observed belonged to the MedDRA system organ classes General disorders and administration site conditions, Nervous system disorders, and gastrointestinal disorders. The frequency of subjects with gastrointestinal disorders was higher with the oral formulation compared to the IV formulation (14.9% vs. 6.1%). The frequency of subjects presenting administration site reactions was only slightly higher with the IV formulation compared to the oral formulation (18.9% vs. 14.9%) due to vessel puncture site thrombosis at the contralateral arm observed in both groups. The most frequently reported TEAE after both administration routes was headache, which is a common and easy manageable event in clinical trials. The frequency of subjects with headache was higher with the oral formulation compared to the IV formulation (15.7% vs. 8.1%). Please refer to table below.

**Table 54 – TEAEs Reported by more than 1% of Subjects by SOC and Preferred Term
PNET 12-23**

MedDRA (Version 15.0) System Organ Class Preferred Term	19.5 mg N=8			32.5 mg N=8			65 mg N=8			130 mg N=10			S-195 mg N=10			P-195 mg N=18			S+P-195 mg N=28			F-234 mg N=19		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Subjects with at least 1 TEAE	5	62.5	6	3	37.5	4	1	12.5	1	3	30.0	8	3	30.0	7	4	22.2	5	7	25.0	12	7	36.8	17
Gastrointestinal disorders																								
Abdominal pain																								
Abdominal pain upper																								
Constipation																								
Nausea																								
General disorders and administration site conditions																								
Fatigue																								
Feeling hot																								
Infusion site thrombosis																								
Vessel puncture site thrombosis	1	12.5	1	1	12.5	1				1	10.0	1	1	10.0	1									
Infections and infestations																								
Nasopharyngitis																								
Musculoskeletal and connective tissue disorders																								
Muscle spasms																								
Nervous system disorders																								
Dizziness																								
Headache	1	12.5	1	1	12.5	1																		
Vascular disorders																								
Phlebosclerosis																								

MedDRA (Version 15.0) System Organ Class Preferred Term	S-260 mg N=10			P-260 mg N=20			S+P-260 mg N=30			F-286 mg N=18			325 mg N=10			390 mg N=9			Overall IV N=148			Overall Oral N=134			Total N=158		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Subjects with at least 1 TEAE	5	50.0	12	5	25.0	8	10	33.3	20	2	11.1	4	4	40.0	6	4	44.4	5	46	31.1	83	57	42.5	86	80	50.6	169
Gastrointestinal disorders																											
Abdominal pain																											
Abdominal pain upper																											
Constipation																											
Nausea																											
General disorders and administration site conditions																											
Fatigue																											
Feeling hot																											
Infusion site thrombosis	2	20.0	2	2	10.0	2	4	13.3	4	1	5.6	1	1	10.0	1	1	11.1	1	6	4.1	6	3	2.2	3	9	5.7	9
Vessel puncture site thrombosis	3	30.0	3	2	10.0	2	5	16.7	5										8	5.4	8	2	1.5	2	10	6.3	10
Infections and infestations																											
Nasopharyngitis																											
Musculoskeletal and connective tissue disorders																											
Muscle spasms																											
Nervous system disorders																											
Dizziness	2	20.0	3				2	6.7	3										3	2.0	4	5	3.7	5	8	5.1	9
Headache	1	10.0	2	1	5.0	1	2	6.7	3	1	5.6	1							12	8.1	14	21	15.7	26	28	17.7	40
Vascular disorders																											
Phlebosclerosis																											

(Source – Study Report PNET 12-23 Pages 156-157)

PALO 15-17

Severe TEAEs were reported for 16 (7.1%) patients in the infusion group and 18 (8.4%) patients in the bolus group. One patient (0.4%) in the infusion group experienced 2 severe TEAEs (atrial flutter [Grade 5] and dyspnea [Grade 4], discussed in Section 8.4.1) related to study drug. Please see table below. Please see Section 8.5.1 for a further discussion of the cardiac disorders in the infusion arm.

Table 55 – Severe TEAE by SOC and Dictionary Derived Term PALO 15-17

Severe TEAE Char	Analysis Primary System Organ Class	Dictionary Derived Term	PALONOSETRON 0.25 MG IV BOLUS	PALONOSETRON 0.25 MG IV INFUSION	Subjects(filtered)
Y	Blood and lymphatic system disorders	Anaemia	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Leukopenia	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Neutropenia	8 (3.72%)	5 (2.22%)	13 (2.95%)
		Thrombocytopenia	0 (0.00%)	2 (0.89%)	2 (0.45%)
	Cardiac disorders	Arrhythmia supraventricular	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Atrial fibrillation	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Atrial flutter	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Cardiac arrest	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Cardio-respiratory arrest	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Gastrointestinal disorders	Diarrhoea	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Mesenteric vein thrombosis	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Vomiting	1 (0.47%)	0 (0.00%)	1 (0.23%)
	General disorders and administration site conditions	Death	2 (0.93%)	0 (0.00%)	2 (0.45%)
		Disease progression	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Infections and infestations	Pneumonia	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Sepsis	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Investigations	Alanine aminotransferase increased	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Blood creatinine increased	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Blood urea increased	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Creatinine renal clearance decreased	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Monocyte count decreased	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Metabolism and nutrition disorders	Dehydration	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Hyperglycaemia	2 (0.93%)	0 (0.00%)	2 (0.45%)
		Hypokalaemia	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Hyponatraemia	0 (0.00%)	2 (0.89%)	2 (0.45%)
	Musculoskeletal and connective tissue disorders	Pain in extremity	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Nervous system disorders	Syncope	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Renal and urinary disorders	Renal failure	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Respiratory, thoracic and mediastinal disorders	Dyspnoea	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Hypoxia	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Pulmonary embolism	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Respiratory failure	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Skin and subcutaneous tissue disorders	Angioedema	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Vascular disorders	Hypertension	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Hypotension	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Peripheral circulatory failure	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Subjects(filtered)	18 (8.37%)	16 (7.11%)	441 (100.00%)
		1stCol temSubjects	215 (100.00%)	225 (100.00%)	(Denom=1stColTot)

(Source – Reviewers Table)

NEPA 15-18

Severe TEAEs were reported for 86 (42.4%) patients in the IV NEPA FDC group and 90 (44.8%) patients in the Oral NEPA FDC group. For IV NEPA FDC, 2 patients (1.0%) experienced 9 severe TEAEs related to study drug and 3 patients (1.5%) experienced 4 severe TEAEs related to dexamethasone. For Oral NEPA FDC, 3 patients (1.5%) experienced 5 severe TEAEs related to study drug and 6 patients (3.0%) experienced 12 severe TEAEs related to dexamethasone. Please see table below.

Table 56 – Severe TEAE by SOC and Dictionary Derived Term NEPA 15-18

Severe TEAE Char	Analysis Primary System Organ Class	Dictionary Derived Term	IV PRO-NETUPITANT / PALONOSETRON 5.2 mg/mL / 5 ug/mL	ORAL NETUPITANT / PALONOSETRON 300 mg / 0.50 mg	Subjects(filtered)
Y	Blood and lymphatic system disorders	Agranulocytosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Anaemia	5 (2.46%)	8 (3.98%)	13 (3.21%)
		Febrile neutropenia	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Granulocytopenia	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Leukocytosis	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Leukopenia	6 (2.96%)	7 (3.48%)	13 (3.21%)
		Neutropenia	37 (18.23%)	37 (18.41%)	74 (18.27%)
		Pancytopenia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Thrombocytopenia	1 (0.49%)	7 (3.48%)	8 (1.98%)
	Cardiac disorders	Cardiac failure	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Ear and labyrinth disorders	Deafness	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Gastrointestinal disorders	Constipation	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Duodenal ulcer	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Gastric haemorrhage	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Gastric ulcer haemorrhage	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Gastritis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Gastrointestinal haemorrhage	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Ileus	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Intestinal obstruction	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Mouth ulceration	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Nausea	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Oesophageal stenosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Stomatitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Vomiting	1 (0.49%)	1 (0.50%)	2 (0.49%)
	General disorders and administration site conditions	Asthenia	2 (0.99%)	2 (1.00%)	4 (0.99%)
		Death	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Disease progression	2 (0.99%)	3 (1.49%)	5 (1.23%)
		Fatigue	3 (1.48%)	2 (1.00%)	5 (1.23%)
		General physical health deterioration	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Oedema peripheral	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pain	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Sudden death	1 (0.49%)	3 (1.49%)	4 (0.99%)
	Hepatobiliary disorders	Hepatic failure	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hepatic lesion	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Jaundice cholestatic	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Infections and infestations	Bronchitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Infection	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Oral infection	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Perirectal abscess	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pneumonia	2 (0.99%)	3 (1.49%)	5 (1.23%)
		Pyopneumothorax	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Respiratory tract infection	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Sepsis	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Urinary tract infection	1 (0.49%)	1 (0.50%)	2 (0.49%)
	Injury poisoning and procedural complications	Accidental overdose	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Femoral neck fracture	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pneumothorax traumatic	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Investigations	Alanine aminotransferase increased	2 (0.99%)	14 (6.97%)	16 (3.95%)
		Aspartate aminotransferase increased	3 (1.48%)	5 (2.49%)	8 (1.98%)
		Blood creatinine increased	3 (1.48%)	0 (0.00%)	3 (0.74%)
		Blood urea increased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Creatinine renal clearance decreased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Lymphocyte count decreased	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Neutrophil count decreased	3 (1.48%)	3 (1.49%)	6 (1.48%)
		Neutrophil count increased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		White blood cell count decreased	1 (0.49%)	1 (0.50%)	2 (0.49%)
	Metabolism and nutrition disorders	Dehydration	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Hyperglycaemia	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Hyperkalaemia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hypocalcaemia	1 (0.49%)	3 (1.49%)	4 (0.99%)
		Hypokalaemia	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Hyponatraemia	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Malnutrition	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Musculoskeletal and connective tissue disorders	Back pain	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Neoplasms benign malignant and unspecified (incl cysts and polyps)	Malignant neoplasm progression	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Metastases to central nervous system	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Nervous system disorders	Cerebrovascular accident	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Syncope	1 (0.49%)	1 (0.50%)	2 (0.49%)
	Renal and urinary disorders	Acute kidney injury	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Lower urinary tract symptoms	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Nephropathy	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Renal failure	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Renal injury	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Respiratory, thoracic and mediastinal disorders	Dyspnoea	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Haemoptysis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Pulmonary embolism	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Respiratory distress	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Vascular disorders	Deep vein thrombosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Haemorrhage	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hypertension	3 (1.48%)	0 (0.00%)	3 (0.74%)
		Hypotension	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Peripheral embolism	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Vasculitis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Subjects(filtered)	86 (42.36%)	90 (44.78%)	405 (100.00%)
		1stColItemSubjects	203 (100.00%)	201 (100.00%)	(Denom=1stColTot)

Note: The deafness case day of onset was Day 29.

Note: The hepatic failure case day of onset was Day 22

Note: For the hypertension cases, day of onset was Day 2 (Subject (b) (6)), Day 22 (Subject (b) (6)) and Day 23 (Subject (b) (6)). Although there were 3 cases of severe hypertension AE's in the IV arm, the day of onset for 2 of the 3 cases was considerably later (Days 22 and 23) suggesting that

these are not related. In addition, it should be noted that the overall hypertension AE's (regardless of severity) were reported at a higher rate in the oral arm than the IV arm (see Section 8.4.5)

Note: There appeared to be an imbalance in transaminase elevations in the oral Akynzeo arm vs. the IV Akynzeo arm. However, this Reviewer conducted further analyses (see Hy's Law plot in Section 8.5.2 of this review) which showed that none of the patients met Hy's Law criteria.
(Source-Reviewers Table)

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

PNET 12-23

The most frequently reported TEAEs assessed as drug-related by the Investigator and DSMB were headache, constipation, infusion site thrombosis, abdominal pain upper, fatigue, dizziness, and nausea. The number of drug-related TEAEs or frequency of subjects with drug-related TEAEs did not increase with ascending pro-netupitant doses.

It is plausible that the route of administration, together with the presence of palonosetron in the oral FDC formulation, could have played a role in the development of the observed events after administration of the new IV formulation and the approved oral formulation; i.e., more gastrointestinal disorders were observed after oral administration and more administration site reactions were observed after IV administration. In fact, gastrointestinal adverse events as constipation, abdominal pain upper and nausea occurred more frequently following the administration of oral netupitant 300 mg/palonosetron 0.5 mg compared to IV pro-netupitant, while infusion site thrombosis, fatigue and dizziness occurred more frequently with IV pro-netupitant administration. The most frequently reported TEAE after the active drug administration following both routes was headache. The frequency of headache was lower after IV administration (8.1% of IV treated subjects) compared to oral administration (12.7% of oral treated subjects).

The local safety and tolerability profile of pro-netupitant was very good throughout all dose groups, as confirmed by thorough vascular surveillance by Doppler ultrasound examinations as well as by specific laboratory parameters. There was a total of about 283 IV infusions during the study, being applied via indwelling cannulas and there has been the same number of indwelling cannulas inserted at the contralateral site for blood drawing reasons. Altogether, a total of 38 thrombotic events have been observed. These TEAEs were reported as 28 events detected at the blood drawing sites and 10 events detected on the infusion arm, respectively. This pattern strongly suggests an underlying mechanical rather than a chemical cause. The numerical difference of AEs by almost a factor of 3 between both insertion sites may be explained by the difference in the time of presence of the cannulas inside the vein; in fact, infusion site catheters were generally withdrawn shortly after the end of the 30-minute infusion, whereas the blood drawing cannulas were generally removed after 12 hours. The different length of time of device permanence supports the mechanical origin of the observed events.

No drug-related infusion site thrombosis events were observed after IV pro netupitant administration at doses of 19.5 mg, 32.5 mg, 65 mg and 130 mg pro-netupitant, nor at the two highest dose levels tested (325 mg and 390 mg pronetupitant). Few drug-related infusion site

thrombosis cases were reported at the intermediate IV pro-netupitant dose levels 195 mg (1 out of 28 treated subjects, 3.6%), 234 mg (2 out of 19 treated subjects, 10.5%), 260 mg (4 out of 30 treated subjects, 13.3%) and 286 mg (1 out of 18 treated subjects, 5.6%). These data, together with the absence of thrombosis adverse events at 325 mg and 390 mg IV-pro-netupitant as well as considering the other local tolerability assessments, allows concluding on the good local tolerability of the IMP. Please refer to table below.

Table 57 – Drug Related TEAEs Reported by more than 1% of Subjects by SOC and Preferred Term PNET 12-23

MedDRA (Version 15.0) System Organ Class Preferred Term	19.5 mg N=8			32.5 mg N=8			65 mg N=8			130 mg N=10			S-195 mg N=10			P-195 mg N=18			S+P-195 mg N=28			F-234 mg N=19								
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E			
Subjects with at least 1 TEAE	2	25.0	2	3	37.5	3	1	12.5	1	2	20.0	7	3	30.0	5	3	16.7	3	6	21.4	8	6	31.6	13						
Gastrointestinal disorders																														
Abdominal pain																														
Abdominal pain upper													2	20.0	2				2	7.1	2				2	10.5	2			
Constipation																														
Nausea										1	10.0	1													1	5.3	1			
General disorders and administration site conditions																														
Fatigue							2	25.0	2	1	12.5	1	1	10.0	1	1	10.0	1				1	3.6	1	1	5.3	1	1	5.3	1
Infusion site thrombosis																1	5.6	1	1	3.6	1	1	3.6	1	2	10.5	2			
Nervous system disorders																														
Dizziness																												1	5.3	1
Headache	1	12.5	1	1	12.5	1										2	20.0	2	1	5.6	1	3	10.7	3	4	21.1	5	1	5.3	1
	S-260 mg N=10			P-260 mg N=20			S+P-260 mg N=30			286 mg* N=18			325 mg N=10			390 mg N=9			Overall IV N=148			Overall Oral N=134			Total N=158					
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Subjects with at least 1 TEAE	4	40.0	8	5	25.0	6	9	30.0	14	2	11.1	3	1	10.0	1	2	22.2	3	3	34	23.0	55	37	27.6	53	59	37.3	108		
Gastrointestinal disorders																														
Abdominal pain																						2	1.5	2	2	1.5	2	2	1.3	2
Abdominal pain upper													1	10.0	1				3	2.0	3	5	3.7	6	7	4.4	9			
Constipation																			2	1.4	2	10	7.5	10	12	7.6	12			
Nausea																			2	1.4	2	4	3.0	4	4	2.5	6			
General disorders and administration site conditions																														
Fatigue																			6	4.1	6	3	2.2	3	9	5.7	9			
Infusion site thrombosis	2	20.0	2	2	10.0	2	4	13.3	4	1	5.6	1							8	5.4	8	2	1.5	2	10	6.3	10			
Nervous system disorders																														
Dizziness	2	20.0	3				2	6.7	3										3	2.0	4	3	2.2	3	6	3.8	7			
Headache	1	10.0	1	1	5.0	1	2	6.7	2	1	5.6	1							12	8.1	13	17	12.7	20	25	15.8	33			

(Source – Study Report PNET 12-23 Pages 158-159)

PALO 15-17

In general, TEAEs were distributed evenly between the treatment groups. The most frequent TEAE affecting study patients throughout the study was neutropenia reported in 119 (29.5%) patients (61 [30.0%] patients in the IV NEPA FDC group and 58 [28.9%] patients in the Oral NEPA FDC group). The second most frequent TEAE was anemia reported in 71 (17.6%) patients (33 [16.3%] patients in the IV NEPA FDC group and 38 [18.9%] patients in the Oral NEPA FDC group). Other frequently reported TEAEs included alopecia (32 [15.8%] patients in the IV NEPA FDC group and 29 [14.4%] patients in the Oral NEPA FDC group), constipation (21 [10.3%] patients in the IV NEPA FDC group and 26 [12.9%] patients in the Oral NEPA FDC group), and leukopenia (21 [10.3%] patients in the IV NEPA FDC group and 22 [10.9%] patients in the Oral NEPA FDC group).

The frequency of TEAEs potentially referred to local tolerability was small and reported also for the Oral treatment group (where the placebo infusion was administered); these TEAEs included: injection site extravasation (1 [0.5%] patient in the IV NEPA FDC group [verbatim term: lesion on the skin of the left forearm, probably after extravasation of last dose chemotherapy] and 0

patients in the Oral NEPA FDC group); infusion site extravasation (0 patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group [verbatim term: erythema on left arm after extravasation of drug]); and injection site reaction (0 patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group [verbatim term: 2 episodes of cutaneous reaction in the place of injection]).

In addition, the frequency was small and very similar between the two treatment groups for phlebitis (2 [1.0%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group), phlebitis superficial (0 patients in the IV NEPA FDC group and 2 [1.0%] patients in the Oral NEPA FDC group), thrombophlebitis (1 [0.5%] patient in each treatment group), and thrombophlebitis superficial (2 [1.0%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group). Please refer to table below.

Table 58 – TEAEs by SOC and Dictionary Derived Term – PALO 15-17

Treatment Emergent AE Flag	Analysis Primary System Organ Class	Dictionary Derived Term	PALONOSETRON 0 25 MG IV BOLUS	PALONOSETRON 0 25 MG IV NFUSION	Subjects(filtered)
Y	Blood and lymphatic system disorders	Anaemia	2 (0.93%)	2 (0.89%)	4 (0.91%)
		Granulocytopenia	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Leukopenia	5 (2.33%)	3 (1.33%)	8 (1.81%)
		Lymphopenia	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Neutropenia	11 (5.12%)	8 (3.56%)	19 (4.31%)
		Neutrophilia	2 (0.93%)	1 (0.44%)	3 (0.68%)
		Pancytopenia	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Thrombocytopenia	2 (0.93%)	4 (1.78%)	6 (1.36%)
	Cardiac disorders	Arrhythmia supraventricular	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Atrial fibrillation	0 (0.00%)	3 (1.33%)	3 (0.68%)
		Atrial flutter	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Atrial tachycardia	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Bundle branch block right	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Cardiac arrest	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Cardio-respiratory arrest	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Palpitations	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Sinus tachycardia	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Tachycardia	0 (0.00%)	3 (1.33%)	3 (0.68%)
	Gastrointestinal disorders	Abdominal pain	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Abdominal pain lower	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Abdominal pain upper	2 (0.93%)	1 (0.44%)	3 (0.68%)
		Breath odour	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Chronic gastritis	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Constipation	3 (1.40%)	7 (3.11%)	10 (2.27%)
		Diarrhoea	6 (2.79%)	11 (4.89%)	17 (3.85%)
		Duodenal ulcer	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Duodenitis	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Dyspepsia	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Gastroesophageal reflux disease	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Mesenteric vein thrombosis	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Nausea	5 (2.33%)	5 (2.22%)	10 (2.27%)
		Retching	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Salivary hypersecretion	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Stomatitis	2 (0.93%)	1 (0.44%)	3 (0.68%)
		Vomiting	2 (0.93%)	3 (1.33%)	5 (1.13%)
	General disorders and administration site conditions	Asthenia	11 (5.12%)	6 (2.67%)	17 (3.85%)
		Chest pain	1 (0.47%)	1 (0.44%)	2 (0.45%)
		Death	2 (0.93%)	0 (0.00%)	2 (0.45%)
		Disease progression	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Fatigue	3 (1.40%)	1 (0.44%)	4 (0.91%)
		Hyperthermia	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Malaise	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Mucosal inflammation	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Oedema peripheral	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Pain	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Pyrexia	0 (0.00%)	3 (1.33%)	3 (0.68%)

Hepatobiliary disorders	Hepatocellular injury	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Hyperbilirubinaemia	0 (0.00%)	1 (0.44%)	1 (0.23%)
Immune system disorders	Drug hypersensitivity	0 (0.00%)	1 (0.44%)	1 (0.23%)
Infections and infestations	Bronchitis	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Fungal infection	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Nasopharyngitis	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Pneumonia	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Respiratory tract infection	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Sepsis	1 (0.47%)	0 (0.00%)	1 (0.23%)
Injury poisoning and procedural complications	Brain contusion	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Radiation skin injury	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Subdural haematoma	0 (0.00%)	1 (0.44%)	1 (0.23%)
Investigations	Alanine aminotransferase increased	4 (1.86%)	1 (0.44%)	5 (1.13%)
	Aspartate aminotransferase increased	3 (1.40%)	0 (0.00%)	3 (0.68%)
	Blood bilirubin increased	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Blood calcium decreased	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Blood chloride decreased	1 (0.47%)	2 (0.89%)	3 (0.68%)
	Blood creatine increased	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Blood creatine phosphokinase increased	2 (0.93%)	0 (0.00%)	2 (0.45%)
	Blood creatinine increased	6 (2.79%)	3 (1.33%)	9 (2.04%)
	Blood potassium decreased	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Blood urea increased	3 (1.40%)	5 (2.22%)	8 (1.81%)
	Breath sounds abnormal	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Creatinine renal clearance decreased	2 (0.93%)	0 (0.00%)	2 (0.45%)
	ECG signs of myocardial infarction	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Electrocardiogram QT prolonged	3 (1.40%)	0 (0.00%)	3 (0.68%)
	Gamma-glutamyltransferase increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Monocyte count decreased	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Neutrophil count increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Platelet count increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Transaminases increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Weight decreased	1 (0.47%)	1 (0.44%)	2 (0.45%)
	White blood cell count increased	0 (0.00%)	1 (0.44%)	1 (0.23%)
Metabolism and nutrition disorders	Decreased appetite	2 (0.93%)	3 (1.33%)	5 (1.13%)
	Dehydration	2 (0.93%)	2 (0.89%)	4 (0.91%)
	Diabetes mellitus	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Hyperglycaemia	2 (0.93%)	1 (0.44%)	3 (0.68%)
	Hyperkalaemia	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Hypocalcaemia	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Hypokalaemia	1 (0.47%)	2 (0.89%)	3 (0.68%)
	Hyponatremia	0 (0.00%)	2 (0.89%)	2 (0.45%)
Musculoskeletal and connective tissue disorders	Bone pain	0 (0.00%)	2 (0.89%)	2 (0.45%)
	Myalgia	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Pain in extremity	1 (0.47%)	0 (0.00%)	1 (0.23%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bone cancer metastatic	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Malignant neoplasm progression	0 (0.00%)	1 (0.44%)	1 (0.23%)
Nervous system disorders	Dizziness	3 (1.40%)	2 (0.89%)	5 (1.13%)
	Epilepsy	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Headache	4 (1.86%)	4 (1.78%)	8 (1.81%)
	Paraesthesia	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Somnolence	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Syncope	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Transient ischaemic attack	0 (0.00%)	1 (0.44%)	1 (0.23%)
Psychiatric disorders	Insomnia	1 (0.47%)	2 (0.89%)	3 (0.68%)
Renal and urinary disorders	Acute kidney injury	1 (0.47%)	2 (0.89%)	3 (0.68%)
	Chronic kidney disease	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Glycosuria	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Pollakiuria	2 (0.93%)	0 (0.00%)	2 (0.45%)
	Proteinuria	3 (1.40%)	2 (0.89%)	5 (1.13%)
	Renal failure	2 (0.93%)	3 (1.33%)	5 (1.13%)
	Renal impairment	3 (1.40%)	2 (0.89%)	5 (1.13%)
	Urinary retention	1 (0.47%)	0 (0.00%)	1 (0.23%)
Respiratory, thoracic and mediastinal disorders	Bronchitis chronic	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Cough	1 (0.47%)	2 (0.89%)	3 (0.68%)
	Dyspnoea	0 (0.00%)	3 (1.33%)	3 (0.68%)
	Epistaxis	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Hiccups	3 (1.40%)	6 (2.67%)	9 (2.04%)
	Hypoxia	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Productive cough	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Pulmonary embolism	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Respiratory failure	1 (0.47%)	1 (0.44%)	2 (0.45%)
Skin and subcutaneous tissue disorders	Alopecia	8 (3.72%)	5 (2.22%)	13 (2.95%)
	Angioedema	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Dermatitis	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Dermatitis allergic	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Erythema	0 (0.00%)	1 (0.44%)	1 (0.23%)
Vascular disorders	Deep vein thrombosis	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Hypertension	2 (0.93%)	8 (3.56%)	10 (2.27%)
	Hypertensive crisis	3 (1.40%)	1 (0.44%)	4 (0.91%)
	Hypotension	1 (0.47%)	4 (1.78%)	5 (1.13%)
	Peripheral circulatory failure	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Phlebitis deep	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Superior vena cava syndrome	1 (0.47%)	0 (0.00%)	1 (0.23%)
	Subjects(filtered)	77 (35.81%)	85 (37.78%)	441 (100.00%)
	1stColItemSubjects	215 (100.00%)	225 (100.00%)	(Denom=1stColTot)

Note:

Atrial arrhythmias: For a discussion of cardiac TEAEs in Study PALO-15-17, see Section 8.5.1 – Cardiac TEAEs.
Hypertension: See day of onset below. All cases were deemed by the investigator as not related to either the study drug or dexamethasone except for one case (Day 3 in Subject (b) (6) – deemed possibly related to

dexamethasone). In the bolus arm, none of the events were Grade 3; in the infusion arm, two events were Grade 3 (Day 2 in Subject (b) (6) and Day 2 in Subject (b) (6)).

IV Bolus Arm (2 cases): Day of onset was Day 8 (Subject (b) (6)) and Day 3 (Subject (b) (6)).

IV Infusion Arm (8 cases): Day of onset was Day 3 (Subject (b) (6)), Day 6 (Subject (b) (6)), Days 1 and 2 (Subject (b) (6)), Day 8 (Subject (b) (6)), Day 6 (Subject (b) (6)), Days 11, 13, and 19 (Subject (b) (4)), Day 2 (Subject (b) (6)) and Days 2 and 3 (Subject (b) (6)).

Hypertensive Crisis: See day of onset below. All cases were deemed by the investigator as not related to the study drug, but either definitely or possibly related to dexamethasone. None of the events were Grade 3 in severity.

IV Bolus Arm (3 cases): Day of onset was Day 1 (Subject (b) (6)), Day 1 (Subject (b) (6)) and Day 2 (Subject (b) (6)).

IV Infusion Arm (1 case): Day of onset was Day 1 (Subject (b) (6)).

(Source – Reviewers Table and Section 16.2.7 Adverse Event Listings of the CSR for Study PALO-15-17)

Study-drug-related TEAEs were reported for a total of 8 (3.6%) patients (14 events) in the infusion group and 3 (1.4%) patients (4 events) in the bolus group. One patient in the infusion group experienced 2 severe TEAEs classified as possibly related to study drug (atrial flutter Grade 5] and dyspnea [Grade 4], please see sections 8.4.1 and 8.5.1 for further discussions of the cardiac disorders in the infusion arm). Please refer to table below.

Table 59 – Study Drug Related TEAEs – PALO 15-17

Drug related TEAE Char	Analysis Primary System Organ Class	Dictionary Derived Term	PALONOSETRON 0.25 MG IV BOLUS	PALONOSETRON 0.25 MG IV INFUSION	Subjects(filtered)
Y	Cardiac disorders	Atrial flutter	0 (0.00%)	2 (0.89%)	2 (0.45%)
		Bundle branch block right	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Palpitations	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Tachycardia	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Gastrointestinal disorders	Constipation	2 (0.93%)	5 (2.22%)	7 (1.59%)
	General disorders and administration site conditions	Chest pain	1 (0.47%)	0 (0.00%)	1 (0.23%)
		Malaise	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Respiratory, thoracic and mediastinal disorders	Dyspnoea	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Hiccups	0 (0.00%)	1 (0.44%)	1 (0.23%)
		Subjects(filtered)	3 (1.40%)	8 (3.56%)	441 (100.00%)
		1stColItemSubjects	215 (100.00%)	225 (100.00%)	(Denom=1stColTot)

(Source – Reviewers Table)

Overall, Grade 3 or 4 TEAEs were distributed evenly between the two treatment groups, with Grade 3 TEAEs experienced by 8 (3.6%) patients in the infusion group and 9 (4.2%) patients in the bolus group, and Grade 4 TEAEs experienced by 2 (0.9%) patients in the infusion group and 2 (0.9%) patients in the bolus group.

No Grade 3 or 4 TEAEs of nausea were reported for any patient during this study. One Grade 4 TEAE of vomiting was reported for 1 [0.5%] patient in the bolus group. Please see table below.

Table 60 – TEAES of CTCAE Grade 3 or 4 – PALO 15-17

Palonosetron 0.25 mg IV MedDRA System Organ Class MedDRA Preferred Term	30-min Infusion		30-sec Bolus	
	N = 225		N = 215	
	n (%)		n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any TEAE	8 (3.6)	2 (0.9)	9 (4.2)	2 (0.9)
Blood and lymphatic system disorders	4 (1.8)	3 (1.3)	6 (2.8)	2 (0.9)
Anaemia	1 (0.4)	0	0	0
Leukopenia	0	1 (0.4)	1 (0.5)	0
Neutropenia	2 (0.9)	3 (1.3)	6 (2.8)	2 (0.9)
Thrombocytopenia	1 (0.4)	1 (0.4)	0	0
Cardiac disorders	3 (1.3)	0	0	0
Arrhythmia supraventricular	1 (0.4)	0	0	0
Atrial fibrillation	2 (0.9)	0	0	0
Cardiac arrest	0	1 (0.4)	0	0
Gastrointestinal disorders	0	0	0	1 (0.5)
Vomiting	0	0	0	1 (0.5)
Investigations	1 (0.4)	0	2 (0.9)	0
Alanine aminotransferase increased	0	0	1 (0.5)	0
Blood creatinine increased	1 (0.4)	0	1 (0.5)	0
Blood urea increased	1 (0.4)	0	1 (0.5)	0
Creatinine renal clearance decreased	0	0	1 (0.5)	0
Monocyte count decreased	0	0	1 (0.5)	0
Metabolism and nutrition disorders	2 (0.9)	1 (0.4)	4 (1.9)	0
Dehydration	1 (0.4)	0	1 (0.5)	0
Hyperglycaemia	0	0	2 (0.9)	0
Hypokalaemia	0	1 (0.4)	1 (0.5)	0
Hyponatraemia	2 (0.9)	0	0	0

Note: For a discussion of cardiac disorders, see Section 8.5.1.
(Source – Study Report PALO 15-17 pages 105-106)

NEPA 15-18

In general, TEAEs were distributed evenly between the treatment groups. The most frequent TEAE affecting study patients throughout the study was neutropenia reported in 119 (29.5%) patients (61 [30.0%] patients in the IV NEPA FDC group and 58 [28.9%] patients in the Oral NEPA FDC group). The second most frequent TEAE was anemia reported in 71 (17.6%) patients (33 [16.3%] patients in the IV NEPA FDC group and 38 [18.9%] patients in the Oral NEPA FDC group). Other frequently reported TEAEs included alopecia (32 [15.8%] patients in the IV NEPA FDC group and 29 [14.4%] patients in the Oral NEPA FDC group), constipation (21 [10.3%] patients in the IV NEPA FDC group and 26 [12.9%] patients in the Oral NEPA

FDC group), and leukopenia (21 [10.3%] patients in the IV NEPA FDC group and 22 [10.9%] patients in the Oral NEPA FDC group).

The frequency of TEAEs potentially referred to local tolerability was small and reported also for the Oral treatment group (where the placebo infusion was administered); these TEAEs included: injection site extravasation (1 [0.5%] patient in the IV NEPA FDC group [verbatim term: lesion on the skin of the left forearm, probably after extravasation of last dose chemotherapy] and 0 patients in the Oral NEPA FDC group); infusion site extravasation (0 patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group [verbatim term: erythema on left arm after extravasation of drug]); and injection site reaction (0 patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group [verbatim term: 2 episodes of cutaneous reaction in the place of injection]).

In addition, the frequency was small and very similar between the two treatment groups for phlebitis (2 [1.0%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group), phlebitis superficial (0 patients in the IV NEPA FDC group and 2 [1.0%] patients in the Oral NEPA FDC group), thrombophlebitis (1 [0.5%] patient in each treatment group), and thrombophlebitis superficial (2 [1.0%] patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group). None of these TEAEs were considered by the Investigator as related to treatment with study drug or dexamethasone. Please see table below.

Table 61 – TEAEs by SOC and Dictionary Derived Term - NEPA 15-18

Treatment Emergent Analysis Flag	Analysis Primary System Organ Class	Dictionary Derived Term	IV PRO- NETUPITANT / PALONOSETRON 5.2 mg/mL / 5 ug/mL	ORAL NETUPITANT / PALONOSETRON 300 mg / 0.50 mg	Subjects(filtered)
Y	Blood and lymphatic system disorders	Agranulocytosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Anaemia	33 (16.26%)	38 (18.91%)	71 (17.53%)
		Febrile neutropenia	4 (1.97%)	1 (0.50%)	5 (1.23%)
		Granulocytopenia	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Leukocytosis	2 (0.99%)	3 (1.49%)	5 (1.23%)
		Leukopenia	21 (10.34%)	22 (10.95%)	43 (10.62%)
		Lymphopenia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Neutropenia	61 (30.05%)	58 (28.86%)	119 (29.38%)
		Neutrophilia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pancytopenia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Thrombocytopenia	8 (3.94%)	11 (5.47%)	19 (4.69%)
		Thrombocytosis	4 (1.97%)	3 (1.49%)	7 (1.73%)
	Cardiac disorders	Atrial fibrillation	3 (1.48%)	2 (1.00%)	5 (1.23%)
		Atrioventricular block	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Bradycardia	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Cardiac failure	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Extrasystoles	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Palpitations	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Sinus bradycardia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Sinus tachycardia	4 (1.97%)	2 (1.00%)	6 (1.48%)
		Tachycardia	1 (0.49%)	4 (1.99%)	5 (1.23%)
		Ventricular tachyarrhythmia	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Ear and labyrinth disorders	Deafness	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Hearing impaired	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Vertigo	5 (2.46%)	2 (1.00%)	7 (1.73%)
	Endocrine disorders	Adrenal insufficiency	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Eye disorders	Diplopia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Vision blurred	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Visual impairment	1 (0.49%)	1 (0.50%)	2 (0.49%)
	Gastrointestinal disorders	Abdominal distension	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Abdominal pain	3 (1.48%)	7 (3.48%)	10 (2.47%)
		Abdominal pain upper	7 (3.45%)	7 (3.48%)	14 (3.46%)
		Aphthous stomatitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Colitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Constipation	21 (10.34%)	26 (12.94%)	47 (11.60%)
		Diarrhoea	8 (3.94%)	10 (4.98%)	18 (4.44%)
		Duodenal ulcer	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Duodenogastric reflux	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Dyspepsia	3 (1.48%)	2 (1.00%)	5 (1.23%)
		Epi-gastric discomfort	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Flatulence	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Gastric haemorrhage	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Gastric ulcer haemorrhage	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Gastritis	1 (0.49%)	3 (1.49%)	4 (0.99%)
		Gastrointestinal haemorrhage	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Gastroesophageal reflux disease	5 (2.46%)	0 (0.00%)	5 (1.23%)
		Haematochezia	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Haemorrhoids	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Ileus	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Intestinal obstruction	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Mouth ulceration	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Nausea	20 (9.85%)	14 (6.97%)	34 (8.40%)
		Oesophageal stenosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pancreatitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Rectal haemorrhage	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Retching	1 (0.49%)	4 (1.99%)	5 (1.23%)
		Stomatitis	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Vomiting	5 (2.46%)	3 (1.49%)	8 (1.98%)
	General disorders and administration site conditions	Asthenia	13 (6.40%)	17 (8.46%)	30 (7.41%)
		Chest discomfort	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Chest pain	3 (1.48%)	0 (0.00%)	3 (0.74%)
		Chills	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Condition aggravated	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Death	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Disease progression	6 (2.96%)	7 (3.48%)	13 (3.21%)
		Drug intolerance	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Fatigue	18 (8.87%)	17 (8.46%)	35 (8.64%)
		General physical health deterioration	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hyperthermia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Infusion site extravasation	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Injection site extravasation	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Injection site reaction	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Mucosal inflammation	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Oedema	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Oedema peripheral	2 (0.99%)	6 (2.99%)	8 (1.98%)
		Pain	3 (1.48%)	2 (1.00%)	5 (1.23%)
		Pyrexia	8 (3.94%)	9 (4.48%)	17 (4.20%)
		Sudden death	1 (0.49%)	3 (1.49%)	4 (0.99%)
	Hepatobiliary disorders	Hepatic cyst	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hepatic failure	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hepatic function abnormal	2 (0.99%)	4 (1.99%)	6 (1.48%)
		Hepatic lesion	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Jaundice cholestatic	1 (0.49%)	0 (0.00%)	1 (0.25%)

	Immune system disorders	Hypersensitivity	0 (0.00%)	2 (1.00%)	2 (0.49%)
	Infections and infestations	Bronchitis	4 (1.97%)	3 (1.49%)	7 (1.73%)
		Conjunctivitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Cystitis	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Folliculitis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Herpes zoster	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Infection	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Influenza	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Nasopharyngitis	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Oral candidiasis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Oral infection	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Perirectal abscess	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pharyngitis	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Pneumonia	6 (2.96%)	7 (3.48%)	13 (3.21%)
		Pyopneumothorax	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Respiratory tract infection	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Respiratory tract infection viral	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Sepsis	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Sialoadenitis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Sinusitis	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Subperiosteal abscess	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Tonsillitis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Tooth abscess	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Upper respiratory tract infection	4 (1.97%)	0 (0.00%)	4 (0.99%)
		Urinary tract infection	4 (1.97%)	5 (2.49%)	9 (2.22%)
		Viral upper respiratory tract infection	2 (0.99%)	0 (0.00%)	2 (0.49%)
	Injury, poisoning and procedural complications	Accidental overdose	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Contrast media reaction	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Fall	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Femoral neck fracture	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Laceration	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Ligament sprain	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pneumothorax traumatic	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Procedural pain	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Superficial injury of eye	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Upper limb fracture	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Wound secretion	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Investigations	Alanine aminotransferase increased	15 (7.39%)	24 (11.94%)	39 (9.63%)
		Amylase increased	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Aspartate aminotransferase increased	12 (5.91%)	19 (9.45%)	31 (7.65%)
		Blood alkaline phosphatase increased	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Blood bilirubin increased	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Blood calcium decreased	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Blood creatine increased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Blood creatinine increased	12 (5.91%)	6 (2.99%)	18 (4.44%)
		Blood magnesium decreased	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Blood potassium increased	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Blood urea increased	4 (1.97%)	1 (0.50%)	5 (1.23%)
		Blood urine present	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Computerised tomogram abnormal	0 (0.00%)	1 (0.50%)	1 (0.25%)
		C-reactive protein increased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Creatinine renal clearance decreased	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Electrocardiogram change	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Electrocardiogram QT prolonged	3 (1.48%)	2 (1.00%)	5 (1.23%)
		Electrocardiogram ST segment depression	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Glomerular filtration rate decreased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Glucose urine	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Haemoglobin decreased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hepatic enzyme increased	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Lymphocyte count decreased	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Neutrophil count decreased	4 (1.97%)	4 (1.99%)	8 (1.98%)
		Neutrophil count increased	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Platelet count decreased	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Platelet count increased	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Protein urine present	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Weight decreased	9 (4.43%)	4 (1.99%)	13 (3.21%)
		Weight increased	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Metabolism and nutrition disorders	White blood cell count decreased	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Decreased appetite	7 (3.45%)	11 (5.47%)	18 (4.44%)
		Dehydration	2 (0.99%)	4 (1.99%)	6 (1.48%)
		Diabetes mellitus	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Glucose tolerance impaired	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Hyperglycaemia	3 (1.48%)	2 (1.00%)	5 (1.23%)
		Hyperkalaemia	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Hyperphosphataemia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hyperuricaemia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hypoabuminaemia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hypocalcaemia	2 (0.99%)	4 (1.99%)	6 (1.48%)
		Hypokalaemia	0 (0.00%)	5 (2.49%)	5 (1.23%)
		Hypomagnesaemia	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Hyponatraemia	5 (2.46%)	4 (1.99%)	9 (2.22%)
		Hypovolaemia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Malnutrition	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Type 2 diabetes melitus	1 (0.49%)	0 (0.00%)	1 (0.25%)

	Musculoskeletal and connective tissue disorders	Arthralgia	2 (0.99%)	4 (1.99%)	6 (1.48%)
		Back pain	3 (1.48%)	4 (1.99%)	7 (1.73%)
		Bone pain	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Musculoskeletal chest pain	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Musculoskeletal pain	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Myalgia	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Neck pain	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Osteosclerosis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Pain in extremity	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Spinal osteoarthritis	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Spinal pain	1 (0.49%)	1 (0.50%)	2 (0.49%)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung carcinoma cell type unspecified recurrent	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Malignant neoplasm progression	0 (0.00%)	4 (1.99%)	4 (0.99%)
		Metastases to central nervous system	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Renal haemangioma	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Tumour pain	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Nervous system disorders	Cerebral ischaemia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Cerebrovascular accident	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Coordination abnormal	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Dizziness	2 (0.99%)	2 (1.00%)	4 (0.99%)
		Dizziness postural	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Dysgeusia	2 (0.99%)	2 (1.00%)	4 (0.99%)
		Encephalopathy	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Headache	11 (5.42%)	9 (4.48%)	20 (4.94%)
		Hypotonia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Migraine	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Neuralgia	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Neuropathy peripheral	4 (1.97%)	0 (0.00%)	4 (0.99%)
		Paraesthesia	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Parosmia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Peripheral sensory neuropathy	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Somnolence	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Spinal cord herniation	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Syncope	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Tremor	1 (0.49%)	1 (0.50%)	2 (0.49%)
	Psychiatric disorders	Anxiety	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Depressed mood	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Depression	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Insomnia	3 (1.48%)	9 (4.48%)	12 (2.96%)
		Restlessness	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Sleep disorder	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Renal and urinary disorders	Acute kidney injury	1 (0.49%)	2 (1.00%)	3 (0.74%)
		Anuria	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Dysuria	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Glycosuria	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Haematuria	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Lower urinary tract symptoms	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Micturition urgency	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Nephropathy	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Nocturia	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Pollakiuria	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Polyuria	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Proteinuria	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Renal cyst	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Renal failure	3 (1.48%)	8 (3.98%)	11 (2.72%)
		Renal injury	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Respiratory, thoracic and mediastinal disorders	Broncholithiasis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Chronic obstructive pulmonary disease	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Cough	2 (0.99%)	5 (2.49%)	7 (1.73%)
		Dysphonia	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Dyspnoea	7 (3.45%)	6 (2.99%)	13 (3.21%)
		Epistaxis	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Haemoptysis	3 (1.48%)	1 (0.50%)	4 (0.99%)
		Hiccups	7 (3.45%)	4 (1.99%)	11 (2.72%)
		Oropharyngeal pain	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Pleural effusion	0 (0.00%)	3 (1.49%)	3 (0.74%)
		Pneumonitis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Pneumothorax	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Pulmonary embolism	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Pulmonary fibrosis	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Respiratory distress	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Tracheal pain	1 (0.49%)	0 (0.00%)	1 (0.25%)
	Skin and subcutaneous tissue disorders	Alopecia	32 (15.76%)	29 (14.43%)	61 (15.06%)
		Dry skin	2 (0.99%)	0 (0.00%)	2 (0.49%)
		Erythema	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Hyperhidrosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Night sweats	2 (0.99%)	2 (1.00%)	4 (0.99%)
		Pruritus	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Rash	4 (1.97%)	1 (0.50%)	5 (1.23%)
		Rash vesicular	0 (0.00%)	1 (0.50%)	1 (0.25%)
	Vascular disorders	Deep vein thrombosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Haemorrhage	1 (0.49%)	0 (0.00%)	1 (0.25%)
		Hypertension	8 (3.94%)	13 (6.47%)	21 (5.19%)
		Hypotension	2 (0.99%)	3 (1.49%)	5 (1.23%)
		Peripheral embolism	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Phlebitis	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Phlebitis superficial	0 (0.00%)	2 (1.00%)	2 (0.49%)
		Subclavian vein thrombosis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Thrombophlebitis	1 (0.49%)	1 (0.50%)	2 (0.49%)
		Thrombophlebitis superficial	2 (0.99%)	1 (0.50%)	3 (0.74%)
		Vasculitis	0 (0.00%)	1 (0.50%)	1 (0.25%)
		Subjects(filtered)	169 (83.25%)	174 (86.57%)	405 (100.00%)
		1stColItemSubjects	203 (100.00%)	201 (100.00%)	(Denom=1stColTot)

Note:

- Cardiac Disorders: For a discussion of cardiac disorders, see Section 8.5.1 of this review

- **Transaminase Elevations:** There appeared to be an imbalance in transaminase elevations in the oral Akynzeo arm vs. the IV Akynzeo arm. However, this Reviewer conducted further analyses (see Hy's Law plot in Section 8.5.2 of this review) which showed that none of the patients met Hy's Law criteria.
- **Elevated Creatinine:** For a discussion of elevated creatinine, see Section 8.5.2.
- **Blood Urea Increased:** See day of onset below. All cases were deemed by the investigator as not related to either the study drug or dexamethasone. In the IV arm, one event was Grade 3 (Subject (b) (6))
 - IV group (4 cases): Day of onset was Day 8 (Subject (b) (6)), Day 55 (Subject (b) (6)), Day 6 (Subject (b) (6)), and Day 64 (Subject (b) (6)).
 - PO group (1 case): Day of onset was Day 28 (Subject (b) (6)).
- **Deafness:** See day of onset below. Both cases were deemed by the by the investigator as not related to either the study drug or dexamethasone. One of the cases was Grade 3 (Subject (b) (6))
 - IV group (2 cases): Day of onset was Day 29 (Subject (b) (6)) and Day 50 (Subject (b) (6))
 - PO group (no cases)
- **Vertigo:** See day of onset below. All cases were deemed by the investigator as not related to either the study drug or dexamethasone except for one case in the IV group (Day 1 in Subject (b) (6) – deemed possibly related to the study agent). None of the events were Grade 3.
 - IV group (5 cases): Day of onset was Day 60 (Subject (b) (6)), Day 6 (Subject (b) (6)), Day 62 (Subject (b) (6)), Day 40 (Subject (b) (6)), and Day 1 (Subject (b) (6)).
 - PO group (2 cases): Day of onset was Day 59 (Subject (b) (6)) and Day 1 (Subject (b) (6))

(Source – Reviewers Table and Section 16.2.7 Adverse Event Listings in the (b) (6))

Study-drug-related TEAEs were reported for 26 (12.8%) patients (75 events) in the IV NEPA FDC group and 23 (11.4%) patients (71 events) in the Oral NEPA FDC group. There were only 2 TEAEs reported in $\geq 2\%$ of patients, i.e., constipation and ALT increased. The most frequently reported study-drug-related TEAE in both treatment groups was constipation (13 [6.4%] patients in the IV NEPA FDC group and 12 [6.0%] patients in the Oral NEPA FDC group). ALT increase was experienced by 4 patients (2.0%) in each treatment group. Please see table below.

Table 62 – Study Drug Related TEAEs – NEPA 15-18

Drug related TEAE Char	Analysis Primary System Organ Class	Dictionary Derived Term	IV PRO-NETUPITANT / PALONOSETRON 5.2 mg/mL / 5 ug/mL	ORAL NETUPITANT / PALONOSETRON 300 mg / 0.50 mg	Subjects(filtered)
Y	Cardiac disorders	Atrioventricular block	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Bradycardia	0 (0.00%)	1 (0.25%)	1 (0.25%)
		Sinus tachycardia	2 (0.49%)	2 (0.49%)	4 (0.99%)
		Tachycardia	0 (0.00%)	1 (0.25%)	1 (0.25%)
	Ear and labyrinth disorders	Vertigo	1 (0.25%)	0 (0.00%)	1 (0.25%)
	Gastrointestinal disorders	Abdominal pain	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Abdominal pain upper	1 (0.25%)	1 (0.25%)	2 (0.49%)
		Constipation	13 (3.21%)	12 (2.96%)	25 (6.17%)
		Diarrhoea	0 (0.00%)	1 (0.25%)	1 (0.25%)
		Dyspepsia	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Haematochezia	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Haemorrhoids	1 (0.25%)	0 (0.00%)	1 (0.25%)
	General disorders and administration site conditions	Disease progression	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Fatigue	0 (0.00%)	1 (0.25%)	1 (0.25%)
	Immune system disorders	Hypersensitivity	0 (0.00%)	2 (0.49%)	2 (0.49%)
	Investigations	Alanine aminotransferase increased	4 (0.99%)	4 (0.99%)	8 (1.98%)
		Aspartate aminotransferase increased	3 (0.74%)	3 (0.74%)	6 (1.48%)
		Blood alkaline phosphatase increased	1 (0.25%)	1 (0.25%)	2 (0.49%)
		Blood bilirubin increased	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Electrocardiogram QT prolonged	3 (0.74%)	1 (0.25%)	4 (0.99%)
		Hepatic enzyme increased	1 (0.25%)	0 (0.00%)	1 (0.25%)
	Nervous system disorders	Headache	3 (0.74%)	3 (0.74%)	6 (1.48%)
		Neuropathy peripheral	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Somnolence	0 (0.00%)	1 (0.25%)	1 (0.25%)
	Psychiatric disorders	Insomnia	1 (0.25%)	1 (0.25%)	2 (0.49%)
	Renal and urinary disorders	Nocturia	1 (0.25%)	0 (0.00%)	1 (0.25%)
	Respiratory, thoracic and mediastinal disorders	Hiccups	2 (0.49%)	2 (0.49%)	4 (0.99%)
	Skin and subcutaneous tissue disorders	Pruritus	0 (0.00%)	1 (0.25%)	1 (0.25%)
		Rash vesicular	0 (0.00%)	1 (0.25%)	1 (0.25%)
	Vascular disorders	Hypertension	2 (0.49%)	1 (0.25%)	3 (0.74%)
		Hypotension	1 (0.25%)	0 (0.00%)	1 (0.25%)
		Subjects(filtered)	26 (6.42%)	23 (5.68%)	405 (100.00%)
					(All patients)

(Source – Reviewers Table)

Overall, Grade 3 TEAEs were experienced by 61 (30.0%) patients in the IV NEPA FDC group and 54 (26.9%) patients in the Oral NEPA FDC group, and Grade 4 TEAEs were experienced by 15 (7.4%) patients in the IV NEPA FDC group and 22 (10.9%) patients in the Oral NEPA FDC group. Neutropenia was the most frequent Grade 3/4 TEAE reported during this study (37 [18.2%] patients in the IV NEPA FDC group and 37 [18.4%] patients in the Oral NEPA FDC group). Please see table below.

Table 63 – TEAE of CTCAE Grade 3 or 4 reported in $\geq 2\%$ of Patients in Either Treatment Group - NEPA 15-18

MedDRA System Organ Class MedDRA Preferred Term	IV NEPA FDC (N=203) n (%)		Oral NEPA FDC (N=201) n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any Grade 3 or Grade 4 TEAE	61 (30.0)	15 (7.4)	54 (26.9)	22 (10.9)
Blood and lymphatic system disorders	34 (16.7)	12 (5.9)	32 (15.9)	21 (10.4)
Anaemia	5 (2.5)	0	7 (3.5)	1 (0.5)
Leukopenia	6 (3.0)	0	4 (2.0)	3 (1.5)
Neutropenia	28 (13.8)	9 (4.4)	21 (10.4)	16 (8.0)
Thrombocytopenia	0	1 (0.5)	5 (2.5)	2 (1.0)
Investigations	7 (3.4)	2 (1.0)	17 (8.5)	1 (0.5)
Alanine aminotransferase increased	2 (1.0)	0	14 (7.0)	0
Aspartate aminotransferase increased	3 (1.5)	0	5 (2.5)	0

(Source – NEPA 15-18 Study Report Page 110)

8.4.6. Laboratory Findings

PNET 12-23

No safety-relevant changes were observed compared to baseline, and no remarkable difference was observed between mean values of both treatments. The number of subjects with abnormal values was low for most of the parameters. None of the abnormal laboratory values were assessed as clinically significant by the Investigator, and no adverse events associated with safety laboratory abnormalities were reported.

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For most hematology parameters, the mean values at baseline and the mean changes from baseline to Day 6 (the time point selected for the summary analysis) were similar between the treatment groups.

For most blood chemistry parameters, the mean values at baseline and the mean changes from baseline to Day 6 were also similar between the treatment groups.

The mean creatinine clearance value was 55.2 mL/min for the infusion group and 53.0 mL/min for the bolus group; by Day 6, the value was lower for the infusion group with respect to the bolus group (44.9 mL/min and 47.6 mL/min, respectively). For ALP, the mean count at baseline was higher for the bolus group (96.8 U/L for the infusion group, 103.2 U/L for the bolus group), but by Day 6, the mean values were almost identical (90.0 U/L and 90.1 U/L, respectively).

Other notable changes in blood chemistry parameters were similar between the treatment groups. For ALT, the mean values at baseline were 24.0 U/L for the infusion group and 22.9 U/L for the bolus group; by Day 6, the mean values increased in both groups to 40.7 U/L and 38.4 U/L, respectively. For blood urea nitrogen (BUN), the mean values at baseline were 5.48 mmol/L for the infusion group and 5.26 mmol/L for the bolus group; by Day 6, the mean values increased in both groups to 9.57 mmol/L and 9.33 mmol/L, respectively. For total bilirubin, the mean values at baseline were 8.50 μ mol/L for the infusion group and 8.88 μ mol/L for the bolus group; by Day 6, the mean values had increased substantially in both groups to 11.22 μ mol/L and 11.71 μ mol/L, respectively.

For most urinalysis parameters, the percentage of patients with a positive test result at screening was comparable between the treatment groups; frequency distributions were also similar between the treatment groups on Day 6.

Overall, the proportion of patients with values within the normal ranges at baseline and on Day 6 was similar between the treatment groups, and changes from normal to abnormal or from abnormal to normal were generally similar between the treatment groups on Day 6. In hematology, the greatest shifts from baseline in the percentage of patients with normal values were observed for monocytes/total cells and neutrophils/total cells. For monocytes/total cells, 31.1% of patients in the infusion group and 24.9% of patients in the bolus groups had shifts from normal at baseline to low measurements on Day 6. For neutrophils/total cells, 28.8% of patients in the infusion group and 27.4% of patients in the bolus groups had shifts from normal at baseline to high measurements on Day 6, as might be expected following exposure to corticosteroids, which may transiently release mature neutrophils from bone marrow.

For blood chemistry parameters, the greatest shifts from baseline normal to high ranges on Day 6 were observed for blood urea nitrogen (45.7% and 43.5% of patients in the infusion and bolus groups, respectively), ALT (23.3% and 25.6%), creatinine clearance (12.6% and 15.5%), and creatinine (10.8% and 14.0%). The greatest shifts from baseline normal to low ranges on Day 6 were observed for chloride (30.0% and 36.7% of patients in the infusion and bolus groups, respectively), creatinine kinase (31.8% and 33.8%), and calcium (23.8% and 20.8%).

The type, frequency, and intensity of clinically significant laboratory abnormalities were comparable across the treatment groups.

A number of laboratory abnormalities were recorded that are common for oncology patients receiving chemotherapy: either chemotherapy-induced toxicity (leukocytes, neutrophils, hemoglobin, platelets, ALT, ALP, AST, total bilirubin, creatinine) and/or potential corticosteroid-induced toxicity (i.e., glucose, potassium and sodium). Marked abnormalities (i.e., those of CTC grades 3 or 4) in hematological and blood chemistry variables reported during the study are summarized in the tables below.

Marked abnormalities in hematology parameters included decreased white blood cell count for 3 (1.4%) patients in the infusion group and for 2 (1.0%) patients in the bolus group, decreased neutrophil count and anemia, each for 1 (0.5%) patients in the infusion group and for 2 (1.0%)

patients in the bolus group, and decreased platelet count for 1 (0.5%) patient in the infusion group and no patients in the bolus group. Please refer to table below.

Table 64 – Laboratory Abnormalities PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Parameter	N = 225	N = 215
Category	n (%)	n (%)
Anemia		
Patients with results	220	206
Any Grade 3 or 4	1 (0.5)	2 (1.0)
White blood cell decreased		
Patients with results	217	205
Any Grade 3 or 4	3 (1.4)	2 (1.0)
Grade 3	2 (0.9)	2 (1.0)
Grade 4	1 (0.5)	0
Palonosetron 0.25 mg IV		
Parameter	N = 225	N = 215
Category	n (%)	n (%)
Neutrophil count decreased		
Patients with results	215	201
Any Grade 3 or 4	1 (0.5)	2 (1.0)
Grade 3	0	0
Grade 4	1 (0.5)	2 (1.0)
Platelet count decreased		
Patients with results	219	204
Any Grade 3 or 4	1 (0.5)	0
Grade 3	0	0
Grade 4	1 (0.5)	0

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Parameter	N = 225	N = 215
Category	n (%)	n (%)
ALT increased		
Patients with results	223	207
Any Grade 3 or 4	3 (1.3)	1 (0.5)
Grade 3	3 (1.3)	1 (0.5)
Grade 4	0	0
ALP increased		
Patients with results	223	207
Any Grade 3 or 4	1 (0.4)	1 (0.5)
Grade 3	1 (0.4)	1 (0.5)
Grade 4	0	0
AST increased		
Patients with results	223	207
Any Grade 3 or 4	1 (0.4)	0
Grade 3	1 (0.4)	0
Grade 4	0	0
Glucose (hyperglycemia)		
Patients with results	223	207
Any Grade 3 or 4	3 (1.3)	3 (1.4)
Grade 3	3 (1.3)	3 (1.4)
Grade 4	0	0
Potassium (hypokalemia)		
Patients with results	221	206
Any Grade 3 or 4	0	2 (1.0)
Grade 3	0	2 (1.0)
Grade 4	0	0
Sodium (hyponatremia)		
Patients with results	223	207
Any Grade 3 or 4	2 (0.9)	1 (0.5)
Grade 3	2 (0.9)	1 (0.5)
Grade 4	0	0

(Source- PALO 15-17 Study Report Pages 115-117)

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For most hematology and blood chemistry parameters, the mean values at baseline and the mean changes from baseline throughout the study were similar between the treatment groups.

For urinalysis parameters, the majority of test results were negative/trace for both treatment groups throughout the study.

Overall, the percentage of patients with values within the normal range was comparable between the treatment groups, and changes from normal to abnormal or from abnormal to normal throughout the study were generally comparable between the treatment groups. Many of the hematology parameters had a high percentage of patients (>20%) in both treatment groups whose values shifted from normal to low/high over the course of the study including erythrocyte blood, hematocrit, hemoglobin, leukocytes blood, lymphocytes, lymphocytes/total cells, monocytes, monocytes/total cells, neutrophils (absolute), neutrophils/total cells, and platelets. In general, the percentage of patients whose values shifted from normal to abnormal was comparable between the treatment groups.

The blood chemistry parameters of ALT, AST, and blood urea nitrogen (BUN) consistently showed a higher percentage of patients whose values shifted from normal to low/high over the course of the study. In general, the percentage of patients whose values shifted from normal to abnormal was comparable between the treatment groups.

Most of the urinalysis parameters showed no change from baseline or showed a shift from positive to negative during the course of the study. The only exception was for protein for which there was a high percentage of patients whose values shifted from negative to positive during the study.

The type, frequency, and intensity of clinically significant laboratory abnormalities were comparable across the treatment groups.

A number of laboratory abnormalities were recorded that are common for oncology patients receiving chemotherapy; these were either chemotherapy-induced toxicity (leukocytes, neutrophils, hemoglobin, platelets, ALT, ALP, AST, total bilirubin, creatinine) and/or potential corticosteroid-induced toxicity (i.e., glucose, potassium and sodium).

Marked abnormalities in hematology parameters (any Grade 3 or 4) included decreased neutrophil count (6 [3.0%] patients in the IV NEPA FDC group and 8 [4.0%] patients in the Oral NEPA FDC group), decreased WBC (5 [2.5%] patients in the IV NEPA FDC group and 7 [3.5%] patients in the Oral NEPA FDC group), anemia (3 [1.5%] patients in the IV NEPA FDC group and 3 [1.5%] patients in the Oral NEPA FDC group), and decreased platelet count (no patients in the IV NEPA FDC group and 1 [0.5%] patient in the Oral NEPA FDC group). Please see table below.

Table 65 – Hematology Abnormalities (CTCAE Grade 3 or 4) - NEPA 15-18

Parameter Category	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)
Anemia		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	3 (1.5)	3 (1.5)
Grade 3	3 (1.5)	3 (1.5)
Grade 4	0	0
Neutrophil count decreased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	6 (3.0)	8 (4.0)
Grade 3	4 (2.0)	4 (2.0)
Grade 4	2 (1.0)	4 (2.0)
Platelet count decreased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	0	1 (0.5)
Grade 3	0	1 (0.5)
Grade 4	0	0
White blood cell count decreased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	5 (2.5)	7 (3.5)
Grade 3	5 (2.5)	3 (1.5)
Grade 4	0	4 (2.0)

(Source – NEPA 15-18 Study Report Page 120)

The highest incidences of marked abnormalities in blood chemistry parameters occurred for increased ALT (13 [6.4%] patients in the IV NEPA FDC group and 23 [11.4%] patients in the Oral NEPA FDC group), increased AST (8 [3.9%] patients in the IV NEPA FDC group and 13 [6.5%] patients in the Oral NEPA FDC group), hyperglycemia (13 [6.4%] patients in the IV NEPA FDC group and 9 [4.5%] patients in the Oral NEPA FDC group), and hyponatremia (8 [3.9%] patients in the IV NEPA FDC group and 3 [1.5%] patients in the Oral NEPA FDC group). The higher rates of hyperglycemia observed in the IV group vs. PO group can be explained by a higher proportion of patients with diabetes mellitus at baseline in the IV group vs. PO group (5.9% vs. 1.5%).¹⁶ The higher rates of hyperglycemia appear to have been driven by the diabetic patients (2.5% in the IV group vs. 0.5% in PO group); the rates were similar for non-diabetic patients (3.9% vs. 4.0%).¹⁷ Please see table below.

¹⁶ Page 201 of CSR for NEPA 15-18 (Table 14.1.2.13 Medical History: Concomitant diseases – Safety Population)

¹⁷ Page 36 of Response to Information Request received April 5, 2018

Table 66 – Marked Blood Chemistry Abnormalities (CTCAE Grade 3 or 4) - NEPA 15-18

Parameter Category	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)
ALT increased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	13 (6.4)	23 (11.4)
Grade 3	12 (5.9)	22 (10.9)
Grade 4	1 (0.5)	1 (0.5)
ALP increased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	1 (0.5)	1 (0.5)
Grade 3	1 (0.5)	1 (0.5)
Grade 4	0	0
AST increased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	8 (3.9)	13 (6.5)
Grade 3	8 (3.9)	13 (6.5)
Grade 4	0	0
Blood bilirubin increased		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	1 (0.5)	0
Grade 3	1 (0.5)	0
Grade 4	0	0
Glucose (hyperglycemia)		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	13 (6.4)	9 (4.5)
Grade 3	13 (6.4)	8 (4.0)
Grade 4	0	1 (0.5)
Potassium (hypokalemia)		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	2 (1.0)	1 (0.5)
Grade 3	2 (1.0)	1 (0.5)
Grade 4	0	0
Parameter Category	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)
Sodium (hyponatremia)		
Patients with results at any cycle, any visit	203	201
Any Grade 3 or 4	8 (3.9)	3 (1.5)
Grade 3	8 (3.9)	3 (1.5)
Grade 4	0	0

Note that Grade 3 hyponatremia is defined in CTCAE as the following:¹⁸ 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms. Of the 8 events in the IV group, 2 were considered by the investigator as not related to the NEPA IV or dexamethasone, and the remaining 6 were considered by the investigator as not clinically relevant.¹⁹ Each of the 3 events in the PO group was considered by the investigator as not clinically relevant.²⁰ (Source NEPA 15-18 Study Report Pages 121-122)

¹⁸ Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017

¹⁹ Pages 37-39 of Response to Information Request received April 5, 2018

²⁰ Pages 39-40 of Response to Information Request received April 5, 2018

8.4.7. Vital Signs

PNET 12-23

No safety-related changes were observed over time compared to baseline and no clinically relevant difference was observed between both treatments. No statistically significant results were obtained for blood pressure changes over doses. For pulse rate changes over doses, statistically significant results were observed at several timepoints. No clear trend was, however, observed over all doses, i.e. median values of changes increased or decreased with ascending doses. Thus, no clear trend in vital sign changes was observed for the analyzed dose levels.

There were two clinically significant abnormalities. After IV administration of 130 mg pro-netupitant, mild intermittent palpitations were reported for 1 subject (Subject No. (b) (6)) about 18.5 hours after start of infusion (a.s.i.) and lasted 7 hours and 30 min. The event was assessed as possibly related to the investigational medicinal product (IMP) by the Investigator and by the DSMB. After administration of 390 mg pro-netupitant, orthostatic hypotension was observed in 1 subject (Subject No. (b) (6)) about 8 hours a.s.i. and lasted 4 min. The event was assessed as possibly related to the IMP by the Investigator and by the DSMB. No other TEAEs associated with vital sign abnormalities were reported.

Clinical Reviewer's Comment:

Regarding mild intermittent palpitations, this reviewer notes that the onset was 18.5 hours a.s.i. suggesting that the event is not related to the IMP. Even if it was related to the IMP as the Investigator and DSMB concluded, this reviewer does not recommend it be included in the labeling as the event was reported at low frequency in Study NEPA 15-18 (IV Akynzeo arm: 0; PO Akynzeo arm: 2/201 (1%)). The current labeling for Akynzeo PO (Section 6.1 Clinical Trials Experience) includes a table with adverse reactions occurring at $\geq 3\%$ of patients in Cycle 1 of the single-cycle study of oral Akynzeo described.

The above reported orthostatic hypotension case is consistent with the description of the effects observed in the nonclinical studies; see the following (from the QT-IRT Review):

“In conscious dogs and in anesthetized whole animals netupitant and its metabolites or palonosetron/netupitant combinations have been associated with bradycardia, hypotension dose-dependent decreases in atrioventricular conduction (increased PR) and in ventricular depolarisation rate (prolonged QRS) and prolonged QT.”

This Reviewer notes that orthostatic hypotension is not currently included in the labeling (Section 6 Adverse Reactions). This Reviewer notes that this adverse event occurred at a supratherapeutic dose that is not recommended in the labeling; therefore, this reviewer does not recommend that orthostatic hypotension be added to the labeling.

PALO 15-17

The mean values for pulse rate, systolic blood pressure and diastolic blood pressure were similar in the two treatment groups at baseline and all time points reported thereafter. The mean changes from baseline were small, not clinically relevant and similar between the treatment groups.

NEPA 15-18

The pulse, systolic blood pressure, and diastolic blood pressure were analyzed with respect to changes from baseline at each study visit. The changes from baseline were not clinically significant and were reasonably comparable between the two treatment groups.

8.4.8. Electrocardiograms (ECGs)

PNET 12-23

No safety-relevant changes were observed compared to baseline and no marked difference was observed between both treatments. Most of the subjects had normal ECGs (according to Investigator's interpretation) on Day -1. In both, active IV infusion and oral active treatment groups, 20 subjects (13.5% and 14.9% of the subjects, respectively) had ECG abnormalities on Day -1, all assessed as not clinically significant. During the study, ECG abnormalities were observed in less than 15% of the subjects in each treatment group on Days 1, 3, and 6. All ECG abnormalities were assessed as not clinically significant.

PALO 15-17

The percentage of patients with at least one treatment-emergent ECG abnormality after baseline was similar in the two treatment groups (21.3% and 21.9% of patients in the infusion group and bolus group, respectively). The most frequently reported treatment emergent ECG abnormalities were flat ST segment, T-wave and U-wave (4.0% and 5.1% of patients in the infusion group and bolus group, respectively), atrial premature complexes (4.4% and 3.3%, respectively), and depressed ST segment, T-wave and U-wave (1.8% and 4.2%, respectively). Please see table below.

Table 67 – ECG – Abnormalities – PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Grouped Term	N = 225	N = 215
Abnormality in ECG	n (%)	n (%)
Patient with at least one treatment-emergent abnormality	48 (21.3)	47 (21.9)
Atrioventricular Conduction		
2:1 Atrioventricular Block	1 (0.4)	0
First Degree Atrioventricular Block	1 (0.4)	0
Chamber Hypertrophy or Enlargement		
Left Atrial Abnormality	1 (0.4)	0
Left Ventricular Hypertrophy	1 (0.4)	1 (0.5)
Right Atrial Abnormality	0	1 (0.5)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Grouped Term	N = 225	N = 215
Abnormality in ECG	n (%)	n (%)
Intraventricular-Intraatrial Conduction		
Intraventricular Conduction Defect	0	1 (0.5)
Left Anterior Hemiblock	1 (0.4)	0
Left Posterior Hemiblock	0	1 (0.5)
Right Bundle Branch Block	2 (0.9)	0
Myocardial Infarction		
Inferior MI (2), 3, F	0	1 (0.5)
ST Segment, T wave, and U wave		
Biphasic	3 (1.3)	1 (0.5)
Depressed	4 (1.8)	9 (4.2)
Flat	9 (4.0)	11 (5.1)
Inverted	3 (1.3)	8 (3.7)
Prolonged QTc	0	2 (0.9)
Sinus Node Rhythms and Arrhythmias		
Sinus Bradycardia	2 (0.9)	0
Sinus Tachycardia	8 (3.6)	8 (3.7)
Supraventricular Arrhythmias		
Atrial Premature Complexes	10 (4.4)	7 (3.3)
Ectopic Supraventricular Rhythm	2 (0.9)	0
Frequent Atrial Premature Complexes (>3)	1 (0.4)	0
Supraventricular Tachyarrhythmias		
Atrial Fibrillation	2 (0.9)	0
Atrial Flutter	2 (0.9)	0
Ventricular Arrhythmias		
Frequent Ventricular Premature Complexes (>2)	1 (0.4)	1 (0.5)
Ventricular Premature Complexes	4 (1.8)	6 (2.8)

(Source PALO 15-17 Study Report Pages 121-122)

NEPA 15-18

The percentage of patients with at least one treatment-emergent ECG abnormality after baseline was 75.9% in the IV NEPA FDC group and 68.7% in the Oral NEPA FDC group. The most frequently reported treatment-emergent ECG abnormalities were atrial premature complexes (25.1% in the IV NEPA FDC group and 18.9% in the Oral NEPA FDC group), sinus tachycardia (18.2% in the IV NEPA FDC group and 19.4% in the Oral NEPA FDC group), and flat ST segment, T-wave and U-wave (21.7% in the IV NEPA FDC group and 16.9% in the Oral NEPA FDC group). Please see table below.

Table 68 – ECG – Abnormalities Reported for $\geq 5\%$ of Patients in Either Treatment Group for All Cycles – NEPA 15-18

Grouped Term Abnormality in ECG	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)
Patient with at least one treatment-emergent abnormality	154 (75.9)	138 (68.7)
Atrioventricular Conduction	20 (9.9)	24 (11.9)
First Degree AV Block	19 (9.4)	24 (11.9)
Intraventricular-Intraatrial Conduction	15 (7.4)	14 (7.0)
ST Segment, T-wave, and U-wave	77 (37.9)	59 (29.4)
Flat	44 (21.7)	34 (16.9)
Inverted	29 (14.3)	24 (11.9)
Depressed	23 (11.3)	25 (12.4)
Biphasic	13 (6.4)	4 (2.0)
Sinus Node Rhythms and Arrhythmias	48 (23.6)	52 (25.9)
Sinus Tachycardia	37 (18.2)	39 (19.4)
Sinus Bradycardia	12 (5.9)	13 (6.5)
Supraventricular Arrhythmias	57 (28.1)	43 (21.4)
Atrial Premature Complexes	51 (25.1)	38 (18.9)
Ventricular Arrhythmias	28 (13.8)	35 (17.4)
Ventricular Premature Complexes	27 (13.3)	31 (15.4)

(Source NEPA 15-18 Study Report Page 128)

The Clinical Reviewers concluded that the numeric differences do not reflect cardiac safety differences between the products. First, there were no nonclinical findings suggesting a reason for the differences. Second, the QT evaluation results do not provide an explanation for the differences; see discussion of the QT evaluation results in Section 4.5.3 Pharmacokinetics subsection “QT Evaluation”. Third, because all patients were on background medications, it is possible that these EKG findings are attributable to background medications and do not reflect a true difference.

8.4.9. QT

The CDER DCRP QT Interdisciplinary Review Team (QT-IRT) determined prior to submission of the NDA that the sponsor had conducted sufficient evaluation of the QTc interval in both the oral and IV programs to support a TQT study waiver for IV NEPA FDC. The QT-IRT was consulted during the review of this NDA; see Section 4.5.3 above for a summary of their review conclusions.

PNET 12-23

No QTcB and QTcF intervals >480 ms were observed. QTcB intervals between 450 ms and 480 ms were observed in 1 subject at baseline on Day -1 of Period 1 prior to active IV treatment, 2 subjects at baseline on Day -1 of Period 2 prior to active oral treatment and in 2 subjects after active treatment on Day 6 (1 IV treated subject and 1 oral treated subject). QTcF intervals between 450 ms and 480 ms were observed in 2 subjects at baseline on Day -1 of Period 2 prior to active oral treatment, in 4 subjects after active treatment on Day 1 (1 IV treated subject and 3 oral treated subjects), in 2 subjects after active treatment on Day 3 (1 IV treated subject and 1

oral treated subject), and in 3 subjects after active treatment on Day 6 (2 IV treated subjects and 1 oral treated subject).

No QTcB or QTcF changes from baseline > 60 ms were observed. QTcB changes from baseline between 30 ms and 60 ms were observed after active treatment in 2 subjects (1 IV treated and 1 oral treated subject) on Day 1, 4 subjects (2 IV treated and 2 oral treated subject) on Day 3, and 5 subjects (4 IV treated and 1 oral treated subject) on Day 6. QTcF changes from baseline between 30 ms and 60 ms were observed after active treatment in 2 subjects (2 IV treated subject) on Day 6.

None of the ECG findings, including the QTcB and QTcF observed changes described above, was assessed as clinically significant by the Investigator and no TEAEs associated with ECG abnormalities were reported.

PALO 15-17

At Visit 4, the mean (SD) PR intervals had decreased slightly compared to baseline in both treatment groups; the mean change observed with the 30-minute infusion was similar to that of the 30 second bolus group [-7.2 (14.9) msec for the infusion group vs. -9.3 (13.9) msec for the bolus group]. Thus, no greater risk of effects from PR interval decreases from baseline is expected with the 30-minute infusion of palonosetron in the proposed product vs. the approved administration of palonosetron in Aloxi IV of 30 seconds. At Visit 4, changes from baseline in HR, QRS interval, QT interval, QTcB interval and QTcF interval were small and similar between treatment groups. See additional discussion in Section 4.5.3 of this Review.

QT prolongation was identified as an AE of special interest for the study, and changes in QT intervals were monitored closely. At baseline, the mean (SD) QTcF interval was comparable between treatment groups: 412.5 (22.7) msec for the infusion group and 409.7 (22.8) msec for the bolus group. At Visit 4, the mean (SD) changes in QTcF interval from baseline were small and comparable between treatment groups: -0.8 (22.3) msec for the infusion group and 1.7 (21.3) msec for the bolus group. Please see table below.

Table 69 – QTcF Interval Observed Values and Changes from Baseline – PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
QTcF Interval (msec) at Baseline^a		
n	225	215
Mean (SD)	412.5 (22.7)	409.7 (22.8)
Median	411.0	410.0
Min, Max	354, 491	338, 498
QTcF Interval (msec) at Visit 4		
n	224	208
Mean (SD)	411.7 (23.3)	411.6 (25.1)
Median	410.0	411.0
Min, Max	350, 483	348, 540
Change from Baseline to Visit 4		
n	224	208
Mean (SD)	-0.8 (22.3)	1.7 (21.3)
Median	-1.0	2.0
Min, Max	-73, 79	-62, 98

(Source – PALO 15-17 Study Report Page 119)

An outlier analysis was performed to depict the number and percentage of patients who met specific criteria. For HR, 4.4% and 1.4% of patients in the infusion group and bolus group, respectively, had ECG data that were outside the criteria of HR increase $\geq 25\%$ and >100 bpm. Only one patient (0.4%, infusion group) recorded a measurement outside the criteria of HR decrease $\geq 25\%$ and <50 bpm.

No patient met outlier criteria for PR interval. For QRS and QT intervals, the percentages of patients whose ECG data met outlier criteria were comparable between the treatment groups. The highest percentage of patients whose ECG data met the QT interval outlier criteria were in the range of QT increase of >30 and ≤ 60 msec, affecting 11.1% and 10.2% of patients in the infusion and bolus groups, respectively. QT increases of >60 msec affected 3.1% and 5.1% of patients in the infusion and bolus groups, respectively. QTcB outliers were reported for similar proportions of patients in the infusion and bolus groups in each outlier category (from ≤ 450 msec, ≤ 480 msec, and ≤ 500 msec at baseline to >450 msec, >480 msec >500 msec, respectively, at Visit 4). Only 3 (1.4%) patients in the bolus group had an increase in QTcB from ≤ 500 msec at baseline to a value of >500 msec. QTcB increases of >30 and ≤ 60 msec affected 3.1% and 6.5% of patients in the infusion and bolus groups, respectively, while increases of >60 msec affected 2.7% and 0.9% of patients in the respective groups. Comparing to QTcB outliers, QTcF outliers were reported for lower proportions of patients in the infusion and bolus groups in each outlier category. Only one (0.5%) patient in the bolus group had an increase in QTcF from ≤ 500 msec at baseline to a value of >500 msec. QTcF increases of >30 and ≤ 60 msec affected 4.9% and 5.1% of patients in the infusion and bolus groups, respectively, while increases of >60 msec affected 1.8% and 0.9% of patients in the respective groups. Please see table below.

Table 70 – QTcF Interval Observed Values and Changes from Baseline – PALO 15-17

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
	N = 225	N = 215
QTcF Interval (msec) at Baseline^a		
n	225	215
Mean (SD)	412.5 (22.7)	409.7 (22.8)
Median	411.0	410.0
Min, Max	354, 491	338, 498
QTcF Interval (msec) at Visit 4		
n	224	208
Mean (SD)	411.7 (23.3)	411.6 (25.1)
Median	410.0	411.0
Min, Max	350, 483	348, 540
Change from Baseline to Visit 4		
n	224	208
Mean (SD)	-0.8 (22.3)	1.7 (21.3)
Median	-1.0	2.0
Min, Max	-73, 79	-62, 98

(Source – PALO 15-17 Study Report Page 119)

NEPA 15-18

At Cycle 1 Visit 4 (120 h post-dose), there was a slight mean (SD) decrease from baseline in PR interval that was comparable between the treatment groups (-10.8 [16.7] msec for the IV NEPA FDC group and -10.1 [14.1] msec for the Oral NEPA FDC group). Similar decreases from baseline in PR interval were observed at Visit 4 during Cycles 2, 3, and 4 for both treatment groups.

QT prolongation was identified as an AE of special interest for the study, and changes in QT intervals were monitored closely. At Cycle 1 Visit 4 (120 h post-dose), there was a slight mean (SD) decrease from baseline in QTcF interval that was comparable between the treatment groups (-3.0 [19.5] msec for the IV NEPA FDC group and -5.2 [17.7] msec for the Oral NEPA FDC group). Similar decreases from baseline in QTcF interval were observed at Visit 4 during Cycles 2, 3, and 4 for both treatment groups.

Changes for heart rate and all other intervals were small and comparable between treatment groups.

For all ECG parameters over all cycles, the percentages of patients who had ECG data that met the outlier criteria were comparable between the treatment groups. The highest percentage of patients who met the outlier criteria was for heart rate increase from baseline $\geq 25\%$ and >100 bpm for all cycles at Visit 4, 120 h post-dose (6.4% for the IV NEPA FDC group and 8.0% for the Oral NEPA FDC group).

Across all cycles, the percentage of patients with a QTcB post-baseline value >500 msec and baseline value ≤500 msec was similar for both treatment groups and less than 1.0% overall at each timepoint. The percentage of patients with QTcB change from baseline >60 msec was also similar for both treatment groups and less than or equal to 2.0% overall at each timepoint. Please see table below.

Table 71 - 12-Lead ECG Outlier Analysis – All Cycles QTcB – NEPA 15-18

Abnormality in ECG Change from Baseline	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)	Overall (N=404) n (%)
Post-baseline QT >450 msec and baseline ≤450 msec	86 (42.4)	85 (42.3)	171 (42.3)
Visit 1, Screening	19 (9.4)	19 (9.5)	38 (9.4)
Visit 2, Pre-dose	17 (8.4)	21 (10.4)	38 (9.4)
Visit 2, end of IV	25 (12.3)	25 (12.4)	50 (12.4)
Visit 2, 5 h post-dose	65 (32.0)	64 (31.8)	129 (31.9)
Visit 3, 24 h post-dose	41 (20.2)	49 (24.4)	90 (22.3)
Visit 4, 120 h post-dose	36 (17.7)	25 (12.4)	61 (15.1)
Post-baseline QT >480 msec and baseline ≤480 msec	16 (7.9)	30 (14.9)	46 (11.4)
Visit 1, Screening	1 (0.5)	3 (1.5)	4 (1.0)
Visit 2, Pre-dose	2 (1.0)	4 (2.0)	6 (1.5)
Visit 2, end of IV	5 (2.5)	8 (4.0)	13 (3.2)
Visit 2, 5 h post-dose	9 (4.4)	16 (8.0)	25 (6.2)
Visit 3, 24 h post-dose	10 (4.9)	16 (8.0)	26 (6.4)
Visit 4, 120 h post-dose	2 (1.0)	5 (2.5)	7 (1.7)
Post-baseline QT >500 msec and baseline ≤500 msec	5 (2.5)	2 (1.0)	7 (1.7)
Visit 1, Screening	0	1 (0.5)	1 (0.2)
Visit 2, Pre-dose	1 (0.5)	0	1 (0.2)
Visit 2, end of IV	1 (0.5)	0	1 (0.2)
Visit 2, 5 h post-dose	2 (1.0)	1 (0.5)	3 (0.7)
Visit 3, 24 h post-dose	2 (1.0)	0	2 (0.5)
Visit 4, 120 h post-dose	2 (1.0)	0	2 (0.5)
QT change from baseline >30 and ≤60 msec	93 (45.8)	80 (39.8)	173 (42.8)
Visit 1, Screening	15 (7.4)	13 (6.5)	28 (6.9)
Visit 2, Pre-dose	14 (6.9)	21 (10.4)	35 (8.7)
Visit 2, end of IV	19 (9.4)	19 (9.5)	38 (9.4)
Visit 2, 5 h post-dose	68 (33.5)	57 (28.4)	125 (30.9)
Visit 3, 24 h post-dose	52 (25.6)	43 (21.4)	95 (23.5)
Visit 4, 120 h post-dose	35 (17.2)	21 (10.4)	56 (13.9)
QT change from baseline >60 msec	7 (3.4)	9 (4.5)	16 (4.0)
Visit 1, Screening	0	1 (0.5)	1 (0.2)
Visit 2, Pre-dose	2 (1.0)	3 (1.5)	5 (1.2)
Visit 2, end of IV	0	2 (1.0)	2 (0.5)
Visit 2, 5 h post-dose	2 (1.0)	6 (3.0)	8 (2.0)
Visit 3, 24 h post-dose	4 (2.0)	3 (1.5)	7 (1.7)
Visit 4, 120 h post-dose	2 (1.0)	1 (0.5)	3 (0.7)

(Source- NEPA 15-18 Study Report 124-125)

Across all cycles, no patient had a QTcF >500 msec with a baseline value of ≤500 msec. One (0.5%) patient had a change from baseline in QTcF interval of >60 msec at 24 h after treatment

with IV NEPA FDC, and 1 (0.5%) patient had a change from baseline of >60 msec at the end of infusion, 5 h, 24 h, and 120 h after treatment with Oral NEPA FDC.

Overall, no relevant differences between IV NEPA FDC and Oral NEPA FDC were detected with regard to increased QTc pre- and post-dose. This study showed no evidence of any increase in QTc duration and no clinically relevant specific outliers. Please see table below.

Table 72 – ECG- Abnormalities Reported for $\geq 5\%$ of Patients in Either Treatment Group for All Cycles – NEPA 15-18

Grouped Term Abnormality in ECG	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)
Patient with at least one treatment-emergent abnormality	154 (75.9)	138 (68.7)
Atrioventricular Conduction	20 (9.9)	24 (11.9)
First Degree AV Block	19 (9.4)	24 (11.9)
Intraventricular-Intraatrial Conduction	15 (7.4)	14 (7.0)
ST Segment, T-wave, and U-wave	77 (37.9)	59 (29.4)
Flat	44 (21.7)	34 (16.9)
Inverted	29 (14.3)	24 (11.9)
Depressed	23 (11.3)	25 (12.4)
Biphasic	13 (6.4)	4 (2.0)
Sinus Node Rhythms and Arrhythmias	48 (23.6)	52 (25.9)
Sinus Tachycardia	37 (18.2)	39 (19.4)
Sinus Bradycardia	12 (5.9)	13 (6.5)
Supraventricular Arrhythmias	57 (28.1)	43 (21.4)
Atrial Premature Complexes	51 (25.1)	38 (18.9)
Ventricular Arrhythmias	28 (13.8)	35 (17.4)
Ventricular Premature Complexes	27 (13.3)	31 (15.4)

(Source- NEPA 15-18 Study Report 124-125)

8.4.10. Immunogenicity

PNET 12-23

Not relevant to this study.

PALO 15-17

Not relevant to this study.

NEPA 15-18

Not relevant to this study.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. PALO 15-17 – Additional Analysis

Specific TEAEs Occurring at $\geq$ 2% Higher Frequency in Infusion Arm vs. Bolus Arm

The percentage of patients who experienced at least 1 TEAE was slightly higher in the IV palonosetron infusion group, 85 (37.8 %), as opposed to IV palonosetron bolus group, 77 (35 %). In addition, there was slightly more diarrhea and hypertension in the 30-minute infusion group. Please see table below.

Table 73 - AEs occurring $\geq$ 2 % higher in the IV Palonosetron Infusion Arm vs. IV Palonosetron Bolus Arm

	Adverse Event	IV Palonosetron Infusion	IV Palonosetron Bolus
Study Palo 15-17	% patients who experienced at least 1 TEAE	85 (37.8 %)	77 (35.8%)
	Diarrhea	11 (4.9%)	6 (2.8%)
	Hypertension	8 (3.6%)	2 (0.9%)

Note: See Section 8.4.5 regarding Hypertension cases.
(Source – Reviewers Table)

These adverse events are addressed in the Aloxi (palonosetron) labels. Furthermore, given the multiple other confounding variables (concurrent chemotherapy administration, overall health of the subjects, etc.), these findings cannot be conclusively attributed to the longer infusion time of the palonosetron.

Cardiac TEAEs

Another concern with the PALO 15-17 study was that there were more cardiac events as a whole in the 30-minute infusion arm. Please see below.

Table 74 – Cardiac TEAEs PALO 15-17

Analysis Primary System Organ Class	Dictionary Derived Term	PALONOSETRON 0.25 MG IV BOLUS	PALONOSETRON 0.25 MG IV INFUSION	Subjects(filtered)
Cardiac disorders	Atrial fibrillation	0 (0.00%)	3 (1.33%)	3 (0.68%)
	Tachycardia	0 (0.00%)	3 (1.33%)	3 (0.68%)
	Cardio-respiratory arrest	1 (0.47%)	1 (0.44%)	2 (0.45%)
	Atrial flutter	0 (0.00%)	2 (0.89%)	2 (0.45%)
	Arrhythmia supraventricular	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Cardiac arrest	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Palpitations	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Sinus tachycardia	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Bundle branch block right	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Atrial tachycardia	0 (0.00%)	1 (0.44%)	1 (0.23%)
	Subjects(filtered)	1 (0.47%)	11 (4.89%)	441 (100.00%)
	1stColItemSubjects	215 (100.00%)	225 (100.00%)	(Denom=1stColTot)

(Source – Reviewers Table)

One of the subjects (b) (6) developed atrial flutter [Grade 5] and dyspnea [Grade 4] which were both classified as severe and considered potentially related to the study drug. This subject ultimately died of cardiopulmonary arrest 12 days after the last infusion of study drug. This was discussed further in Sections 8.4.1 and 8.4.5. The narratives of the subjects who had who had serious cardiac events were reviewed. They are summarized in the table below.

Table 75 – Narratives of Patients Who Experienced Serious Cardiac TEAEs PALO 15-17

Patient ID #	Adverse event	Relevant Narrative Information
IV 30-minute Infusion Group		
(b) (6)	Atrial flutter, respiratory failure, dyspnea, cardiac arrest.	• Death due to cardiopulmonary arrest at Day 13 • Atrial flutter onset at Day 6 • History of Atrial Flutter, small cell neuroendocrine carcinoma (T4N3M1), myocardial ischemia, and DM • A. Flutter possibly related to the drug • Respiratory failure and cardiac arrest not attributed.
(b) (6)	Atrial fibrillation	• Atrial fibrillation onset at Day 7 • The patient lived • History of lung cancer and COPD. • Not attributed to drug • Attributed to the cardiac toxicity of Cisplatin
(b) (6)	Cardio-respiratory arrest	• Death due to cardio-respiratory arrest at Day 6 • History of stage IV A head and neck cancer • Symptoms leading up to arrest included dehydration, leukopenia, thrombocytopenia, dyspnea. • Not attributed to drug.
IV Bolus Group		
(b) (6)	Cardio-respiratory Arrest	• Death due to cardio-respiratory arrest at Day 11 • History of lung cancer, COPD, infective exacerbations of bronchiectasis and pneumonitis, chronic respiratory failure, A fib, CHF, and prior MI • Prior to arrest, the pt. had productive cough and abnormal breath sounds. Pt didn't respond to treatment • Not attributed to drug.

(Source – Reviewer's Table and Listing 16.2.7 of the PALO-15-17 CSR)

The other cases were not attributed to the study drug. Based on a concern for a potential cardiac signal, an IR was sent to the Sponsor on 08/25/2017 requesting the narratives of patients cardiac TEAEs not classified as serious. Please see table below.

Table 76 - Listing of Patients Who Experienced Non-Serious Cardiac TEAEs PALO 15-17

PT ID N.	Actual Arm	Event (Preferred Term)	Seriousness
(b) (6)	PALO IV infusion	Atrial tachycardia	No
	PALO IV infusion	Bundle branch block right	No
	PALO IV infusion	Atrial flutter	No
		Tachycardia	No
	PALO IV infusion	Atrial fibrillation	Yes
	PALO IV infusion	Tachycardia	No
	PALO IV infusion	Atrial fibrillation	No
	PALO IV infusion	Cardio-respiratory arrest	Yes
	PALO IV bolus	Cardio-respiratory arrest	Yes
	PALO IV infusion	Atrial flutter	Yes
		Cardiac arrest	Yes
		Palpitations	No
		Tachycardia	No
	PALO IV infusion	Sinus tachycardia	No
	PALO IV infusion	Arrhythmia supraventricular	No
	PALO IV infusion	Atrial fibrillation	Yes

(Source – Sponsor’s IR Response)

Subject (b) (6) developed a right bundle branch block which occurred after receiving the study drug, but the timing was such that it was unlikely related to drug administration (Day of onset was Day 8). It was characterized, however, as possibly related.

Subject (b) (6) developed atrial flutter after study drug administration (Day of onset was Day 7). Other explanations for the atrial flutter included possible cisplatin toxicity, mild electrolyte abnormalities, and concomitant chemotherapy administration. Given these issues, it was not possible to conclusively attribute the atrial flutter to study drug administration; however, the event was considered possibly related.

The other events were not considered by the Investigator to be related to study drug.

Medical Histories of PALO 15-17 Subjects

There were more cardiac disorders in the medical histories in the subjects of the 30 minute infusion arm compared to the 30 second bolus arm. Please see table below.

Table 77 – Medical Histories of PALO 15-17 Subjects

PALO-15-17
Table 14.1.2.18 Medical History: Prior diseases - Safety Population

MedDRA System Organ Class (SOC) MedDRA Preferred Term	IV PALO Infusion (N=225) n(%)	IV PALO Bolus (N=215) n(%)	Overall (N=440) n(%)
Number of patients with at least one prior disease	55 (24.4)	54 (25.1)	109 (24.8)
Blood and lymphatic system disorders			
Anaemia	3 (1.3)	3 (1.4)	6 (1.4)
Lymphadenitis	2 (0.9)	1 (0.5)	3 (0.7)
Lymphadenopathy mediastinal	0 (0.0)	1 (0.5)	1 (0.2)
Neutropenia	0 (0.0)	1 (0.5)	1 (0.2)
Neutropenia	1 (0.4)	0 (0.0)	1 (0.2)
Cardiac disorders			
Acute myocardial infarction	8 (3.6)	3 (1.4)	11 (2.5)
Arrhythmia	1 (0.4)	0 (0.0)	1 (0.2)
Atrial fibrillation	1 (0.4)	0 (0.0)	1 (0.2)
Atrial flutter	1 (0.4)	0 (0.0)	1 (0.2)
Atrial tachycardia	1 (0.4)	0 (0.0)	1 (0.2)
Bradycardia	1 (0.4)	0 (0.0)	1 (0.2)
Extrasystoles	0 (0.0)	1 (0.5)	1 (0.2)
Myocardial infarction	2 (0.9)	2 (0.9)	4 (0.9)
Endocrine disorders			
Goitre	1 (0.4)	2 (0.9)	3 (0.7)
Hyperthyroidism	1 (0.4)	1 (0.5)	2 (0.5)
Hyperthyroidism	0 (0.0)	1 (0.5)	1 (0.2)
Gastrointestinal disorders			
Abdominal hernia	14 (6.2)	16 (7.4)	30 (6.8)
Abdominal pain	0 (0.0)	1 (0.5)	1 (0.2)
Chronic gastritis	0 (0.0)	1 (0.5)	1 (0.2)
Duodenal ulcer	0 (0.0)	3 (1.4)	7 (1.6)
Duodenitis	4 (1.8)	1 (0.5)	2 (0.5)
Dysphagia	1 (0.4)	0 (0.0)	1 (0.2)
Enterocolitis	1 (0.4)	0 (0.0)	1 (0.2)
Gastric haemorrhage	0 (0.0)	1 (0.5)	1 (0.2)
Gastric haemorrhage	0 (0.0)	1 (0.5)	1 (0.2)

(Source – PALO 15-17 Study Report Page 198)

With all of these issues in mind (i.e., confounding concomitant medications, underlying conditions such as electrolyte disorders related to disease or chemotherapy, and the individual medical history of cardiac abnormalities), it was determined that the 30-minute infusion of IV palonosetron did not result in a cardiac signal.

8.5.2. NEPA 15-18 – Additional Analyses

Overall TEAE's (IV NEPA FDC vs. Oral NEPA FDC)

The percentage of patients who experienced at least 1 TEAE was slightly lower in the IV NEPA FDC group, 169 (83.3 %), as opposed to oral NEPA FDC group, 174 (86.6 %).

Specific TEAEs Occurring at ≥ 2% Higher Frequency in IV NEPA FDC Arm vs. Oral NEPA FDC Arm

The specific adverse events in greater than 2 percent more subjects as compared to the oral arm included GERD 5 (2.5%), Blood Creatinine Increase 12 (5.9%), Weight Decreased 9 (4.4%), and Nausea 20 (9.9%). Please see table below.

Table 78 - AEs occurring > 2 % more in the IV NEPA FDC Arm

Study NEPA 15-18	Adverse Event	IV NEPA FDC	Oral NEPA FDC
	% patients who experienced at least 1 TEAE	169 (83.3 %)	174 (86.6%)
	GERD	5 (2.5%)	0
	Blood Creatinine increased	12 (5.9%)	6 (3.0%)
	Weight Decreased	9 (4.4%)	4 (2.0%)
	Nausea*	20 (9.9%)	14 (7.0%)

(Source – Reviewer’s Table)

GERD and Weight Decreased

(b) (4)

Weight loss is also an expected phenomenon in cancer patients.

Blood Creatinine Increased

The blood creatinine increase was evaluated by looking at the shift tables provided by the applicant. Please see table below.

Table 79 – Shift Table Creatinine, Cycle 4, Visit 4 (Day 6) NEPA 15-18

NEPA-15-18
Table 14.3.4.5 Blood Chemistry - Shift Tables - Safety Population
Laboratory Parameter: Creatinine (umol/L)
Analysis Cycle: 4

	IV NEPA FDC (N=202)			Oral NEPA FDC (N=201)			Overall (N=404)		
	Baseline			Baseline			Baseline		
	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Visit 4 (day 6)									
Number of patients with Test Done		120			117			237	
Shift from baseline									
Low	2 (1.7)	3 (2.5)	0	3 (2.6)	3 (2.6)	0	5 (2.1)	6 (2.5)	0
Normal	14 (11.7)	90 (75.0)	0	17 (14.5)	84 (71.8)	0	31 (13.1)	174 (73.4)	0
High	0	11 (9.2)	0	0	10 (8.5)	0	0	21 (8.9)	0
Shift from same cycle last pre-Treatment value		118			116			234	
Low	2 (1.7)	3 (2.5)	0	4 (3.4)	2 (1.7)	0	6 (2.6)	5 (2.1)	0
Normal	3 (2.5)	98 (82.1)	1 (0.8)	9 (7.8)	88 (75.9)	3 (2.6)	12 (5.1)	186 (79.5)	4 (1.7)
High	0	7 (5.9)	4 (3.4)	0	7 (6.0)	3 (2.6)	0	14 (6.0)	7 (3.0)

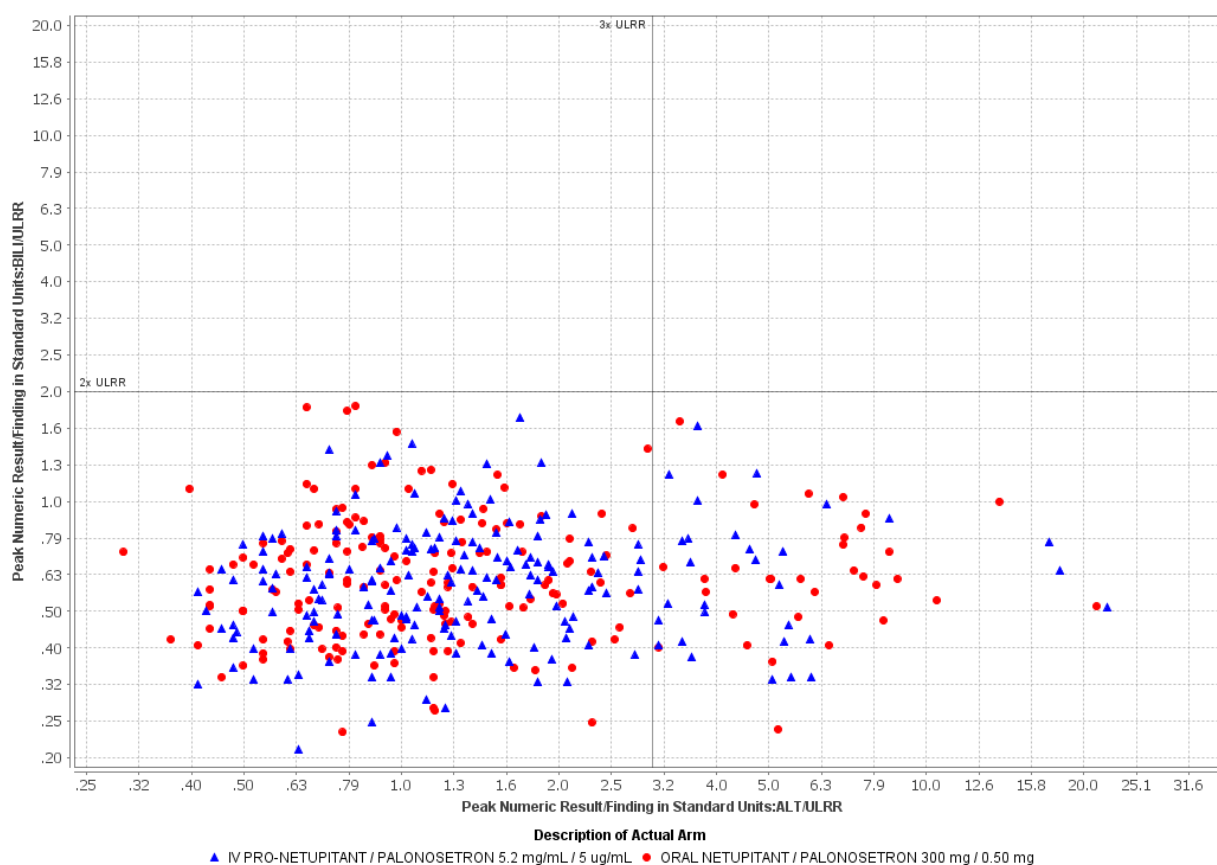
(Source – NEPA 15-18 Study Report Page 1579)

The number of patients with normal creatinine levels that shifted to a high level at the end of the study was 11 for the IV arm and 10 for the oral arm. The number of patients who developed renal failure in the IV arm was 3 (1.5%) and 8 (4.0%) in the oral arm. In general, an increase in creatinine may be expected in cancer patients undergoing cisplatin-based chemotherapy.

Transaminase Elevations

Finally, the number of patients in the NEPA 15-18 study with an increased ALT in the IV arm was 15 (7.4%) and 24 (11.9%) in the oral arm. The number of patients with an increased AST in the IV arm was 12 (5.9%) and 19 (9.5%) in the oral arm. None of the patients in this study met Hy's Law criteria. Please see figure below.

Figure 4 – Hy's Law Plot NEPA 15-18



(Source – Reviewer's Plot)

8.6. Specific Safety Studies/Clinical Trials

There were no additional safety studies conducted.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

Assessments of Human Carcinogenicity and/or Tumor Development were not made in the any of the human trials previously discussed (PNET 12-23, PALO 15-18, and NEPA 15-18). Please see Section 4.4.

8.7.2. Human Reproduction and Pregnancy

No patients became pregnant during the three studies in this development program. As such, no further information on pregnancy and lactation was obtained from these studies.

8.7.3. Pediatrics and Assessment of Effects on Growth

There are active two post-marketing requirements in place (for Akynzeo Capsules):

2769-2 - 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 an oral single administration of palonosetron in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

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

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 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

(b) (4)

Figure 5 - Bioequivalence Approach for Pediatric Development Program

(b) (4)

(Source – Agreed iPSP page 29)

The study that will meet the oral Akynzeo PREA PMR 2769-2 requirement is called (b) (4) followed by a multicenter, multinational, open-label, PK and safety study of IV pro-netupitant/palonosetron combination in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy patients 1 month to 17 years of age. The applicant plans to conduct studies in the (b) (4)

(b) (4)

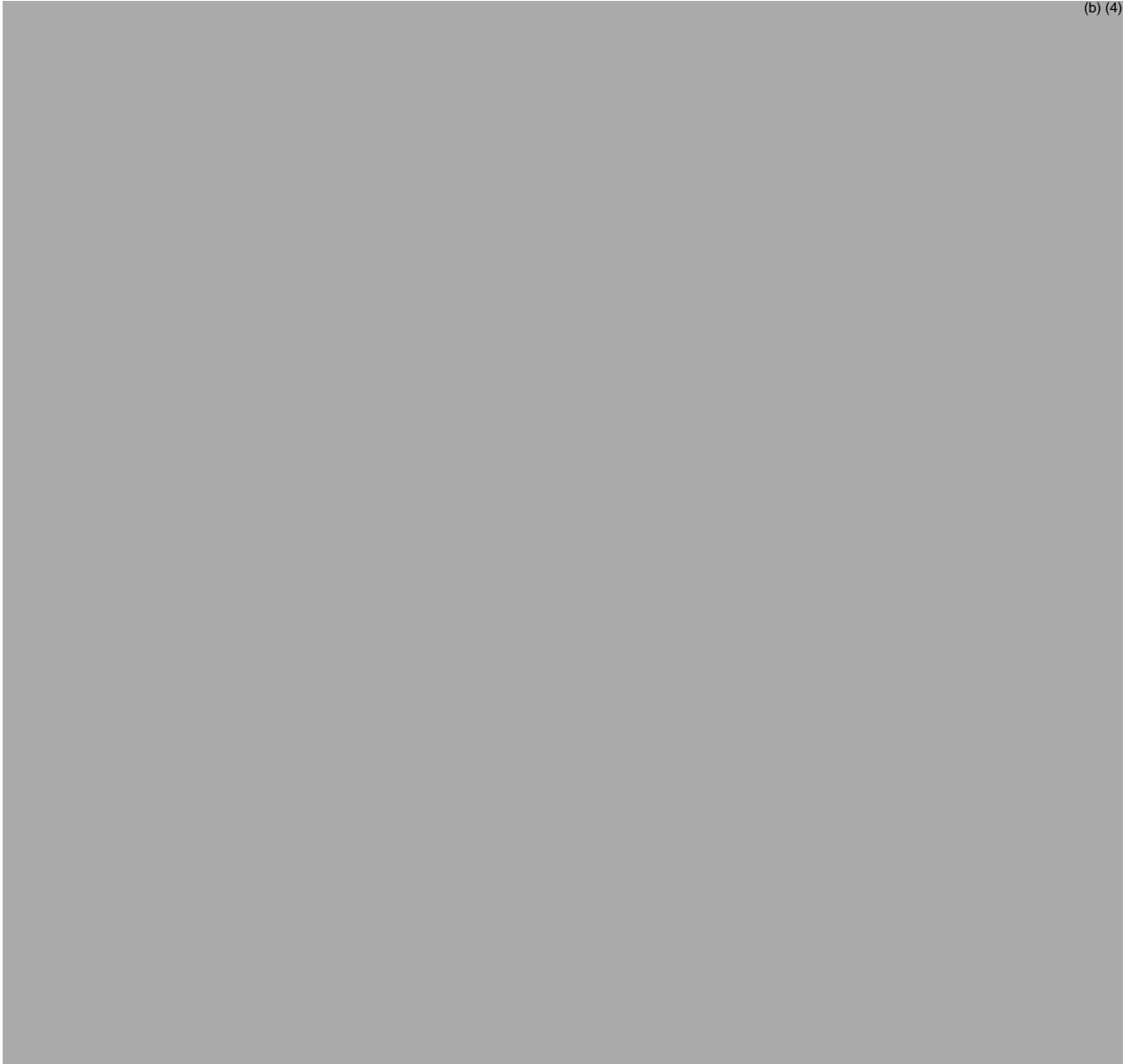
An IV nonclinical juvenile animal study with fosnetupitant administered to neonatal rats will be required. This study is needed to provide supporting safety data for the netupitant C_{max} and area under the curve (AUC) that may occur in their pediatric studies, both of which may exceed the respective values associated with the approved dose of oral netupitant in adults.

(b) (4) consistent with other pediatric study plans the Division has reviewed; the Division has encouraged sponsors to make every effort to enroll patients in this age range, to provide safety information for product labeling.

Please see the following table for the applicant's timeline.

Table 80 - Timetable for the NEPA IV FDC Pediatric Plan

(b) (4)



The PeRC reviewed the above information on November 29, 2017. The following is taken from the draft minutes of that meeting:

The PeRC agreed with the Division to grant a deferral in all pediatric studies because the product is ready for approval in adults.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No specific information is available on the treatment of overdose with Akynzeo[®] for injection. The highest dose of fosnetupitant administered to 203 cancer patients in a multiple cycle study was 235 mg (the recommended dose). The highest fosnetupitant dose administered to 9 healthy subjects was 353 mg (1.5 times the recommended dose). In addition, there is a low expectation of abuse potential, withdrawal, and/ or rebound with administration of Akynzeo[®] for injection based upon its mechanism of action and context of use.

The Controlled Substances Staff (CSS) concluded that Akynzeo for Injection should not be recommended for control under the Controlled Substances Act (CSA) because “the

results from the preclinical abuse potential studies show that the drug combination lacks abuse potential.” This conclusion is primarily based on the Applicant’s submission of pharmacokinetic information showing that fosnetupitant converts completely to netupitant in rats, dogs, and monkeys, and information showing that fosnetupitant is not CNS-active because it cannot cross the blood-brain barrier (although its metabolite, netupitant, does penetrate the CNS). Although CSS informed the Applicant (in a meeting in 2014²¹) that additional self-administration studies with fosnetupitant alone or with the combination of fosnetupitant + palonosetron would not be necessary, the Applicant conducted two self-administration studies in baboons with netupitant (the active metabolite of fosnetupitant) and with netupitant + palonosetron anyway; CSS concluded that neither drug treatment produced self-administration that was statistically significantly different than that produced by placebo, thus suggesting that these drug treatments do not produce rewarding effects.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

²¹Minutes of December 9, 2014 Meeting filed in DARRTS under IND 115,191

The Division of Pharmacovigilance – 1 (DPV-1) conducted a postmarket safety analysis dated August 29, 2016. This review was conducted in fewer than 10,000 patients, and at the time of its completion, Akynzeo® had been approved for 18 months. This analysis involved conducting a FAERS database search. The results are summarized in the following table.

Table 81 – Most Frequently Reported MedDRA Preferred Terms for Akynzeo Received by FDA October 10, 2014 to August 25, 2016.

Total Number of Reports* = 15			
Row	MedDRA PT	Number of FAERS Reports	Labeled [†] (Yes/No), Location or Other Category
1	Nausea	6	No; IR
2	Vomiting	5	No; IR
3	Disease progression	3	No; DR
4	Drug ineffective	3	No; DR
5	Dehydration	2	No; DR, the two cases reported refractory nausea and vomiting leading to dehydration
6	Alanine aminotransferase increased	1	Yes; AR (labeled under liver function laboratory abnormalities)
7	Arrhythmia	1	No; a single case contained strong alternative causes such as receipt of concomitant medications ^a (cisplatin, thymopentin) and underlying pulmonary hypertension
8	Atrial fibrillation	1	No; see Row 7
9	Blood chloride decreased	1	No; a single case reported that a patient who received concomitant cisplatin developed refractory nausea with laboratory value abnormalities
10	Blood creatine phosphokinase increased	1	No; see Row 7
11	Blood pressure systolic decreased	1	No; see Row 7
12	Cardiotoxicity	1	No; see Row 7
13	Constipation	1	Yes; AR
14	Diarrhoea	1	No; a single case contained strong alternative causes of receipt of concomitant medications ^b (cyclophosphamide, epirubicin)
15	Dizziness	1	No; see Row 7
16	Face oedema	1	No; a single case contained a strong alternative cause such as receipt of concomitant paclitaxel ^c
17	Fatigue	1	Yes; AR
18	Gamma-glutamyltransferase increased	1	No; see Row 9
19	Heart injury	1	No; see Row 7
20	Hepatic failure	1	No; a single case reported a patient with

			pancreatic cancer and hepatic metastases developed hepatic failure temporal to the administration of Akynzeo and unknown chemotherapy medications
21	Jaundice	1	No; see Row 20
22	Myocardial infarction	1	No; a single case reported a patient received multiple chemotherapy medications (cyclophosphamide, doxorubicin, vincristine, rituximab) prior to the event and had negative rechallenge to Akynzeo, the health care professional reporter attributed the event to the concomitant chemotherapy medications or progression of underlying disease (lung cancer)
23	Pancreatic carcinoma	1	No; see Row 20
24	Pulse abnormal	1	No; see Row 7
25	Retching	1	No; DR
26	Type I hypersensitivity	1	Yes; W/P
27	Urticaria	1	No; see Row 16

* A report may contain more than one preferred term.
[†] Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide or Other Categories: DR = Disease-related, IR = Indication-related, PR = Procedure-related, U = Uninformative

^a Cisplatin has been associated with the development of atrial fibrillation in multiple published literature cases. Thymopentin is an active pentapeptide moiety of thymopoietin (immunomodulatory hormone secreted by thymic epithelial cells). Tachycardia and slight decreases in blood pressure have been seen in 10-20% of patients treated with thymopentin.

^b Diarrhea is listed in the Adverse Reactions Section of the product label of cyclophosphamide and epirubicin.

^c Angioedema is listed in the Warnings Section of the paclitaxel product label.

(Source – DPV-1 Review Page 3)

A search of the FAERS database from October 10, 2014 (date of US approval) through August 25, 2016 yielded 15 reports; 11 reported a serious outcome. There were no reports with a serious outcome of death. Of the 27 most frequently reported MedDRA PTs, four were labeled events (Alanine aminotransferase increased, Constipation, Fatigue, Type I hypersensitivity) within the Akynzeo product label and six were indication-related or related to the patient's underlying disease (Nausea, Vomiting, Disease progression, Drug ineffective, Dehydration, Retching). The remaining 17 most frequently reported MedDRA PTs were associated with six unique reports. Because each of the six reports contained strong alternative causes for the adverse event (such as receipt of concomitant chemotherapy medications or progression of underlying disease), no causal role of Akynzeo with any of the unlabeled events could be established.

The postmarket safety summary suggested no new potential safety issues requiring additional safety reviews.

DPV-1 conducted another FAERS search on 11/22/2017 which identified 38 adverse event reports with netupitant and palonosetron. Of the 38 reports, 4 were duplicates, 2 contained limited information for assessment, and 1 did not report an adverse event. Of the remaining 31 reports, four were associated with a serious outcome of death. The four reports of death were not attributable to netupitant and palonosetron; two were from disease progression, one was from ileus in a patient who received multiple concomitant medications, and one did not provide a cause of death.

Twenty-six non-fatal reports described events that were indication-related (nausea/vomiting n=6), related to the patient's underlying disease (disease progression n=3, pain n=1), associated with strong alternative causes (n=13), or were already contained in the netupitant and palonosetron product label (allergic reaction n=2, headache n=1). The 13 reports that contained strong alternative causes described the events of cytopenias (n=9), cardiac dysfunction (n=2), or dermatitis (n=1) after receipt of concomitant chemotherapy and back pain from pre-existing degenerative vertebral changes (n=1). No change in frequency or severity was noted with the three reports of the labeled adverse events of allergic reaction (n=2) and headache (n=1).

The remaining non-serious report contained the unlabeled event of euphoric mood. The report described a 75-year-old female receiving denosumab and erlotinib (administration dates unknown) for treatment of lung cancer, who felt "high" after receiving netupitant and palonosetron for prophylaxis of nausea and vomiting. Netupitant and palonosetron was discontinued and the patient recovered on an unknown date. Euphoric mood is listed in the Adverse Reactions (Section 6.1) of the Aloxi (palonosetron) label.

Reviewer Comment: No safety issues/ signals were identified that are expected to require further post-marketing requirements or commitments for Akynzeo® for injection.

8.8.2. Expectations on Safety in the Postmarket Setting

Please see Section 8.8.1. There were no safety issues identified in this drug development program that would be cause for concern in the post-marketing setting.

8.9 Additional Safety Issues from Other Disciplines

There are no additional safety issues from other disciplines requiring discussion here.

8.10 Integrated Assessment of Safety

PNET 12-23 was conducted in healthy subjects. No new safety signals were identified in this study.

The PALO 15-17 study's focus was determining non-inferiority the 30-minute infusion dosing of IV palonosetron compared to the previously approved 30 second bolus dosing. Patients in this trials did not receive both components of Akynzeo® for injection. As such, the safety focus was to evaluate for safety signals were related to change in the infusion duration. In general, the TEAEs were evenly balanced between the two treatment arms. The adverse events that were higher in the 30-minute infusion arm were not new issues and had been addressed in the Aloxi label. Review of the narratives for cardiac events that occurred in the 30- minute infusion arm revealed that the events could not be conclusively attributed to the change in duration in infusion. Moreover, the patients in the 30-minute infusion arm collectively had more cardiac diseases in their medical histories. As such, no new safety signals were identified in this study.

The NEPA 15-18 trial was the dedicated safety study. The subjects were cancer patients, and they received both components of the drug. Again, the TEAEs were evenly balanced between the two treatment arms. For the most part, there were no new adverse events that were not already addressed in the label. The two exceptions were nausea and blood creatinine increase. When analyzed using shift tables, the numbers of subjects with normal creatinine levels that became elevated by the end of the study was similar between the two treatment arms. Nausea was considered part of the underlying disease (i.e., CINV) rather than a true adverse event. Again, no new safety signals were identified in this study.

Akynzeo® for injection does not appear to have new safety signals based on the data from PNET 12-23, PALO 15-18, and NEPA 15-18.

Reviewer Comment: From a safety perspective, Akynzeo® for injection poses no additional risks to cancer patients compared to oral Akynzeo®.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meetings or other external consultations were required.

10 Labeling Recommendations

10.1 Prescribing Information

For proposed labeling changes, please see table below.

Table 82 – Labeling Recommendations

FDA Proposed	Rationale
Combining the Labels of oral and IV Akynzeo®	In a meeting that occurred with the Sponsor on November 2016, the Division encouraged the Sponsor to combine oral and IV products into one label unless there was a compelling reason to separate them, such as a different indication. The Division determined that the information of the two products was similar enough to keep the labels together.
1 INDICATIONS AND USAGE AKYNZEO for injection is indicated <u>in combination with dexamethasone</u> in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy <u>not including anthracycline plus cyclophosphamide chemotherapy</u>.	“<u>in combination with dexamethasone</u>”: Per the labeling regulations (21 CFR 201.57), if a drug is used for an indication only in conjunction with a primary mode of therapy (e.g., another drug), a statement that the drug is indicated as an adjunct to that mode of therapy must be included in the Indications and Usage section. “<u>not including anthracycline plus cyclophosphamide chemotherapy</u>”: The applicant has not submitted a study that establishes the contribution of the fosnetupitant component of Akynzeo® for injection to prevention of delayed phase CINV in cancer patients receiving anthracycline plus cyclophosphamide chemotherapy. Intravenous palonosetron is approved for prevention of delayed phase CINV, based on a trial that primarily enrolled patients treated with anthracycline plus cyclophosphamide chemotherapy. As such, this statement is required per prior agreement between the Division and applicant.
14 CLINICAL STUDIES <u>Study 5</u> (b) (4)	This language must be deleted because the study was not designed to answer an efficacy question. As such, efficacy claims could not be made in the label per prior agreement between the Division and the Sponsor. This safety study is presented in Section 6 (Adverse Reactions) of the label.

6 ADVERSE REACTIONS <u>6.1 Clinical Trials Experience</u> <u>Akynzeo for Injection</u> The safety of AKYNZEO for injection was evaluated in 203 patients in an active-controlled multi-cycle (median 4 cycles, range of 1-4 cycles) safety clinical study in patients receiving HEC (including cisplatin, cyclophosphamide, carmustine, dacarbazine and mechlorethamine) compared to 201 patients receiving AKYNZEO capsules (NCT 02517021). The median age was 60 years, 46% were female, 99.5 % were White, 0.3% were Asian, and 0.3% were Hispanic. All patients received a single dose of AKYNZEO for injection 30 minutes prior to the start of each chemotherapy cycle; dexamethasone was co-administered with AKYNZEO. The safety profile of AKYNZEO for injection was generally similar to that seen with AKYNZEO capsules.	A description of Study NEPA-15-18 appears in Section 6.1 of the label only (not in Section 14 of the label). (b) (4) This statement requires removal as these issues are no longer concerns after the safety review.

10.2. Patient Labeling

The applicant’s proposed Patient Package Insert, which is not a Medication Guide, in the prescribing information adequately explains the use of Akynzeo® for injection.

10.3. Nonprescription Labeling

This is not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

This is not applicable. No REMS is currently recommended, because of the favorable safety profile of Akynzeo for Injection; there are no additional risk management strategies required beyond the recommended labeling.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not Applicable.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

Not applicable.

12 Postmarketing Requirements and Commitments

The following two PREA post-marketing requirements will be included in the approval letter:

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

Final Protocol Submission: 06/2020

Study Completion: 06/2021

Final Report Submission: 09/2021

3292-2 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

Study Completion: 07/2024

Final Report Submission: 12/2024

13 Appendices

13.1. References

1. Lorusso, V. Management of chemotherapy-induced nausea and vomiting by risk profile: role of netupitant/ palonosetron. *Therapeutics and Clinical Risk Management*. 2016 Jun 7;12:917-25. doi: 10.2147/TCRM.S89215. eCollection 2016.
2. Hesketh, P.J. *et. al.* Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology*. 2017 35:28, 3240-3261.
3. www.asco.org/guidelines/antiemetics

13.2. Financial Disclosure

APPEARS THIS WAY ON ORIGINAL

Covered Clinical Study (Name and/or Number): PNET 12-23

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>13</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PALO-15-17

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>274</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>n/a</u> Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>n/a</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NEPA-15-18

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>362</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>n/a</u> Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details	Yes ☐	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>n/a</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

CHARLES G LINE
04/16/2018

ANIL K RAJPAL
04/16/2018

DONNA J GRIEBEL
04/19/2018

JULIE G BEITZ
04/19/2018

Comments on NDA 210493 AKYNZEO® (fosnetupitant and palonosetron) for injection

From: R. Wange, AD (Acting)

Date: 04/06/2018

1. I have reviewed both the primary and secondary reviews and concur that there are no pharm-tox related approval issues.
2. Comments previously relayed to the pharm-tox review team were addressed as appropriate.
3. I have reviewed and concur with the proposed product labeling.

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

/s/

RONALD L WANGE
04/06/2018

MEMORANDUM

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

FROM: David B. Joseph, PhD
Lead Pharmacologist
Division of Gastroenterology and Inborn Errors Products

DATE: December 21, 2017

SUBJECT: NDA 210493 (SD # 1 dated April 20, 2017)

Sponsor: Helsinn Healthcare SA

Drug Product: AKYNZEO® (fosnetupitant and palonosetron) for injection

Comments:

There are no nonclinical issues which preclude the approval of Akynzeo for injection. I concur with the recommendations related to approvability and labeling revisions, as stated in the Pharmacology/Toxicology review by Dr. Ke Zhang, dated 12/20/2017.

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

/s/

DAVID B JOSEPH
12/21/2017

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 210493
Supporting document/s: 1
Applicant's letter date: April 20, 2017
CDER stamp date: April 20, 2017
Product: AKYNZEO / Fosnetupitant-Palonosetron
Combination Powder for infusion
Indication: Prevention of acute and delayed nausea and
vomiting associated with initial and repeat
courses of highly emetogenic cancer
chemotherapy [REDACTED] (b) (4)
[REDACTED] in adults
Applicant: Helsinn Healthcare SA
Pazzallo – Lugano, Switzerland
U.S. Agent
August Consulting, Inc.
Austin, TX
Review Division: Gastroenterology and Inborn Errors Products
Reviewer: Ke Zhang, PhD
Supervisor/Team Leader: David Joseph, PhD
Division Director: Donna Griebel, MD
Project Manager: Mary Chung

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210,493 are owned by Helsinn Healthcare SA or are data for which Helsinn Healthcare SA has obtained a written right of reference. Any information or data necessary for approval of NDA 210,493 that Helsinn Healthcare SA does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of this NDA.

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1. Executive Summary

1.1 Introduction

AKYNZEO IV is a fixed-dose combination of two active drug substances, fosnetupitant chloride hydrochloride and palonosetron hydrochloride. Fosnetupitant is quickly converted to netupitant in vivo. Netupitant is a substance P/NK-1 (neurokinin-1) receptor antagonist. Palonosetron is a 5-HT₃ receptor antagonist.

Oral AKYNZEO® (capsules) was approved as a fixed-dose combination of 300 mg netupitant and 0.5 mg palonosetron equivalent in 2014 under NDA 205718 for the prevention of chemotherapy-induced nausea and vomiting (CINV).

Palonosetron HCl is approved as a single agent for prevention of CINV under the tradename ALOXI® (0.25 mg solution for intravenous injection, under NDA 21372). An oral formulation (50 mg softgel capsules) was approved under NDA 22233, but was later withdrawn from marketing.

The sponsor seeks market approval for AKYNZEO injection for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

1.2 Brief Discussion of Nonclinical Findings

Given the rapid metabolic conversion of fosnetupitant to netupitant, the Agency accepted the sponsor's proposal to conduct intravenous toxicity studies of fosnetupitant alone and the combination of fosnetupitant + palonosetron using a maximum duration of 4 weeks, to support marketing approval. It is noted that the toxicology program for oral Akynzeo included oral studies of up to 6 months in rats and 9 months in dogs using netupitant alone, and 3-month studies of the combination of netupitant + palonosetron in rats and dogs. The toxicity studies of fosnetupitant alone and the combination of fosnetupitant + palonosetron did not produce any novel findings, as compared to the toxicology program for oral Akynzeo.

Fosnetupitant alone was tested in intravenous toxicity studies of up to 4 weeks in rats and dogs.

In the 4-week intravenous toxicity study in rats, fosnetupitant was tested at 0, 3.95, 13.16, and 39.47 mg/kg/day. The high dose of 39.47 mg/kg/day is considered as the NOAEL.

In the 4-week intravenous toxicity study in dog, fosnetupitant was tested at 0, 1.32, 3.95, and 13.16 mg/kg/day. The high dose of 13.16 mg/kg/day was NOAEL.

4-Week intravenous toxicity studies with the combination of fosnetupitant and palonosetron were conducted in rats and dogs. In the 4-week intravenous toxicity study in rats, fosnetupitant was tested at 3.95, 13.16, and 39.47 mg/kg/day in combination with palonosetron at 1, 3, and 10 mg/kg/day, respectively. The high dose of 39.47/10 mg/kg/day was the NOAEL.

In the 4-week intravenous toxicity study in dogs, fosnetupitant in combination with palonosetron was tested at 1.316 + 1 mg/kg/day, 3.95 + 3 mg/kg/day, and 13.16 + 10/6 mg/kg/day. The dose of 10 mg/kg/day palonosetron was reduced to 6 mg/kg/day on day 15 due to convulsions. The treatment resulted in convulsion, salivation, and swelling at injection site in high dose group. Treatment increased heart rate and prolonged QT_c intervals in the mid- and high-dose groups. The dose of 1.316 mg/kg/ day fosnetupitant + 1 mg/kg/day palonosetron was the NOAEL.

Fosnetupitant was negative in the Ames test, in vitro chromosome aberration test in human lymphocytes, and the in vivo rat micronucleus test.

In an embryo-fetal development study in rats, intravenous administration of 39.47 mg/kg/day fosnetupitant (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) produced delayed ossification of pubis. No effects on embryo-fetal development were observed with IV administration of up to 13.16 mg/kg/day fosnetupitant in rats (2 times the human AUC for netupitant). In a rabbit embryo-fetal development study, an increase in resorptions was observed with intravenous administration of fosnetupitant at 6.25 mg/kg/day and higher in rabbits (9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). No effects were observed in rabbits at 3.13 mg/kg/day (5.4 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant). In rabbits, the embryo-fetal effects of intravenous fosnetupitant differed from the effects of oral netupitant, and this difference can be attributed to the minimal transformation of fosnetupitant to netupitant in rabbits, in contrast to the rapid metabolism of fosnetupitant in rats and humans.

In a pre-/postnatal study in rats, intravenous administration of 39.47 mg/kg/day fosnetupitant in rats (3 times the human AUC for netupitant) produced lower

bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13.16 mg/kg/day (2 times the human AUC for netupitant).

Fosnetupitant produced no effects on fertility or early embryonic development in rats, at doses up to 39.47 mg/kg IV.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, there are no approvability issues.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

Established Pharmacologic Class (EPC) in HIGHLIGHTS

The following statement containing the proposed EPC (FDA text phrase) for fosnetupitant appears in the Indications and Usage section of the Highlights:

AKYNZEO is a (b) (4) combination of palonosetron, a serotonin-3 (5-HT₃) receptor antagonist, and netupitant or fosnetupitant, (b) (4) a substance P/neurokinin-1 (NK-1) receptor antagonist

The term, “*substance P/neurokinin-1 (NK-1) receptor antagonist*”, is the FDA text phrase for netupitant, shown in the eList. Since fosnetupitant is rapidly converted to netupitant following administration, the proposed fosnetupitant EPC, “*substance P/neurokinin-1 (NK-1) receptor antagonist*”, is acceptable.

Sponsor’s Proposed Version:

8.1. Pregnancy

Risk Summary

(b) (4)



Animal Data

Daily administration of up to 30 mg/kg netupitant in rats (3.7 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis produced no effects on

embryo-fetal development. However, an increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternbrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e., loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day. Daily administration of up to 30 mg/kg netupitant (3.7 times the human AUC at the recommended human dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

(b) (4)

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended human oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended human oral dose based on body surface area) during the period of organogenesis.

Evaluation: The proposed version is compliant with the PLLR format, and the text that includes information on studies with oral netupitant or palonosetron is the same as that of the currently approved label for Akynzeo® capsules. Minor changes are recommended for this text, as a result of the addition of studies with intravenous fosnetupitant. We also recommend changes in the text and the animal to human AUC ratios (fosnetupitant and netupitant) for the intravenous studies with fosnetupitant. The animal and human AUC values that were used to calculate the recommended AUC ratios are shown in the tables presented in the Integrated Summary and Safety Evaluation. The recommended version below

was developed in collaboration with the Maternal Health review team (Carrie Ceresa, Jane Liedtka, and Miriam Dinatale).

Recommended Version:

Risk Summary

Limited available data with AKYNZEO use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.

In animal reproduction studies with netupitant, no effects on embryo-fetal development were observed following daily oral administration in pregnant rats during the period of organogenesis at doses up to 3.7 times the human AUC (area under the plasma concentration-time curve) at the recommended single dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily oral administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy. Daily oral administration of netupitant in rats up to 3.7 times the human AUC at the recommended dose during organogenesis through lactation produced no adverse effects in the offspring (*see Data*).

In animal reproduction studies with fosnetupitant, delayed ossification of pubis occurred after intravenous administration in rats during the period of organogenesis at a dose 3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy. In pregnant rabbits, an increase in resorptions was observed with daily intravenous administration of fosnetupitant during the period of organogenesis at doses up to 9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy. Daily intravenous administration of fosnetupitant (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) in rats during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development (*see data*).

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended oral dose in rats and rabbits, respectively (*see Data*).

Based on animal data from netupitant studies, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Netupitant

Daily oral administration of up to 30 mg/kg netupitant in rats (3.7 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced no effects on embryo-fetal development. However, an increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily oral administration of netupitant in rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternbrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e., loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day. Daily oral administration of up to 30 mg/kg netupitant (3.7 times the human AUC at the recommended dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

Fosnetupitant

Daily intravenous administration of 39 mg/kg/day fosnetupitant in rats (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced delayed ossification of pubis. No effects on embryo-fetal development were observed with daily administration of up to 13 mg/kg fosnetupitant in rats (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Due to the limited systemic exposure to fosnetupitant in pregnant rats, it is not possible to provide an AUC-based comparison of fosnetupitant exposure in rats and humans. An increase in resorptions was observed with daily intravenous administration of fosnetupitant at 6 mg/kg/day and higher in rabbits (9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. No effects were observed in rabbits at 3 mg/kg/day (5.4 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended

single dose to be given with each cycle of chemotherapy). Daily intravenous administration of 39 mg/kg fosnetupitant in rats (3 times the AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13 mg/kg/day (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy).

Palonosetron

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended oral dose based on body surface area) during the period of organogenesis.

Sponsor's Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Netupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with netupitant. Netupitant was not genotoxic in the Ames test, the mouse lymphoma cell mutation test, or the *in vivo* rat micronucleus test.

Daily oral administration of netupitant in rats at doses up to 30 mg/kg (1.9 times the human AUC in male rats and 3.7 times the human AUC in female rats at the recommended human dose) had no effects on fertility or reproductive performance.

Fosnetupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with fosnetupitant.

Fosnetupitant was not genotoxic in the Ames test and *in vivo* rat micronucleus test. In human lymphocytes did not induce structural chromosomal aberrations.

(b) (4)

(b) (4)

Palonosetron

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30, and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (plasma AUC) of about 90 to 173 times the human exposure (AUC=49.7 ng•h/mL) at the recommended oral dose of 0.5 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30, and 60 mg/kg/day and 15, 45, and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (plasma AUC) of 82 and 185 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test, or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Evaluation: The text that includes information on studies with oral netupitant or palonosetron is the same as that of the currently approved label for Akynzeo® capsules. The fertility study of fosnetupitant in rats was conducted using intravenous administration, not oral administration (b) (4)

We recommend changes in the text and the animal to human AUC ratios (fosnetupitant and netupitant) for this study. The animal and human AUC values that were used to calculate the recommended AUC ratios are shown in the tables presented in the Integrated Summary and Safety Evaluation. Since TK evaluation was not performed in the fertility study with fosnetupitant, AUC values from the 4-week intravenous toxicity study in rats (mean of male female values) were used for the calculations.

Recommended Version:

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Netupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with netupitant. Netupitant was not genotoxic in the Ames test, the mouse lymphoma cell mutation test, or the *in vivo* rat micronucleus test.

Daily oral administration of netupitant in rats at doses up to 30 mg/kg (1.9 times the human AUC in male rats and 3.7 times the human AUC in female rats at the recommended human dose) had no effects on fertility or reproductive performance.

Fosnetupitant

Long-term studies in animals to evaluate carcinogenic potential have not been performed with fosnetupitant.

Fosnetupitant was not genotoxic in the Ames test and *in vivo* rat micronucleus test. In human lymphocytes, fosnetupitant did not induce structural chromosomal aberrations.

Daily intravenous administration of fosnetupitant in rats at doses up to 39 mg/kg (1.3 times the human AUC for fosnetupitant and 4.3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) had no effects on fertility or reproductive performance.

Palonosetron

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30, and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (plasma AUC) of about 90 to 173 times the human exposure (AUC=49.7 ng•h/mL) at the recommended oral dose of 0.5 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30, and 60 mg/kg/day and 15, 45, and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (plasma AUC) of 82 and 185 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test, or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

2 Drug Information

2.1 Drug

Trade Name: AKYNZEO for injection (235 mg fosnetupitant and 0.25 mg palonosetron)

Fosnetupitant (Pronetupitant)

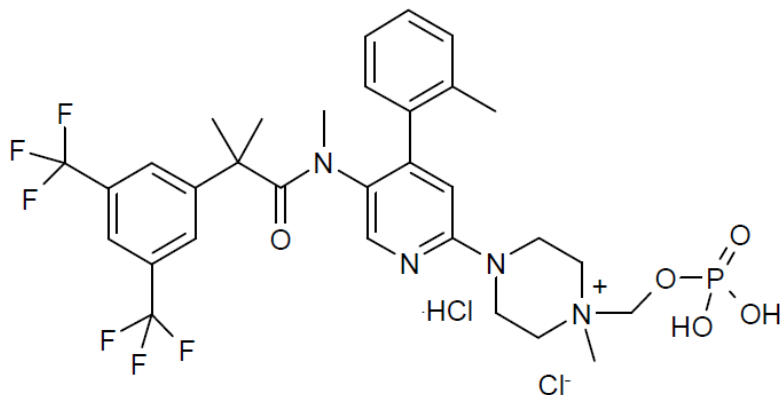
Code Name: 08-PNET

Chemical Name:

2-(3,5-bis-trifluoromethylphenyl)-N-methyl-N-[6-(4-methyl-4-O-methylene-phosphatepiperazinium-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide chloride hydrochloride

Molecular Formula/Molecular Weight: $C_{31}H_{36}F_6N_4O_5P \cdot Cl \cdot HCl$ / 761.53

Structure or Biochemical Description:



Pharmacologic Class: NK₁ receptor antagonist

Palonosetron HCl

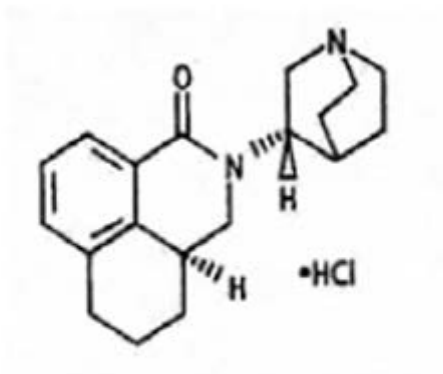
Code Name: RS-25259-197

Chemical Name:

(3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride

Molecular Formula/Molecular Weight: C₁₉H₂₄N₂O•HCl / 332.87

Structure or Biochemical Description:



Palonosetron HCl

Pharmacologic Class: 5-HT₃ receptor antagonist.

2.2 Relevant INDs, NDAs, and DMFs: IND 115191, NDA 205718, DMF

(b) (4)

2.3 Drug Formulation

AKYNZEO for injection is a fixed-dose combination product, supplied as a powder for infusion. The diluent for reconstitution is 5% glucose solution or 0.9% sodium chloride. The formulation ingredients are listed in the sponsor's table below.

Table 1 Quantitative Composition Per Vial

Component	Reference	Function	Quantity per Vial*****
Fosnetupitant*	Internal	Drug substance	235 mg
Palonosetron**	USP	Drug substance	0.25 mg
Edetate disodium (b) (4)	USP, Ph.Eur.	(b) (4)	6.4 mg
Mannitol	USP, Ph.Eur.	(b) (4)	760 mg
Sodium Hydroxide	USP/NF, Ph.Eur.	(b) (4) pH adjustment	q.s. for (b) (4) (b) (4) pH adjustment
Hydrochloric Acid	USP/NF, Ph.Eur.	pH adjustment	q.s. for pH adjustment
(b) (4)			

* Mass expressed as free base: corresponding to 260 mg/vial of fosnetupitant chloride hydrochloride salt (USAN name: fosnetupitant chloride).

** Mass expressed as free base: corresponding to 0.28 mg/vial of palonosetron hydrochloride

(b) (4)

***** No overages of the actives is used during the formulation and manufacturing. There is a (b) (4)% fill excess accordingly with USP <1151> to permit withdrawal and to achieve the administration of the labeled dose of both actives, as described in Table 2.

2.4 Comments on Novel Excipients: None

2.5 Comments on Impurities/Degradants of Concern:

The sponsor’s table below includes compounds designated as potential impurities in fosnetupitant chloride hydrochloride (08-PNET) drug substance.

Table 1 Potential Impurities Monitored in 08-PNET Drug Substance

Compound	Name	Structural formula	Specification
(b) (4)			

(b) (4)

the table above. See Appendix for a summary of the QSAR reports.

The potential impurities, (b) (4) (not listed in the table above), tested positive in the Ames test. (b) (4) (b) (4) has an acceptance criterion of not more than (b) (4) in drug substance (08-PNET), which would allow a maximum exposure of (b) (4) dose. Based on the dosing frequency of Akynzeo injection (once with each cycle of chemotherapy), the acceptable intake for mutagenic impurities in the drug product is considered to be 120 mcg/dose, as per ICH guidance M7. Therefore, the proposed specification for (b) (4) is acceptable.

The sponsor conducted analysis of three validation batches and three registration batches to measure the amount of the genotoxic impurity (b) (4) (see sponsor's table below). (b) (4) was undetected in six batches using a highly sensitive assay (limit of detection = (b) (4)). Therefore, based on the batch analysis results, (b) (4) was not specified, which is acceptable from a nonclinical viewpoint.

Table 7: Results for registration and validation batches

Compound	08-PNET	08-PNET	08-PNET	08-PNET	08-PNET	08-PNET
(b) (4)	Lot 35002359	Lot 35002360	Lot 35003193	Lot 36001994	Lot 36002442	Lot 36003031
	Not detected ¹	Not detected ¹	Not detected ¹	Not detected ¹	Not detected ¹	Not detected ¹
	Not detected ²	Not detected ²	Not detected ²	Not detected ²	Not detected ²	Not detected ²

¹Below LoD = (b) (4)

²Below LoD = (b) (4)

The components of the container closure system (glass vial and rubber stopper) which are in direct contact with the drug product are accepted for use in other FDA-approved drug products. Therefore, there is no concern about the potential for leaching of chemicals, especially since the drug product is a powder.

The sponsor provided an extractables study for (b) (4) used in the manufacturing system for the drug product (b) (4). There are no concerns about the potential exposure to the identified extractables (see Appendix for the review of the extractables study).

2.6 Proposed Clinical Population and Dosing Regimen

AKYNZEO for injection is indicated for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

One vial of AKYNZEO for injection containing 235 mg fosnetupitant equivalent and 0.25 mg palonosetron equivalent will be reconstituted in 50 ml of 5%

dextrose injection or 0.9% sodium chloride injection, which will be given via 30-minute infusion starting approximately 30 minutes prior to the chemotherapy.

Regulatory Background

AKYNZEO (fosnetupitant and palonosetron) for injection was developed under IND 115191 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. A pre-NDA meeting was held on December 23, 2016. The sponsor agreed to submit final study reports of all required nonclinical studies. All study reports needed to support approval were submitted in this NDA.

Oral AKYNZEO® (capsules) was approved as a fixed-dose combination of 300 mg netupitant and 0.5 mg palonosetron equivalent in 2014 under NDA 205718 for the prevention of chemotherapy-induced nausea and vomiting (CINV).

Palonosetron HCl is approved as a single agent for prevention of CINV under the trade name ALOXI® (0.25 mg solution for intravenous injection under NDA 21372).

3 Studies Submitted

Pharmacology

Pharmacokinetics/ADME

Toxicology

Table 15: Drug Substance Toxicology

Test Article: Fosnetupitant

Batch No.	Purity (%)	Specified Impurities (area percent)	Study Number	Type of Study (IV unless otherwise indicated)
PROPOSED SPECIFICATION:				
30005278	94.9	No major impurity	PNET-11-06	Preliminary 2-week rat
30005278	94.4	No major impurity	PNET-11-21	2-Week rat
30005278	94.9	No major impurity	PNET-11-07	Preliminary 2-week dog
30005278	94.4	No major impurity	PNET-11-22	2-Week rat
30005278	94.1	No major impurity	PNET-13-18	4-Week rat
32003228	96.7	No major impurity	PNET-13-27	4-Week dog
30005278/32003068	94.6/97.8	No major impurity	NEPA-13-51	4-Week rat
30005278/32003228	94.6/97.5	No major impurity	NEPA-13-52	4-Week dog
30005278	94.1	No major impurity	PNET-12-04	Ames test
30005278	93.6	No major impurity	PNET-12-05	Chromosome aberrations test
32003228	97.7	No major impurity	PNET-13-49	<i>In vivo</i> Micronucleus assay
32003228	97.7	No major impurity	PNET-13-64	Rat fertility and early embryonic development
32003228/30005278	96.7/94.6	No major impurity	PNET-13-33	Rat embryo-fetal development
32003068	97.8	No major impurity	PNET-13-56	Rat embryo-fetal development (main)
34003433	96.8	No major impurity	PNET-15-85	Rat pre- and postnatal development including maternal function

Batch No.	Purity (%)	Specified Impurities (area percent)	Study Number	Type of Study (IV unless otherwise indicated)
30005278/32003228	94.4/97.8	No major impurity	PNET-13-30	Rabbit embryo-fetal development
30005278	94.6	No major impurity	PNET-13-53	Rabbit embryo-fetal development
32003228	97.8	No major impurity	PNET-13-71	Rabbit embryo-fetal development (main)
116635/P40201A*	102.5	NA	PNET-14-12	Intravenous, paravenous and intra-arterial tolerance study in rabbits
116635/P40201A*	102.5	NA	PNET-13-65	Bovine corneal opacity/permeability (BCOP) assay
116635/P40201A*	102.5	NA	PNET-13-44	Rabbit acute dermal irritation study
116635/P40201A*	102.5	NA	PNET-13-46	Dermal sensitisation study in guinea pigs
116635/P40201A*	102.5	NA	PNET-13-66	Cell phototoxicity assay
116635/P40201A*	102.5	NA	PNET-14-10	Active systemic anaphylaxis study in guinea pigs
116635/P40201A*	102.5	NA	PNET-14-11	Passive cutaneous anaphylaxis study in guinea pigs

NA: Not Applicable

*: Batch number of fosnetupitant lyophile

3.1 Studies Reviewed

All studies mentioned above were reviewed.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Fosnetupitant is quickly converted to netupitant in vivo. Netupitant is a substance P/ NK-1 (neurokinin-1) receptor antagonist. For information on the pharmacology of netupitant and its metabolites, see the Pharmacology/ Toxicology review of NDA 205718 by Dr. Ke Zhang, dated 06/19/2014. Palonosetron is a 5-HT₃ receptor antagonist. Some published reports suggest that a combination of a NK₁ receptor antagonist and a 5-HT₃ receptor antagonist is more effective in the control of acute and delayed emesis as compared to a 5-HT₃ receptor antagonist alone.

In vitro studies:

Binding assays were conducted to assess fosnetupitant in a broad panel of 80 receptors and ion channels. The investigations with an initial batch of

fosnetupitant (batch no: 2014-Netu/219/1) revealed that it produced more than 50% inhibition of the following ligand binding activities: hNK1 agonist ($IC_{50} < 0.28$ nM), hNK3 antagonist and agonist ligands ($IC_{50} = 0.8$ μ M and $IC_{50} = 0.42$ μ M, respectively), h5-HT₆ agonist ($IC_{50} = 6.3$ μ M), Ca²⁺ channel (diltiazem site) antagonist ($IC_{50} = 2$ μ M), and Ca²⁺ channel (verapamil site) antagonist ($IC_{50} = 5.4$ μ M) (PNET-12-32).

An additional receptor/ion channel screening assay with a purified batch of fosnetupitant (batch no. SJ-506-Pool-X) was conducted on the same panel of receptors and ion channels, and the results indicated that fosnetupitant with the purified batch also induced more than 50% inhibition on the same receptors/ion channels as in the above binding study (PNET-13-12).

The in vitro effect of fosnetupitant vs netupitant has been investigated in CHO cells expressing human NK1 receptors (calcium mobilization assay induced by Substance P) and in the assay for Substance P-induced contraction of guinea pig ileum. In CHO cells, 100 nM fosnetupitant was more effective than 100 nM netupitant in causing a rightward shift of the Substance P response with pK_b values of 8.72 and 7.54 for fosnetupitant and netupitant, respectively. In guinea pig ileum preparations, both fosnetupitant and netupitant inhibited the Substance P-induced contractions with pK_a ~9 when pre-incubated for 5 minutes. However, with a 2-minute pre-incubation, only fosnetupitant inhibited the Substance P-induced contractions (Peptides 69: 26–32, 2015, Ruzza et al).

In vivo studies:

In mice, intravenous administration of netupitant and fosnetupitant (0.1, 1 and 10 mg/kg) 120 minutes before dosing with Substance P produced significant dose-dependent inhibition of nociceptive behavior, including scratching, biting, and licking, as induced by Substance P.

4.2 Secondary Pharmacology

No studies with fosnetupitant were submitted. For information on the secondary pharmacology of netupitant, see the Pharmacology/Toxicology review of NDA 205718 by Dr. Ke Zhang, dated 06/19/2014.

4.3 Safety Pharmacology

Central Nervous System:

A single IV dose of fosnetupitant at 13.16 and 39.47 mg/kg had no effects on behavioral, neurological, or autonomic functions in rats. At a higher dose of 118.42 mg/kg, fosnetupitant induced ataxic gait, increased pain response, and increased heart and respiratory rates.

Single IV doses of fosnetupitant at 13.16, 39.47 and 79 mg/kg did not enhance metrazol-induced convulsant activity (twitches and tremors) in rats, but at a dose of 79 mg/kg, fosnetupitant resulted in tonic convulsion in one rat. In another study in rats, single IV doses of fosnetupitant at 13.16, 39.47 and 79 mg/kg did not have any effects on metrazol-induced seizures.

Respiratory:

Single intravenous doses of fosnetupitant at 13.2, 39.5 and 79.2 mg/kg did not have any effects on respiratory functions in rats.

Cardiovascular:

In Vitro studies:

Fosnetupitant at 10 μ M and 30 μ M slightly inhibited the delayed rectifier potassium current (IKr) encoded by hERG in stably transfected human embryonic kidney (HEK293) cells by ~7-8% as compared to vehicle control (-1.8%). In previous studies using a CHO-cell expression system, netupitant and its metabolites M1, M2, and M3 also inhibited hERG channel potassium currents, with IC₅₀ values of 0.76, 0.84, 43, and 4.4 μ M, respectively. For information on the cardiovascular pharmacology of netupitant and its metabolites, see the Pharmacology/Toxicology review of NDA 205718 by Dr. Ke Zhang, dated 06/19/2014.

In Vivo studies:

Repeated intravenous dosing of fosnetupitant at 1.32, 3.95, and 13.2 mg/kg/day for 2 weeks did not have any effects on cardiovascular functions including blood pressure, heart rate, and ECG in conscious dogs.

Fosnetupitant/palonosetron combination:

Repeated intravenous combination doses of fosnetupitant and palonosetron at 1.32/1, 3.95/3, and 13.2/6 mg/kg/day for 2 weeks had no effects on blood pressure, heart rate, or body temperature in conscious dogs. However, at a dose of 13.2/6 mg/kg/day, the combination of fosnetupitant and palonosetron prolonged PR, PQ, and QT intervals, and QRS complex duration.

Renal/Urinary systems:

A single intravenous dose of fosnetupitant at 13.2 mg/kg had no effects on renal function in rats. At higher doses of 39.5 and 79.0 mg/kg, fosnetupitant decreased urine output and K⁺ and Cl⁻ excretion.

Gastrointestinal system:

Single intravenous doses of fosnetupitant at 13.2 and 39.5 mg/kg had no effects on gastrointestinal motility in rats. At 79.0 mg/kg, fosnetupitant significantly decreased the gastrointestinal transit of a charcoal meal (52.3% of total length of small intestine) as compared to vehicle control (65.5%).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption:

Rat

Fosnetupitant was quickly converted to netupitant following intravenous administration of 10 mg/kg in male rats (NETU-09-20). The PK parameters are summarized in the sponsor's table below.

Table 1: Mean (CV%) PK Parameters of Fosnetupitant and Netupitant after Single Dose IV Administration of Fosnetupitant to Rats (10 mg/kg)

PK Parameter	Rats (n=5)	
	Fosnetupitant	Netupitant
$T_{1/2z}$ (min)	28 (44)	NA
T_{max} (min)	3 (0)	3 (0)
C_{max} (ng/mL)	3648 (18)	1406 (24)
MRT_{0-t} (min)	3.5 (7)	NA
V_z (L/kg)	14 (37)	NA
CL_z (ml/min/kg)	328 (15)	NA
AUC_{0-t} (ng.min/mL)	32005 (16)	1317743 (18)
AUC_{0-inf} (ng.min/mL)	32077 (16)	NA

CV: Coefficient of variation

Fosnetupitant formulation: 0.2 mg/ml in 5% glucose solution

Following IV administration of 13.16 mg/kg fosnetupitant or 10 mg/kg netupitant, plasma concentrations of netupitant were slightly higher in the group treated with netupitant (PNETU-13-15). The plasma and brain PK parameters for netupitant, its metabolites, and fosnetupitant are summarized in the sponsor's tables below.

**Text-Table D: Metabolite 2 (M2) - Pharmacokinetic parameter values
Groups 1 and 2 (plasma); Groups 3 and 4 (brain)**

Plasma						
Dose mg/kg	Sex (Group)	C _{max} ng/mL or ng/g	t _{max} h	AUC _(0-tlast) ng/mL*h	t _{1/2} h	AUCratio M2/14-Netu %
13.16*	M (1)	162	0.5	1284	12	4.5
10.0§	M (2)	170	0.5	1600	19	4.4
Brain						
13.16*	M (3)	n.a.	n.a.	n.a.	n.a.	n.a.
10.0§	M (4)	n.a.	n.a.	n.a.	n.a.	n.a.
* in terms of pronetupitant phosphate						
§ in terms of netupitant						

**Text-Table E: Metabolite 3 (M3) - Pharmacokinetic parameter values
Groups 1 and 2 (plasma); Groups 3 and 4 (brain)**

Plasma						
Dose mg/kg	Sex (Group)	C _{max} ng/mL or ng/g	t _{max} h	AUC _(0-tlast) ng/mL*h	t _{1/2} h	AUCratio M3/14-Netu %
13.16*	M (1)	66	8	2264	48	7.9
10.0§	M (2)	62	24	2444	n.c.	6.8
Brain						
13.16*	M (3)	27.5	8	551	n.c.	2.9
10.0§	M (4)	n.a.	n.a.	n.a.	n.a.	n.a.
* in terms of pronetupitant phosphate						
§ in terms of netupitant						

**Text-Table A: Pronetupitant phosphate (204-Netu) - Pharmacokinetic parameter values
Group 1 (plasma) and Group 3 (brain)**

Plasma											
Dose* mg/kg	Sex (Group)	C _{max} ng/mL or ng/g	t _{max} h	AUC _(0-last) ng/mL*h	AUC _(0-inf) ng/mL*h	t _{1/2} h	Cl L/h	Vz L/kg	V _{ss} L/kg	MRT h	AUCratio 204-Netu / 14-Netu %
13.16	M (1)	9662	0.0166	418	419	0.10	31.4	4.5	0.73	0.02	1.46
Brain											
13.16	M (3)	4.33	0.25	2.11	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	0.01

* in terms of pronetupitant phosphate

The results suggest that pronetupitant has low brain permeability to the blood brain barrier.

Following an IV dose of 6.5 mg/kg [¹⁴C] fosnetupitant in rats, total radioactivity was measured in plasma and blood (PNETU-13-37). The results are summarized in the sponsor's tables below.

Table 2: Mean ±SD (n=3) pharmacokinetic parameters of total radioactivity in blood and plasma

Matrix	C _{max}		T _{max}		AUC _{last}		AUC _∞		t _{1/2,z}	
	nmol _{eq} /g		h		h*nmol _{eq} /g		h*nmol _{eq} /g		h	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Blood	2.37	0.647	0.083	0.00	72.4	4.87	75.0	6.69	40.5	1.69
Plasma	4.12	1.10	0.083	0.00	96.7	8.31	98.6	8.75	35.8	4.58

Table 3: Mean ($\pm$ SD, n=3) pharmacokinetic parameters of Fosnetupitant, Netupitant and M1, M2 and M3 metabolites in plasma

Compound	C_{max}		T_{max}		AUC_{last}		AUC_{∞}		$t_{1/2z}$	
	$\mu\text{mol/L}$		h		$\text{h} \cdot \mu\text{mol/L}$		$\text{h} \cdot \mu\text{mol/L}$		h	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Fosnetupitant	0.423	0.0365	0.083	0.00	0.163	0.0516	0.234	n=1	0.569	n=1
Netupitant	1.95	0.561	0.083	0.00	32.6	2.10	33.0	2.14	23.9	2.68
M1	0.329	0.0656	24.0	0.00	26.1	2.10	26.6	2.45	32.5	2.23
M2	0.174	0.0960	0.500	0.00	1.27	0.262	1.47	0.336	19.4	1.71
M3	0.0582	0.0155	7.33	1.15	1.97	0.218	2.17	0.255	23.4	1.24

The PK profile of fosnetupitant and netupitant was investigated in Wistar rats following a single oral dose of 13.16 mg/kg fosnetupitant and 10 mg/kg netupitant (PNET-15-34). The results are summarized in the sponsor's table below.

Text-table A: Netupitant (14-Netu) - Pharmacokinetic parameters

Group / Treatment Dose (mg/kg)	C_{max} § ng/mL	t_{max} h	$AUC_{(0-t_{last})}$ ng/mL*h	$AUC_{(0-inf)}$ ng/mL*h	$t_{1/2}$ h	MRT h	AUCratio Group1/Group2 %
Group 1 / Pronetupitant phosphate 13.16	779.27 $\pm$ 70.22	2	19370.2	26598.4	23.5	35.1	113
Group 2 / Netupitant 10	781.60 $\pm$ 103.81	4	17113.8	21347.5	19.1	28.1	na

§ Mean group value $\pm$ Standard deviation; na = not applicable

Text-table B: Metabolite 1 (M1) - Pharmacokinetic parameters

Group / Treatment Dose (mg/kg)	C _{max} § ng/mL	t _{max} h	AUC _(0-tlast) ng/mL*h	t _{1/2} h	AUCratio M1/14-Netu %	AUCratio M1Group1/M1Group2 %
Group 1 / Pronetupitant phosphate 13.16	517.56±126.26	48	18206.4	NC	94	112
Group 2 / Netupitant 10	412.60±26.44	48	16223.7	NC	95	na

§ Mean group value ± Standard deviation; na = not applicable

Text-table C: Metabolite 2 (M2) - Pharmacokinetic parameters

Group / Treatment Dose (mg/kg)	C _{max} § ng/mL	t _{max} h	AUC _(0-tlast) ng/mL*h	AUC _(0-inf) ng/mL*h	t _{1/2} h	MRT h	AUCratio M2/14-Netu %	AUCratio M2Group1/M2Group2 %
Group 1 / Pronetupitant phosphate 13.16	66.12±22.61	1	668.0	817.3	10.0	13.4	3	215
Group 2 / Netupitant 10	73.86±7.55	1	311.1	491.3	5.3	8.0	2	na

§ Mean group value ± Standard deviation; na = not applicable

Text-table D: Metabolite 3 (M3) - Pharmacokinetic parameters

Group / Treatment Dose (mg/kg)	C _{max} § ng/mL	t _{max} h	AUC _(0-tlast) ng/mL*h	AUC _(0-inf) ng/mL*h	t _{1/2} h	MRT h	AUCratio M3/14-Netu %	AUCratio M3Group1/M3Group2 %
Group 1 / Pronetupitant phosphate 13.16	41.76±3.63	24	1669.8	NC	NC	NC	9	126
Group 2 / Netupitant 10	38.20±7.98	8	1321.5	2364.3	38.6	57.8	8	na

§ Mean group value ± Standard deviation; na = not applicable

Plasma levels of fosnetupitant were below the limit of detection following fosnetupitant oral dose.

Dog

Following an IV dose of 3 mg/kg fosnetupitant in dogs, fosnetupitant was quickly converted to netupitant (NETU-09-20). The PK parameters are summarized in the sponsor's table below.

Table 4: Mean (CV%) PK Parameters of Fosnetupitant and Netupitant after Single Dose IV Administration of Fosnetupitant to Rats (10 mg/kg) and Dogs (3 mg/kg)

PK Parameter	Dogs (n=3)	
	Fosnetupitant	Netupitant
$T_{1/2z}$ (min)	12 (40)	NA
T_{max} (min)	2 (0)	2 (0)
C_{max} (ng/ml)	10168 (85)	802 (20)
MRT_{0-t} (min)	6.5 (13)	NA
V_z (L/kg)	0.825 (73)	NA
CL_z (ml/min/kg)	44 (34)	NA
AUC_{0-t} (ng.min/ml)	73072 (28)	315628 (10)
AUC_{0-inf} (ng.min/ml)	73100 (28)	335871 (8)

CV: Coefficient of variation

Fosnetupitant formulation: 0.2 mg/ml in 5% glucose solution

Following an IV dose of 6.5 mg/kg [^{14}C]-fosnetupitant in rats, total radioactivity was measured in the plasma and blood in dogs (PNETU-13-75). The results are summarized in the sponsor's tables below.

Table 5: Mean $\pm$ SD (n=3) pharmacokinetic parameters of total radioactivity in blood and plasma

	C_{max}		T_{max}		AUC_{last}		AUC_{∞}		$t_{1/2,z}$	
	nmol _{eq} /g		h		h·nmol _{eq} /g		h·nmol _{eq} /g		h	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Blood	6.19	2.55	0.083	0.00	91.6	18.7	106	21.7	92.3	27.4
Plasma	10.3	4.44	0.083	0.00	142	34.6	151	36.1	75.1	15.4

Mean ($\pm$ SD, n=3) pharmacokinetic parameters of Fosnetupitant, Netupitant and M1, M2 and M3 metabolites in plasma are summarized in the following Table 6:

Table 6: Mean ($\pm$ SD, n=3) pharmacokinetic parameters of Fosnetupitant, Netupitant and M1, M2 and M3 metabolites in plasma

Compound	C_{max}		T_{max}		AUC_{last}		AUC_{∞}		$t_{1/2,z}$	
	μ mol/L		h		h· μ mol/L		h· μ mol/L		h	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Fosnetupitant	7.22	3.67	0.083	0.00	2.46	1.21	2.48	1.22	0.328	0.214
Netupitant	1.95	0.305	0.083	0.00	21.4	6.33	21.6	6.36	20.9	8.29
M1	0.276	0.106	24.0	0.00	20.0	4.66	20.3	4.8	28.7	8.49
M2	0.301	0.106	2.33	1.53	3.5	1.41	3.69	1.42	29.0	3.33
M3	0.0418	0.0049	6.67	2.31	1.78	0.927	2.00	0.978	25.2	8.64

Monkey

The PK profile for fosnetupitant and netupitant was evaluated in monkeys following an IV dose of 5 mg/kg fosnetupitant or 3.8 mg/kg netupitant (PNETU-12-16). The PK parameters are summarized in the sponsor's table below.

Table 7: Mean ($\pm$ SD) PK Parameters of Fosnetupitant and Netupitant after Single Intravenous Administration of Fosnetupitant or Netupitant to Male and Female Cynomolgus macaques

	Male (n=3)			Female (n=3)		
	Fosnetupitant	Netupitant after fosnetupitant injection	Netupitant	Fosnetupitant	Netupitant after fosnetupitant injection	Netupitant
T_{max} (hours)	0.05 $\pm$ 0	0.07 $\pm$ 0.04	0.05 $\pm$ 0	0.05 $\pm$ 0	0.05 $\pm$ 0	0.05 $\pm$ 0
C_{max} (ng/ml)	10528 $\pm$ 7052	2582 $\pm$ 1129	3365 $\pm$ 860	19582 $\pm$ 14918	3104 $\pm$ 487	2867 $\pm$ 1875
AUC _{0-last} (ng.h/ml)	1333 $\pm$ 558	4555 $\pm$ 951	4071 $\pm$ 241	2138 $\pm$ 1397	3737 $\pm$ 428	3529 $\pm$ 824
AUC _{0-inf} (ng.h/ml)	1455 $\pm$ 642	5003 $\pm$ 1018	4412 $\pm$ 363	2518 $\pm$ 1280	4171 $\pm$ 505	3842 $\pm$ 794
$t_{1/2}$ (hours)	n.c.	14.5 $\pm$ 0.8	13.7 $\pm$ 1.1	n.c.	16 $\pm$ 0.6	13.7 $\pm$ 3.5
MRT (hours)	n.c.	16.2 $\pm$ 0.6	14.5 $\pm$ 2.2	n.c.	17.7 $\pm$ 1.0	15.4 $\pm$ 2.7
CL (ml/h)	3968 $\pm$ 1871	1029 $\pm$ 218	865 $\pm$ 68	2834 $\pm$ 462	1211 $\pm$ 157	1022 $\pm$ 240
V_z (ml/kg)	n.c.	21688 $\pm$ 5749	17107 $\pm$ 1287	n.c.	27844 $\pm$ 3032	20965 $\pm$ 10326
AUC _{pro-netu/netu} ratio (%)	31 $\pm$ 14.3	NA	NA	57 $\pm$ 17	NA	NA

n.c.: not computable;
NA: not applicable

Distribution:Rat:

To evaluate the tissue distribution, [¹⁴C]-fosnetupitant was given intravenously at 6.5 mg/kg to albino or pigmented rats (PNET-13-39). The total radioactivity in blood and tissues was measured using whole-body autoradioluminography. The highest level of radioactivity was detected in the harderian gland, followed by pituitary in males, meibomian gland in females and lungs. The following tables are taken from the study report for male and female Albino rats.

Total radioactivity in organs and tissues of male Albino rats

Tissue	Cmax $\mu\text{g}_{\text{eq}}/\text{g}$	AUClast $\mu\text{g}_{\text{eq}}\cdot\text{h}/\text{g}$
Harderian gland	50.0	8420
Pituitary	45.9	6020
Lung	80.5	4720
Preputial gland	19.5	3370
Adrenal gland	29.2	2570
Eyelid / Meibomian gland	15.2	2180
Spleen	23.1	2170
Liver	31.6	1790
Intra-orbital lachrymal gland	17.6	1780
Exorbital lachrymal gland	16.9	1660
Pineal body	21.1	1530
Pancreas	19.7	1430
Thyroid	26.5	1420
Kidney (cortex)	18.9	1370
Kidney	16.6	1230
Bone marrow	13.9	1150
Mandibular lymph nodes	10.5	1100
Mucus gland	14.4	1090
Thymus	8.12	1020
Salivary glands	15.3	952
Kidney (medulla)	13.0	938
White fat	9.12	726
Brown fat	26.7	721
Myocardium	8.27	601
Prostate	7.43	514

Tissue	Cmax $\mu\text{g}_{\text{eq}}/\text{g}$	AUClast $\mu\text{g}_{\text{eq}}\cdot\text{h}/\text{g}$
Tongue	8.53	508
Nasal mucosa	2.47	364
Epididymus	3.81	347
Testis	2.24	331
Tooth pulp	7.17	306
Choroid plexus	7.22	296
Uveal tract	4.87	289
Stomach	4.61	282
Muscle	4.35	282
Skin (non pigmented)	3.69	281
Seminal vesicles	2.02	119
Urinary bladder	1.31	107
Blood	1.61	83.6
Brain	0.728	39.5
Spinal cord	0.631	38.5
Eye	0.255	37.3

Total radioactivity in organs and tissues of female Albino rats

Tissue	Cmax µg _{eq} /g	AUClast µg _{eq} ·h/g
Harderian gland	42.7	8140
Eyelid / Meibomian gland	47.4	5360
Lung	47.3	3920
Adrenal gland	25.1	3410

Tissue	Cmax µg _{eq} /g	AUClast µg _{eq} ·h/g
Spleen	30.5	3370
Liver	36.8	3080
Intra-orbital lachrymal gland	19.6	2730
Pineal body	34.7	2590
Exorbital lachrymal gland	19.5	2500
White fat	13.6	2270
Ovary	10.3	2080
Pituitary	19.2	1920
Thyroid	24.7	1890
Pancreas	26.9	1890
Mandibular lymph nodes	12.1	1750
Kidney (cortex)	15.4	1740
Thymus	10.2	1590
Kidney	15.9	1530
Bone marrow	18.1	1480
Brown fat	26.9	1390
Salivary glands	17.8	1290
Mucus gland	16.9	1230
Uterus	7.50	1040
Kidney (medulla)	10.2	919
Myocardium	8.57	797
Tongue	9.26	652
Choroid plexus	9.63	617
Tooth pulp	7.92	537
Stomach	6.40	490
Nasal mucosa	3.26	431
Urinary bladder	2.98	381
Skin (non pigmented)	4.38	334
Muscle	3.32	312
Uveal tract	4.40	226
Blood	2.63	137
Brain	0.671	57.7
Spinal cord	0.418	50.3
Eye	0.161	29.1

The radioactivity levels in the uveal tract and eye in pigmented rats were 4-5 times higher than in albino rats.

Additional information on drug distribution in the brain can be found in the 4-week IV toxicity studies in rats (see General Toxicology section below).

Dog

Measurement of drug distribution in heart tissue can be found in the 4-week IV toxicity studies in dogs (see General Toxicology section below).

Protein binding studies

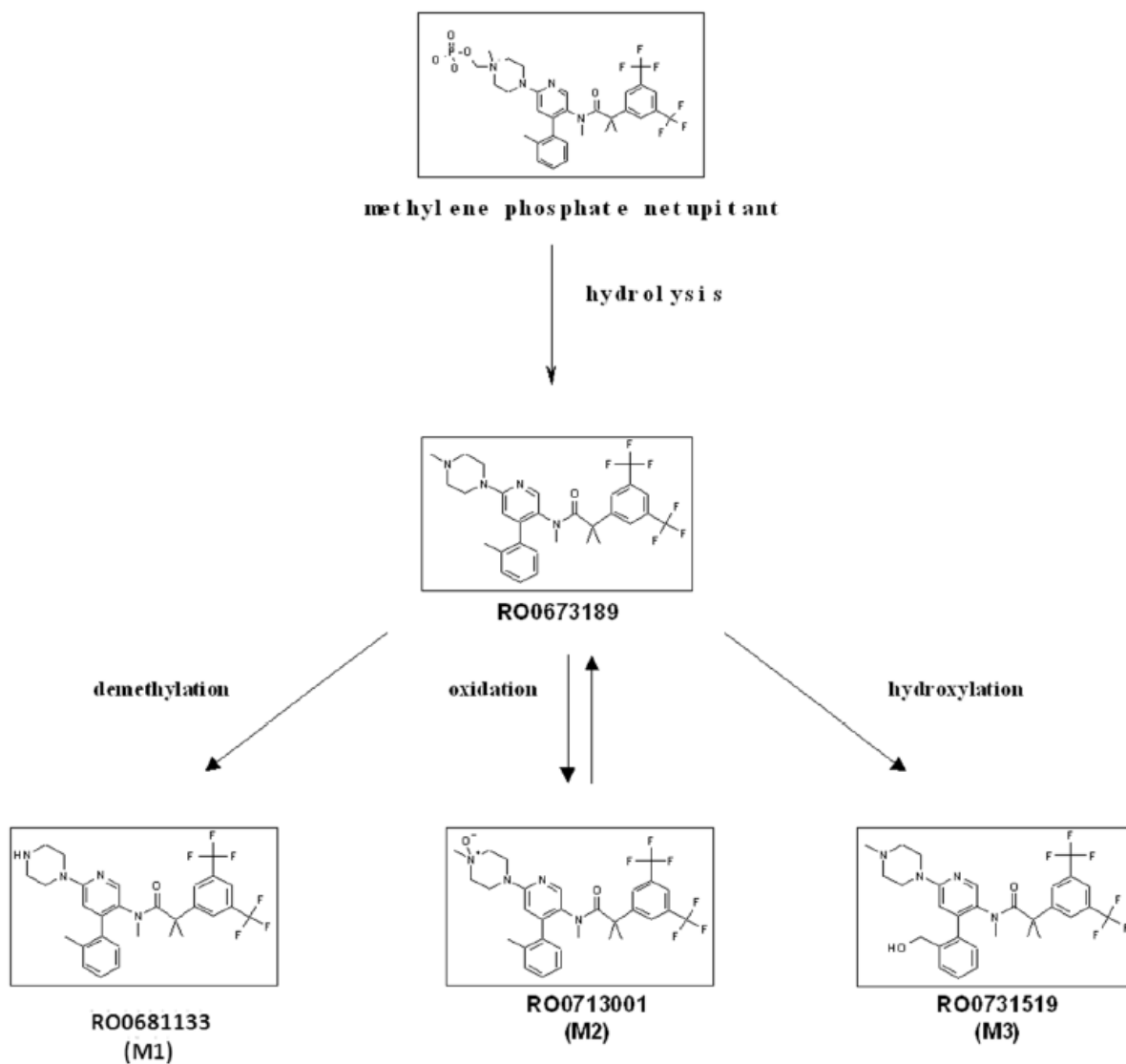
The human plasma protein binding of fosnetupitant was approximately 92-95% (PNET-15-90).

The mean blood to plasma concentration ratio in humans was ~0.4-0.6 (PNET-15-91).

Metabolism:

Following IV administration, fosnetupitant was quickly converted to netupitant and then to the three major netupitant metabolites (M1, M2 and M3) in rats, dogs, and monkeys. The metabolic pathway is depicted in the following figure (submitted by the sponsor).

Figure 6: Proposed Pathways for the Formation of Major Metabolites of Fosnetupitant (methylene netupitant)



Following IV administration in rats, fosnetupitant was quickly converted to netupitant in plasma. M1 was the major metabolite and accounted for 27% of the total radioactivity. M2 and M3 together accounted for approximately 4% of the total radioactivity in plasma. Feces contained 76% of the administered dose, and the major metabolite was M1 (~13-16% of the total radioactivity). Bile contained ~35% of the administered dose and only very small fraction (<0.2%) of the administered dose was found in urine.

In dogs, M2 was the major metabolite identified in plasma following an IV dose of fosnetupitant.

Excretion:

The excretion pattern of fosnetupitant is similar to that of netupitant. The administered dose of fosnetupitant was quickly converted to netupitant, which was eliminated by biliary excretion and hepatic metabolism, mainly mediated by CYP3A and to a lesser extent by CYP2C9 and CYP2D6.

Following IV administration of radiolabeled fosnetupitant, elimination of radioactivity was mainly found in bile and feces, with very small fraction in urine in both rats and dogs. For information on the excretion of netupitant, see the Pharmacology/Toxicology review of NDA 205718 by Dr. Ke Zhang, dated 06/19/2014.

Effects on liver enzymes and human transporters:

The inhibitory effect of fosnetupitant on CYP isoforms was evaluated in human liver microsomes. The results indicated that fosnetupitant produced slight to moderate inhibition of CYP2C9 ($IC_{50} = 27.9 \mu M$), CYP2C19 ($IC_{50} = 46.1 \mu M$), CYP2C8 ($IC_{50} = 56.7 \mu M$), CYP2B6 ($IC_{50} = 106.8 \mu M$), CYP1A2 ($IC_{50} = 208.4 \mu M$), CYP2D6 ($IC_{50} = 217.2 \mu M$), and CYP3A4 ($IC_{50} = 196.8$ or $299.2 \mu M$).

The results of fosnetupitant on human efflux and uptake transporters were summarized in the following tables (submitted by the sponsor).

Table 8: Summary of fosnetupitant efflux and uptake transporter inhibitions

Inhibition results				
Transporter and assay type	Probe substrate	IC ₅₀ (μM)	Maximum inhibition at the highest tested concentration (% of control)	Effect of reference inhibitors (% of control)
BSEP VT	TC (2 μM)	NA	NIO up to 20 μM	91% (Cyclosporin A)
BCRP VT	E3S (1 μM)	NA	NIO up to 50 μM	98% (Ko 134)
MDR1 VT	NMQ (2 μM)	NA	47% at 50 μM	92% (Verapamil)
MATE1 UPT	Metformin (10 μM)	29.48	79% at 300 μM	96% (Pyrimethamine)
OAT1 UPT	Tenofovir (5 μM)	NA	NIO up to 300 μM	97% (Probenecid)
OAT3 UPT	Methotrexate (1 μM)	NA	NIO up to 300 μM	98% (Probenecid)
OATP1B1 UPT	E ₂ 17βG (1 μM)	19.01	91% at 300 μM	100% (Rifampicin)
OATP1B3 UPT	CCK-8 (0.1 μM)	17.37	96% at 300 μM	100% (Rifampicin)
OCT1 UPT	Metformin (10 μM)	NA	44% at 300 μM	100% (Verapamil)
OCT2 UPT	Metformin (10 μM)	NA	NIO up to 300 μM	96% (Verapamil)

VT: vesicular transport assay, UPT: uptake assay, TC: taurocolic acid, E3S: estrone-3-sulfate, NMQ: N-methyl quinidine, E₂17βG: estradiol-17-β-glucuronide, CCK-8: cholecystokinin octapeptide, NA: Not applicable. NT: Not tested. NIO: No interaction observed

Fosnetupitant slightly inhibited organic anion-transporting polypeptide1B3 (IC₅₀ = 17.34 μM), organic anion-transporting polypeptide 1B1 (IC₅₀ = 19.01 μM), multidrug and toxin extrusion protein 1 transporter (IC₅₀ = 29.48 μM), multidrug resistance protein 1 (47% Inhibition at 50 μM).

Table 9: Fosnetupitant uptake transporter substrate assays

Transporter	Fosnetupitant fold accumulation					
	Fosnetupitant 1 μ M		Fosnetupitant 10 μ M		Fosnetupitant 1 μ M Follow-up assay	
	2 min	20 min	2 min	20 min	-rifampicin 20 min	+rifampicin 20 min
OATP1B1	3.65	12.77	3.93	10.53	8.77	0.91
OATP1B3	3.20	8.64	1.90	5.59	8.72	0.83

Fosnetupitant was a substrate for the uptake transporters organic anion-transporting polypeptide 1B1 and 1B3.

5.2 Toxicokinetics

See individual toxicity studies in the following section.

6 General Toxicology

6.1 Single-Dose Toxicity

None.

6.2 Repeat-Dose Toxicity

Rat:

Study title / number: Pronetupitant Phosphate 4 Week Intravenous Toxicity Study in Rats Followed by A 2-Week Recovery Period / PNET-13-18

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Key Study Findings:

In a 4-week intravenous toxicity study in rats, fosnetupitant was tested at 0, 3.95, 13.16, and 39.47 mg/kg/day (equivalent to 3, 10 and 30 mg/kg/day of netupitant, respectively). The high dose of 39.47 mg/kg/day is considered as the NOAEL.

Methods:

Dose and frequency of dosing: daily dose of 3.95, 13.16 and 39.47 mg/kg (equivalent to 3, 10 and 30 mg/kg/day of netupitant)

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: Wistar Hannover rats

Number/Sex/Group: 10/sex/group

Age: 6-8 weeks old

Satellite groups/unique design: 3 (control) or 12/sex/group

Deviation from study protocol affecting interpretation of results:
None

Observations and Results: Changes from control group are listed in the table below.

Parameters	Major findings
Mortality	1 high dose female and 1 control male were found dead
Clinical Signs	Scabs, swelling on the tail in high dose animals
Body Weights	No effects
Ophthalmoscopy	No significant findings
ECG	Not done
Hematology	No significant findings
Clinical Chemistry	Decreases of bilirubin in MD and HD (62% to 74%)
Urinalysis	No significant findings
Gross Pathology	None
Organ Weights	Thymus weight -26% in HD males, liver weights +23% in HD females
Histopathology Adequate battery: Yes	Liver centrilobular hypertrophy with cytoplasmic eosinophilia in MD and HD; minimal atrophy of the cortex in thymus in HD males
[Other evaluations]	None

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

TK data for fosnetupitant, netupitant, and three metabolites are presented in the sponsor's tables below.

Repeat-Dose Toxicity
Test Item: Fosnetupitant

Report Title: 4 Week Intravenous Toxicity Study in Rats Followed by a 2 Week Recovery Period
Study Number: PNET-13-18
(b) (4) Study no.: 95880

Dose (mg/kg/day)	3.95		13.16		39.47		
Toxicokinetic Data (Males)							
Number of Animals:	12		12		12		
- Toxicokinetic groups							
Fosnetupitant (204-NETU)		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
	t_{max} (h)	0.017	0.017	0.017	0.017	0.017	0.017
	C_{max} (ng/ml)	1839±1493	7841±4477	14140±8599	35550±4576	43560±10190	71390±40970
	$AUC_{(0-24h)}$ (ng·h/ml)	195	438	1283	1558	3584	4385
Dose (mg/kg/day)	3.95		13.16		39.47		
Toxicokinetic Data (Females)							
Number of Animals:	12		12		12		
- Toxicokinetic groups							
Fosnetupitant (204-NETU)		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
	t_{max} (h)	0.017	0.017	0.017	0.017	0.083	0.017
	C_{max} (ng/ml)	4355±1326	3042±2069	4718±2616	5433±6462	20560±9570	57290±18780
	$AUC_{(0-24h)}$ (ng·h/ml)	257	204	402	302	3547	3050

Dose (mg/kg/day)	3.95		13.1		39.47		
Toxicokinetic Data (Males)							
Number of Animals:	12		12		12		
- Toxicokinetic groups							
Netupitant (14-NETU)		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
	t_{max} (h)	0.017	0.017	0.017	0.017	0.017	0.017
	C_{max} (ng/ml)	922±67.5	921±412	3779±1313	3393±174	7059±2180	4703±1390
	$AUC_{(0-24h)}$ (ng·h/ml)	8474	10460	14795	35823	43376	43864
Dose (mg/kg/day)	3.95		13.16		39.47		
Toxicokinetic Data (Females)							
Number of Animals:	12		12		12		
- Toxicokinetic groups							
Netupitant (14-NETU)		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
	t_{max} (h)	0.083	0.017	0.083	0.017	0.083	0.017
	C_{max} (ng/ml)	1019±791	1046±305	2657±1529	2757±1604	7086±1119	4925±1047
	$AUC_{(0-24h)}$ (ng·h/ml)	11232	16609	19773	45422	52386	59329

Dose (mg/kg/day)	3.95		13.16		39.47	
Toxicokinetic Data (Males)						
Number of Animals: - Toxicokinetic groups	12		12		12	11
Metabolite 1 (M1)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	24	24	24	24	24	Pre-dose
C_{max} (ng/ml)	177±30	695±215	400±61	1924±831	650±21	1977±260
AUC(0-24h) (ng·h/ml)	2976	12689	6377	38755	10766	41568
Dose (mg/kg/day)	3.95		13.16		39.47	
Toxicokinetic Data (Females)						
Number of Animals: - Toxicokinetic groups	12		12		12	
Metabolite 1 (M1)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	24	24	24	24	24	Pre-dose
C_{max} (ng/ml)		592±79	265±27	1140±409	417±37	1833±525
AUC(0-24h) (ng·h/ml)		10512	3865	25603	5782	29870

Dose (mg/kg/day)	3.95		13.16		39.47	
Toxicokinetic Data (Males)						
Number of Animals: - Toxicokinetic groups	12		12		12	11
Metabolite 2	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.5	0.5	1	0.25	0.5	1
C_{max} (ng/ml)		68±16	166±32	140±2	460±75	198±47
AUC(0-24h) (ng·h/ml)		731	1414	2242	3648	2610
Dose (mg/kg/day)	3.95		13.16		39.47	
Toxicokinetic Data (Females)						
Number of Animals: - Toxicokinetic groups	12		12		12	
Metabolite 2	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.25	0.25	0.5	0.25	0.5	2
C_{max} (ng/ml)		28±10	75±18	107±12	224±69	142±61
AUC(0-24h) (ng·h/ml)		447	473	1226	1207	2508

Dose (mg/kg/day)	3.95		13.16		39.47	
Toxicokinetic Data (Males)						
Number of Animals: - Toxicokinetic groups	12		12		12	11
Metabolite 3	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	4	24	4	4	4	4
C_{max} (ng/ml)		35±7	45±10	132±39	77±8	183±34
AUC(0-24h) (ng·h/ml)		822	926	2657	1750	3592
Dose (mg/kg/day)	3.95		13.16		39.47	
Toxicokinetic Data (Females)						
Number of Animals: - Toxicokinetic groups	12		12		12	
Metabolite 3	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	-	24	24	24	24	24
C_{max} (ng/ml)		31±7	17±2	81±8	35±9	236±30
AUC(0-24h) (ng·h/ml)		578	275	1817	453	4313

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95 Day 29					13.16 Day 29					39.47 Day 29				
Number of Animals: - Toxicokinetic groups	10					10					10				
	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3
Brain Conc (ng/g)	BLOQ	562	413	BLOQ	21	107	1317	989	BLOQ	49	BLOQ	4557	3408	BLOQ	140
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95 Day 29					13.16 Day 29					39.47 Day 29				
Number of Animals: - Toxicokinetic groups	10					10					10				
	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3
Brain Conc (ng/g)	BLOQ	774	402	BLOQ	17	BLOQ	228 4	1171	BLOQ	57	BLOQ	6849	3725	BLOQ	201

Satellite groups were used for toxicokinetics on Day 1 and Day 28 of the study (week 4), and for brain collection on Day 29.

n/a = not applicable

Conc (ng/g) = concentration (ng/g)

BLOQ = below the limit of quantification

Study title / number: Pronetupitant Phosphate – Palonosetron 4 Week Intravenous Toxicity Study in Rats Followed by A 2-Week Recovery Period / NEPA-13-51

Key Study Findings: The high dose of 39.47 mg/kg/day fosnetupitant (pronetupitant phosphate) + 10 mg/kg/day Palonosetron was the NOAEL.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing: see table

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: Wistar Hannover rats

Number/Sex/Group: see table below

Age: 6-8 weeks old

Satellite groups/unique design: see table below

Deviation from study protocol affecting interpretation of results:

None

Group	Treatment (mg/kg/day)		Number of animals
	<i>a</i>	<i>b</i>	
			(Main Groups)
1	0	0	15 M and 15 F
2	3.95	1	10 M and 10 F
3	13.16	3	10 M and 10 F
4	39.47	10	15 M and 15 F
			(Satellite Groups)
5	0	0	3 M and 3 F
6	3.95	1	15 M and 15 F
7	13.16	3	15 M and 15 F
8	39.47	10	15 M and 15 F

M= males; F= females

^ain terms of Pronetupitant Phosphate

^bin terms of Palonosetron

Observations and Results: Changes from control group are listed in the table below.

Parameters	Major findings
Mortality	One high dose female found dead on day 21, cause not known
Clinical Signs	Scab formation, and/or ulceration on the tail in high dose group
Body Weights	No clear treatment related change
Ophthalmoscopy	None
Hematology	Increased reticulocyte count in HD group +46-64%
Clinical Chemistry	Increase AST, ALT in HD group +34-251%
Urinalysis	None
Gross Pathology	None
Organ Weights	Increased liver weight in MD females and HD males/females
Histopathology Adequate battery: Yes	Liver centrilobular hypertrophy associated with increased cytoplasmic eosinophilia in HD group
[Other evaluations]	

The satellite animals (two males and one female from the high dose group, one female from the mid-dose group) were found dead during the study. The cause of death was not identified.

TK data for fosnetupitant, netupitant, and three metabolites are presented in the following tables taken (from the study report).

Repeat-Dose Toxicity
Test Item: Fosnetupitant+ Palonosetron

Report Title: 4 Week Intravenous Toxicity Study in Rats Followed by a 2 Week Recovery Period
Study Number: NEPA-13-51 (b) (4) Study no.: 96440

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	15	15	13
Fosnetupitant (204-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.08	0.016	0.08	0.016	0.016	0.016
C_{max} (ng/ml) #	1615±356	9801±4767	6248±5919	16920±3020	20940±22570	22520±13670
$AUC_{(0-24h)}$ (ng·h/ml)	209	461	882	758	2149	1195
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15 15		15 14		15 14	
Fosnetupitant (204-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.08	0.016	0.08	0.016	0.08	0.016
C_{max} (ng/ml) #	1504±587	7826±1000	6576±5052	32290±31050	19720±14720	19670±8913
$AUC_{(0-24h)}$ (ng·h/ml)	244	358	1010	1452	2818	1160

= Mean group value ± Standard Deviation

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	15	15	13
NETUPITANT (14-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.08	0.016	0.08	0.016	0.016	0.016
C_{max} (ng/ml) #	1445±391	1538±713	3258±492	3650±671	7908±1252	5927±285
$AUC_{(0-24h)}$ (ng·h/ml)	7214	12705	17570	24754	46793	48216
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	14	15	14
NETUPITANT (14-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.08	0.5	0.08	0.016	0.25	0.016
C_{max} (ng/ml) #	1950±149	1720±653	3068±494	3537±672	7965±1552	6339±2104
$AUC_{(0-24h)}$ (ng·h/ml)	12378	20301	24266	37493	61533	74546

= Mean group value ± Standard Deviation

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	15	15	13
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 1 (M1) t_{max} (h)	24	24	24	Pre-dose	24	0.08
C_{max} (ng/ml) #	130±41	613±179	332±114	1647±155	637±55	2027±321
AUC (0-24h) (ng·h/ml)	2414	13504	5821	27473	10594	41996
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	14	15	14
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 1 (M1) t_{max} (h)	24	Pre-dose	24	Pre-dose	24	24
C_{max} (ng/ml) #		642±82	298±69	908±130	405±19	2101±719
AUC (0-24h) (ng·h/ml)		10434	4227	18368	5513	37985

= Mean group value ± Standard Deviation

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	15	15	13
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 2 (M2) t_{max} (h)	0.5	0.5	0.5	05	0.5	1
C_{max} (ng/ml) #		61±15	210±43	108±46	719±177	256±42
AUC (0-24h) (ng·h/ml)		157	1014	731	3117	1865
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	14	15	14
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 2 (M2) t_{max} (h)	0.25	0.25	1	0.5	0.5	0.5
C_{max} (ng/ml) #		31±9	96±36	56±11	252±47	214±12
AUC (0-24h) (ng·h/ml)		89	449	530	1259	1530

= Mean group value ± Standard Deviation

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	15	15	13
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 3 (M3) t_{max} (h)	6	6	6	Pre-dose	3	6
C_{max} (ng/ml) #		35±10	38±8	84±22	70±14	136±24
AUC (0-24h) (ng·h/ml)		728	767	1684	1608	3043
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15 15		15 14		15 14	
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 3 (M3) t_{max} (h)	-	Pre-dose	24	Pre-dose	24	24
C_{max} (ng/ml) #		26±11	13±0.5	57±11	22±3	174±38
AUC (0-24h) (ng·h/ml)		407	-	1139	291	3420

= Mean group value ± Standard Deviation; - = not computable

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15	15	15	15	15	13
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Palonosetron t_{max} (h)	0.08	0.016	0.08	0.016	0.08	0.016
C_{max} (ng/ml)	133±32	233±71	499±186	603±102	2370±308	2474±100
AUC (0-24h) (ng·h/ml)	82	114	278	358	1293	1659
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1		13.16/3		39.47/10	
Number of Animals: - Toxicokinetic groups	15 15		15 14		15 14	
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Palonosetron t_{max} (h)	0.08	0.016	0.08	0.016	0.08	0.08
C_{max} (ng/ml)	147±8	219±31	578±26	466±95	2389±330	2009±871
AUC (0-24h) (ng·h/ml)	66	93	283	335	1339	1537

= Mean group value ± Standard Deviation; - = not computable

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95/1 Day 29					13.16/3 Day 29					39.47/10 Day 29				
Number of Animals: - Toxicokinetic groups	10					10					10				
	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3
Brain Conc (ng/g)#	BLOQ	483 ±74	493 ±104	BLOQ	17 ±3.1	BLOQ	1506 ±360	1124 ±182	BLOQ	57 ±11	BLOQ	5766 ±652	4167 ±662	BLOQ	215 ±27
Dose (mg/kg/day) Toxicokinetic Data (Females)	3.95/1 Day 29					13.16/3 Day 29					39.47/10 Day 29				
Number of Animals: - Toxicokinetic groups	10					10					10				
	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3
Brain Conc (ng/g)#	BLOQ	663 ±80	485 ±129	BLOQ	14 ±2.4	BLOQ	2171 ±760	1141 ±357	BLOQ	58 ±13	BLOQ	7100 ±1692	4163 ±864	BLOQ	328 ±76

Satellite groups were used for toxicokinetics on Day 1 and Day 28 of the study (week 4), and for brain collection on Day 29.
Conc (ng/g) = concentration (ng/g); BLOQ = below the limit of quantification; # = Mean group value ± Standard Deviation

Dog:

Study title and number: Pronetupitant Phosphate 4-Week Intravenous Administration Toxicity Study in Dogs with A 2-Week Treatment-Free Period / PNET-13-27 ((b) (4) study #8289-417)

Key Study Findings: Fosnetupitant (pronetupitant phosphate) was tested at 0, 1.32, 3.95, and 13.16 mg/kg/day in dogs for 4 weeks. The high dose of 13.16 mg/kg/day was the NOAEL.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing: See sponsor’s table below

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: Beagle dogs

Number/Sex/Group: see sponsor’s table below

Age: 7 months old

Satellite groups/unique design: None

Deviation from study protocol affecting interpretation of results:

None

Group Number	Dose Level (mg/kg/day)		No. of Animals		Animal numbers		Concentration (mg/mL)	
	Pronetupitant Phosphate*	Netupitant ^b	Male	Female	Male	Female	Pronetupitant phosphate*	Netupitant ^b
1 ^a	0	0	5	5	1 to 5	17 to 21	0	0
2	1.316	1	3	3	6 to 8	22 to 24	0.53	0.4
3	3.95	3	3	3	9 to 11	25 to 27	1.58	1.2
4	13.16	10	5	5	12 to 16	28 to 32	5.26	4.0

^a group 1 received control article (5% of glucose)

* In terms of test item as supplied

^b In terms of Netupitant

The terminal sacrifices occurred after 4 weeks of dosing, 48 hours after the end of the treatment period, due to the toxicokinetic sampling time points.

Animals designated for the recovery sacrifice (last two animals/sex from groups 1 and 4) were sacrificed after 2 weeks of treatment-free period.

Observations and Results: Changes from control group are listed in the table below.

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	Body weight loss in HD females
Ophthalmoscopy [delete the row if not evaluated]	None
ECG [delete the row for rodents]	None
Hematology	None
Clinical Chemistry	None
Urinalysis	None
Gross Pathology	None
Organ Weights	Decrease in thymus weight in females in all treated groups
Histopathology Adequate battery: Yes	Atrophy of thymic cortex in HD group
[Other evaluations]	None

LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

*: [if the answer is "no" explain why the histopath battery is not adequate]

TK data for fosnetupitant, netupitant, and three metabolites are presented in the sponsor's tables below.

Repeat-Dose Toxicity
Test Item: Fosnetupitant

Report Title: 4 Week Intravenous Toxicity Study in Dogs Followed by a 2 Week Recovery Period
(b) (4) study no.: 96070 (b) (4) study no.: 8289-417

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316		3.95		13.16	
Number of Animals:	3		3		3	
Fosnetupitant (204-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0
C_{max} (ng/mL)	2273±1308	4134±822	5667±2311	11347±591	10968±2232	18630±2541
AUC _(0-24h) (ng·h/mL)	435±293	708±16	956±304	1912±110	1969±499	2858±310
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316		3.95		13.16	
Number of Animals:	3		3		3	
Fosnetupitant (204-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0
C_{max} (ng/mL)		5811±3629	5121±1943	10932±5132	8112±1721	13557±1003
AUC _(0-24h) (ng·h/mL)		1060±577	899±416	1786±874	1311±315	2160±27

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316		3.95		13.16	
Number of Animals:	3		3		3	
netupitant	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.05±0	0.53±0.67	0.25±0	0.20±0.26	0.18±0.12	1±0.87
C_{max} (ng/mL)	655±2	821±82	1627±203	3410±268	5490±1875	6861±2333
AUC _(0-24h) (ng·h/mL)	2662±631	6689±2874	8077±632	20540±1819	30998±6474	85719±62550
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316		3.95		13.16	
Number of Animals:	3		3		3	
netupitant	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	0.05±0	0.18±0.12	0.27±0.23	0.18±0.12	0.27±0.23	0.20±0.26
C_{max} (ng/mL)		696±221	1975±2142	2540±781	5206±1829	4087±433
AUC _(0-24h) (ng·h/mL)		4853±2530	6904±3174	13468±5431	23997±5189	77957±18044

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316		3.95		13.16	
Number of Animals:	3		3		3	
Metabolite 1 (M1)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	6±2.83	4.13±5.48	13.3±9.24	3.5±3.97	18.67±9.24	0.33±0.29
C_{max} (ng/mL)	87±7	281±37	273±46	980±27	1153±233	6840±4810
AUC _(0-24h) (ng·h/mL)	1626±278	8070±3107	5563±1353	34325±7061	21343±2995	176484±154579
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316		3.95		13.16	
Number of Animals:	3		3		3	
Metabolite 1 (M1)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
t_{max} (h)	8±0	4±3.46	13.3±9.24	5.5±4.33	13.3±9.24	17.33±26.63
C_{max} (ng/mL)		210±85	239±183	698±321	753±130	4202±1372
AUC _(0-24h) (ng·h/mL)		5929±2589	4508±3593	23074±14466	15309±3644	141875±20729

Dose (mg/kg/day) Toxicokinetic Data (Males)		1.316		3.95		13.16	
Number of Animals:		3		3		3	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 2 (M2)	t _{max} (h)	2±0	1±0	1.67±0.58	2±0	1.33±0.58	1.5±0.87
	C _{max} (ng/mL)	88.5±3.54	140±42	330±134	487±112	1391±423	700±230
	AUC _(0-24h) (ng·h/mL)	755±14.14	1298±242	1858±580	4888±1630	8698±4230	12973±10733
Dose (mg/kg/day) Toxicokinetic Data (Females)		1.316		3.95		13.16	
Number of Animals:		3		3		3	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 2 (M2)	t _{max} (h)	2.67±1.15	2±0	1.7±0.58	1.67±0.58	1.17±0.76	1.67±0.58
	C _{max} (ng/mL)	87±46	110±58	225±146	308±184	950±139	728±193
	AUC _(0-24h) (ng·h/mL)	771±373	907±626	1323±1136	3334±1724	5352±1432	9502±4018

Dose (mg/kg/day) Toxicokinetic Data (Males)		1.316		3.95		13.16	
Number of Animals:		3		3		3	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 3 (M3)	t _{max}	-	-	6±3.46	2.67±1.15	17.33±11.55	1.42±1.01
	C _{max} (ng/mL)	-	-	32±10	71±5	134±60	262±35
	AUC _(0-24h) (ng·h/mL)	-	-	356±190	1643±46	2228±346	6512±1874
Dose (mg/kg/day) Toxicokinetic Data (Females)		1.316		3.95		13.16	
Number of Animals:		3		3		3	
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Metabolite 3 (M3)	t _{max} (h)	-	-	8±0	5.33±2.31	6.67±2.31	1.17±0.76
	C _{max} (ng/mL)	-	-	31±20	50 ±27	67±13	164±50
	AUC _(0-24h) (ng·h/mL)	-	-	504±602	842±475	1187±213	3738±1302

- = not computable

Dose (mg/kg/day) Toxicokinetic Data (Males)		1.316					3.95					13.16				
Number of Animals:		3					3					3				
		Day 30					Day 30					Day 30				
Heart (ventricles) Conc (ng/g)		204-NETU	14-NETU	M1	M2	M3	204-NETU	14-NETU	M1	M2	M3	204-NETU	14-NETU	M1	M2	M3
			BLOQ	196	638	BLOQ	BLOQ	BLOQ	534	1674	BLOQ	31	BLOQ	1949	18993	BLOQ
Dose (mg/kg/day) Toxicokinetic Data (Females)		1.316					3.95					13.16				
Number of Animals:		3					3					3				
		Day 30					Day 30					Day 30				
Heart (ventricles) Conc (ng/g)		204-NETU	14-NETU	M1	M2	M3	204-NETU	14-NETU	M1	M2	M3	204-NETU	14-NETU	M1	M2	M3
			BLOQ	114	302	BLOQ	BLOQ	BLOQ	454	1381	BLOQ	38.1	BLOQ	2501	20983	BLOQ

Main groups animals were used for toxicokinetics on Day 28 up to 48 hours after the last administration, then heart was collected and analysed.

Conc (ng/g) = concentration (ng/g) as mean group values

BLOQ = below the limit of quantification

Study title/ number: Pronetupitant Phosphate – Palonosetron 4-week Intravenous Administration Toxicity Study in Dogs with A 2-Week Treatment-Free Period / NEPA-13-52 (b) (4) Study # 8292-336)

Key Study Findings: Fosnetupitant (pronetupitant phosphate) in combination with palonosetron was tested at 1.316 + 1 mg/kg/day, 3.95 + 3 mg/kg/day, and 13.16 + 10 / 6 mg/kg/day. The dose of 10 mg/kg/day palonosetron was reduced

to 6 mg/kg/day on day 15 due to convulsions. The test article produced convulsions, salivation, and swelling at injection site in the high dose group. Increase heart rate and prolonged QTc intervals occurred in the mid- and high-dose groups. The dose of 1.316 mg/kg/day fosnetupitant + 1 mg/kg/day palonosetron was the NOAEL.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing: See sponsor's table below

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: Beagle dogs

Number/Sex/Group: See sponsor's table below

Age: 7 months old

Satellite groups/ unique design: None

Deviation from study protocol affecting interpretation of results: None

Group No.	Dose level (mg/kg/day)			Animals		
	Pronetupitant Phosphate	Netupitant	Palonosetron	No of animals	Animal numbers	
					Male	Female
1 ^a	0	0	0	5M ^c + 5F	1 to 5	17 to 21
2	1.316	1	1	3M + 3F	6 to 8	22 to 24
3	3.95	3	3	3M + 3F	9 to 11	25 to 27
4	13.16	10	10/6 ^b	5M ^c + 5F	12 to 16	28 to 32 ^d

^a Goupe 1 received control article (5% of Glucose).

^b The dose level of Palonosetron was decreased from 10 mg/kg/day to 6 mg/kg/day from dosing Day 15 for males and from dosing Day 14 for females.

^c Animals designated for the recovery sacrifice (last two males and females from group 1 and animals nos.15, 16, 29 and 31 from group 4) were sacrificed after 2 weeks of treatment-free period.

^d Animal no. 29 was assigned in the group selected for the treatment-free period due to the stop of the treatment on Day 22 and animal no.32 was reallocated in the terminal sacrifice.

Observations and Results: Changes from control group are listed in the table below.

Parameters	Major findings
Mortality	None
Clinical Signs	Convulsion, vocalization and startle movements, salivation, swelling at the injection site in HD
Body Weights	Body weight loss in HD (-6% HD females)
Ophthalmoscopy	None
ECG	Increase heart rate, prolonged QTc interval in MD and HD
Hematology	None
Clinical Chemistry	None
Urinalysis	None
Gross Pathology	None
Organ Weights	None
Histopathology Adequate battery: Yes	Subchronic inflammation of the blood vessels and the perivascular area at injection sites in HD group
[Other evaluations]	None

TK data for fosnetupitant, netupitant, and three metabolites are presented in the sponsor's tables below.

Repeat-Dose Toxicity
Test Item: Fosnetupitant+ Palonosetron

Report Title: 4 Week Intravenous Toxicity Study in Dogs Followed by a 2 Week Recovery Period
(b) (4) Study no.: 96450 (b) (4) Study no.: 8292-336

Dose (mg/kg/day)	1.316/1		3.95/3		13.16/10 or 6		
Toxicokinetic Data (Males)							
Number of Animals:	3		3		5		
Main groups (Main phase)	3		3		5		
Fosnetupitant (204-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 15	Day 28
$t_{max}(h)$	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0
C_{max}	4399±828	4358±574	9426±1902	10690±4561	12886±4821	8272±2920	13063±5088
AUC (0-24h)	719±147	745±93	1724±288	1941±967	2125±880	1412±418	2211±881
Dose (mg/kg/day)	1.316/1		3.95/3		13.16/10 or 6		
Toxicokinetic Data (Females)							
Number of Animals:	3		3		5		
Main groups (Main phase)	3		3		5		
Fosnetupitant (204-NETU)	Day 1	Day 28	Day 1	Day 28	Day 1	Day 14	Day 28*
$t_{max}(h)$	0.05±0	0.05±0	0.05±0	0.05±0	0.05±0	0.09±0.09	0.05±0
C_{max}	6940±3016	5188±3151	9849±4021	8119±6411	19660±1209	11520±4125	11648±1410
AUC (0-24h)	1276±726	951±699	1590±681	1418±1071	3242±411	2562±2033	1984±279

* Refers to 4 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 15	Day 28
NETUPITANT t_{max}	0.05±0	0.12±0.12	0.18±0.12	0.18±0.12	0.05±0	0.09±0.09	0.09±0.09
C_{max}	566±115	644±81	3505±1077	2834±1838	7107±1093	3493±1737	4469±778
AUC (0-24h)	2714±292	4791±567	9954±2569	19312±13517	28713±4222	4891±586	71028±18268
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 14	Day 28*
NETUPITANT t_{max}	0.05±0	0.12±0.12	0.12±0.12	0.25±0	0.13±0.11	0.30±0.21	0.15±0.12
C_{max}	746±166	679±212	2885±542	2156±544	7340±920	3025±2472	3317±734
AUC (0-24h)	3720±1268	3831±1088	8483±2165	19619±7672	28066±6207	28913±21675	42680±14752

* Refers to 4 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 15	Day 28
Metabolite 1 t_{max}	8.0±0	6.0±3.46	12±10.6	1.1±0.88	11.2±7.16	0.44±0.87	2.3±1.64
C_{max}	88±6	263±61	429±140	1417±1367	789±197	1716±819	3184±611
AUC (0-24h)	1808±24	7929±1837	8927±2807	46521±49136	17174±4342	6859±1272	122200±24126
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 14	Day 28*
Metabolite 1 t_{max}	8.0±0	2.8±2.17	18.7±9.2	5.3±2.31	11.2±7.16	2.7±3.4	5.0±3.83
C_{max}	136±109	293±156	283±146	839±285	806±230	2483±2112	2724±355
AUC (0-24h) (ng·h/mL)	2766±2247	8742±3833	5611±2672	29823±10822	16896±4758	49898±41599	93459±27560

* Refers to 4 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 15	Day 28
Metabolite 2 t_{max}	1.3±0.58	1.3±0.58	1.0±0	1.0±0	0.7±0.27	1.5±0.71	1.3±0.66
C_{max}	99±21	131±14	748±230	562±190	1613±746	973±61	1014±199
AUC (0-24h)	389±50	1070±431	4008±1608	6260±4491	7253±2719	8526±1089	13869±2649
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 14	Day 28*
Metabolite 2 t_{max}	1.3±0.58	1.7±0.58	0.8±0.29	0.83±0.29	0.9±0.22	1.6±0.05	1.25±0.5
C_{max}	170±148	165±129	511±86	452±144	2529±660	1178±562	1180±171
AUC (0-24h)	929±993	1532±928	2399±581	4773±1654	10587±3724	9888±4134	12297±2384

* Refers to 4 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
Metabolite 3	Day 1	Day 28	Day 1	Day 28	Day 1	Day 15	Day 28
	t _{max}	1.7±0.58	4.0±0	3.7±3.79	4.4±2.19	1.51±1.57	2.2±3.25
	C _{max}	17±2	49±14	68±41	79±11	206±64	182±50
AUC (0-24h)	120±12	786±317	1656±1665	1615±253	3722±1025	6417±2248	
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
Metabolite 3	Day 1	Day 28	Day 1	Day 28	Day 1	Day 14	Day 28*
	t _{max}	3.0±1.73	3.3±1.15	3.3±1.15	3.6±2.88	1.55±1.52	3.8±3.1
	C _{max}	21±10	26±9	55±25	87±37	150±76	198±114
AUC (0-24h)	150±67	445±302	1606±1090	1618±732	2782±1297	4537±2014	

nc = not calculated
* Refers to 4 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
Palonosetron	Day 1	Day 28	Day 1	Day 28	Day 1	Day 15	Day 28
	t _{max}	0.12±0.12	0.12±0.12	0.12±0.12	0.12±0.12	0.21±0.09	0.17±0.11
	C _{max}	326±52	430±92	819±342	1368±858	2925±1045	1145±280
AUC (0-24h)	463±95	536±82	1418±657	1722±768	3530±517	3387±310	2783±562
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316/1		3.95/3		13.16/10 or 6		
Number of Animals: Main groups (Main phase)	3		3		5		
Palonosetron	Day 1	Day 28	Day 1	Day 28	Day 1	Day 14	Day 28*
	t _{max}	0.125±0.12	0.12±0.12	0.05±0	0.05±0	0.21±0.09	0.15±0.12
	C _{max}	542±358	563±196	771±392	927±327	3174±704	1206±69
AUC (0-24h)	812±539	765±415	1114±792	1355±586	3519±614	2396±390	2193±453

* Refers to 4 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	1.316/1 Day 30					3.95/3 Day 30					13.16/10 or 6 Day 30				
Number of Animals: Main groups (Main phase)	5					3					5				
Heart (ventricles)	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3
	29.64 ^a	156±94	629±309	-	-	-	483± 423	1481± 966	-	42.27 ^a	-	4661± 3137	17440± 3761	-	360±183
Dose (mg/kg/day) Toxicokinetic Data (Females)	1.316/1 Day 30					3.95/3 Day 30					13.16/10 or 6 Day 30				
Number of Animals: Main groups (Main phase)	5					3					5				
Heart (ventricles)	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3	204- NETU	14- NETU	M1	M2	M3
	-	200±153	621±377	-	-	-	1259±497	2411±491	-	54±18	-	2364 ^b	14000 ^b	-	288 ^b

Main groups animals were used for toxicokinetics on Day 28 up to 48 hours after the last administration, then heart was collected and analysed. Conc (ng/g) = concentration (ng/g) as mean group values.

BLOQ = below the limit of quantification

^a Refers to 1 animal, ^b Refers to 2 animals

Dose (mg/kg/day) Toxicokinetic Data (Males)	13.16/10 or 6 Day 42			
Number of Animals: Main groups (Main phase)	5			
Heart Conc (ng/g) (ventricles)	14-NETU	M1	M2	M3
	56	379	-	-
Dose (mg/kg/day) Toxicokinetic Data (Females)	13.16/10 or 6 Day 42			
Number of Animals: Main groups (Main phase)	5			
Heart Conc (ng/g) (ventricles)	14-NETU	M1	M2	M3
	1055	5723	-	147.9 ^a

Main groups animals were used for toxicokinetics on Day heart was collected and analysed.

C_{conc} (ng/g) = concentration (ng/g) as mean group values.

B the limit of quantification

^a Refers to 1 animal

General toxicology (additional studies)

2-Week IV toxicity studies were conducted in rats (#PNET-11-21) and dogs (#PNET-11-22). Intravenous doses of 0, 3.95, 13.16, and 39.47 mg/kg/day (equivalent to 3, 10, and 30 mg/kg/day of netupitant, respectively) was tested in rats, and 0, 1.32, 3.95, and 13.16 mg/kg/day (equivalent to 0, 1, 3, and 10 mg/kg/day of netupitant, respectively) was tested in dogs. The results of these studies were similar to those of the 4-week studies of fosnetupitant (reviewed above), in which the same doses were tested.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Pronetupitant phosphate Bacterial Mutations Assay / PNET-12-04

Key Study Findings: Treatment with fosnetupitant (pronetupitant phosphate) did not significantly increase the number of revertant colonies.

GLP compliance: Yes

Conducting laboratory and location: [REDACTED] (b) (4)

Test system: See table below

Tester strain	S9	Dose level (µg/plate)
TA1535, TA1537, TA98	±	5000, 2500, 1250, 625 and 313
WP2 <i>uvrA</i>	–	5000, 2500, 1250, 625 and 313
	+	5000, 2500, 1250, 625, 313, 156, 78.1 and 39.1
TA100	±	5000, 2500, 1250, 625, 313 and 156

Study is valid: Yes

7.2 *In Vitro* Assays in Mammalian Cells

Study title/number: Pronetupitant phosphate Chromosome Aberrations in human lymphocytes cultured in vitro / PNET-12-05

Key Study Findings: Treatment with fosnetupitant (pronetupitant phosphate) did not significantly increase the frequency of aberrations as compared to the control.

GLP compliance: Yes

Conducting laboratory and location: [REDACTED] (b) (4)

Test system: human peripheral blood lymphocytes; up to 500 µg/mL +S9, up to 62.5 µg/mL –S9

Study is valid: Yes

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Pronetupitant Phosphate Micronucleus Test in Rats / PNET-13-49

Key Study Findings: Treatment with fosnetupitant phosphate did not significantly increase the frequency of micronucleated polychromatic erythrocytes.

GLP compliance: Yes

Conducting laboratory and location: [REDACTED] (b) (4)

Test system: rat, bone marrow micronuclei; IV doses of 29.6, 59.2, and 118.4 mg/kg/day for two days

Study is valid: Yes

7.4 Other Genetic Toxicity Studies

Ames tests were conducted with following impurities and the results were negative:

[REDACTED] (b) (4)

Ames tests (study PNET-16-08 and study PNET-16-09) were conducted with impurities [REDACTED] (b) (4), respectively, and the results were positive.

Study title/number: [REDACTED] (b) (4) Bacterial Mutations Assay / PNET-16-08

Key Study Findings: Treatment with [REDACTED] (b) (4) significantly increased the number of revertant colonies in TA1535 and TA100 tester strains with S9, and in TA98 without S9 metabolic activation.

GLP compliance: Yes

Conducting laboratory and location: [REDACTED] (b) (4)

Test system: See table below

Tester strain	S9	Dose level ($\mu\text{g}/\text{plate}$)
TA1535	–	5000, 2500, 1250, 625, 313 and 156
	+	2500, 1250, 625, 313 and 156
TA1537	±	2500, 1250, 625, 313, 156 and 78.1
WP2 <i>uvrA</i>	–	5000, 2500, 1250, 625, 313 and 156
	+	2500, 1250, 625, 313 and 156
TA98	±	2500, 1250, 625, 313 and 156
TA100	–	2500, 1250, 625, 313 and 156
	+	2500, 1250, 625, 313, 156 and 78.1

(b) (4) /Batch no: C311-2015122501

Study is valid: Yes

Test results are summarized in the following table (taken from the study report).

(b) (4)		TABLE 2 - Main Assay										
BACTERIAL MUTATION ASSAY (<i>S. typhimurium</i> and <i>E. coli</i>)												
MAIN ASSAY - PLATE INCORPORATION METHOD - TA1535												
STUDY NO.: A2061												
SOLVENT: DMSO												
Strain: TA1535						Titre: 296						
Dose-level [µg/pl]	Without metabolic activation					With metabolic activation						
	Plate counts	Mean	S. E.			Plate counts	Mean	S. E.				
Untreated	13	22	22	19	3.0	20	20	22	21	0.7		
0.00	13	17	16	15	1.2	21	17	15	16	1.8		
156	19	21	22	21	0.9	33	43	34	37	3.2		
313	22	20	24	22	1.2	58	52	65	58	3.8		
625	28	28	27	T	28	0.3	51	50	35	T	45	5.2
1250	7	4	10	T	7	1.7	9	3	3	T	5	2.0
2500	0	0	0	*	0	0.0	0	0	0	*	0	0.0
5000	0	0	0	*	0	0.0	NT					
Regression analysis:												
Points	S9	Intercept	Slope	Corr. coeff.	t	P-value						
1 - 3	-	3.992	0.0025	0.82771	3.9025	0.00588						
1 - 4	-	4.049	0.0020	0.92130	7.4921	0.00002						
1 - 5	-	4.743	-0.0012	-0.54245	2.3281	0.03669						
1 - 6	-	5.007	-0.0019	-0.89628	8.0837	0.00000						
1 - 7	-	4.503	-0.0011	-0.86628	7.5589	0.00000						
1 - 3	+	4.239	0.0110	0.97140	10.8231	0.00001						
1 - 4	+	5.117	0.0038	0.65637	2.7513	0.02043						
1 - 5	+	6.457	-0.0024	-0.52237	2.2087	0.04576						
1 - 6	+	6.533	-0.0026	-0.81616	5.6499	0.00004						
Positive and negative controls												
Treatment	S9	Plate counts	Mean	S. E.								
Untreated	-	13	22	22	19	3.0						
Sodium Aside	1 µg/pl	-	617	585	527	576	26.3					
DMSO	100 µL/pl	+	21	17	15	18	1.8					
2-Aminoanthracene	1 µg/pl	+	136	145	136	139	3.0					
T : thinning of the background lawn												
* : total lack of the background lawn												
NT: not tested												

MAIN ASSAY - PLATE INCORPORATION METHOD - TA100

STUDY NO.: A2061

SOLVENT: DMSO

Strain: TA100						Titre: 276				
Dose-level [µg/pl]	Without metabolic activation					With metabolic activation				
	Plate counts					Plate counts				
	Mean	S. E.				Mean	S. E.			
Untreated	121	126	127	125	1.9	185	165	166	172	6.5
0.00	120	106	120	115	4.7	147	157	120	141	11.1
78.1	NT					142	148	151	147	2.6
156	126	134	128	129	2.4	151	140	148	146	3.3
313	178	152	164	165	7.5	178	184	188	183	2.9
625	178	188	207	T 191	8.5	280	267	265	T 271	4.7
1250	156	132	131	T 140	8.2	357	366	348	T 357	5.2
2500	0	0	0	* 0	0.0	0	0	0	* 0	0.0

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	10.599	0.0067	0.91957	6.1918	0.00045
1 - 4	-	10.792	0.0051	0.93897	8.6314	0.00001
1 - 5	-	11.729	0.0008	0.31174	1.1829	0.25801
1 - 6	-	13.696	-0.0045	-0.82611	5.8640	0.00002
1 - 3	+	11.916	0.0014	0.21613	0.5857	0.57648
1 - 4	+	11.683	0.0053	0.81193	4.3984	0.00134
1 - 5	+	11.428	0.0076	0.96058	12.4581	0.00000
1 - 6	+	11.723	0.0060	0.97587	17.8753	0.00000
1 - 7	+	14.850	-0.0039	-0.58137	3.1145	0.00571

Positive and negative controls

Treatment	S9	Plate counts	Mean	S. E.
Untreated	-	121 126 127	125	1.9
Sodium Azide	1 µg/pl	558 652 585	598	27.9
DMSO	100 µL/pl	147 157 120	141	11.1
2-Aminoanthracene	1 µg/pl	1554 1221 1434	1403	97.4

MAIN ASSAY - PLATE INCORPORATION METHOD - TA98

STUDY NO.: A2061

SOLVENT: DMSO

Strain: TA98

Titre: 379

Dose-level [µg/pl]	Without metabolic activation					With metabolic activation				
	Plate counts			Mean	S. E.	Plate counts			Mean	S. E.
Untreated	38	33	30	34	2.3	31	32	36	33	1.5
0.00	24	27	26	26	0.9	35	32	30	32	1.5
156	29	39	35	34	2.9	35	44	49	43	4.1
313	38	34	44	39	2.9	43	46	45	45	0.9
625	72	58	66	T 65	4.1	60	59	66	T 62	2.2
1250	MIC	MIC	MIC	0	0.0	26	29	31	T 29	1.5
2500	0	0	0	* 0	0.0	0	0	0	* 0	0.0

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	5.136	0.0037	0.83718	4.0499	0.00487
1 - 4	-	5.005	0.0047	0.95331	9.9826	0.00000
1 - 5	-	6.917	-0.0040	-0.65036	3.0869	0.00866
1 - 6	-	6.475	-0.0028	-0.77626	4.9254	0.00015
1 - 3	+	5.795	0.0032	0.78106	3.3093	0.01295
1 - 4	+	5.783	0.0033	0.93070	8.0463	0.00001
1 - 5	+	6.579	-0.0003	-0.16817	0.6151	0.54910
1 - 6	+	7.395	-0.0025	-0.85967	6.7313	0.00000

Positive and negative controls

Treatment	S9	Plate counts	Mean	S. E.
DMSO	100 µL/pl	- 24 27 26	26	0.9
2-Nitrofluorene	2 µg/pl	- 159 179 175	171	6.1
DMSO	100 µL/pl	+ 35 32 30	32	1.5
2-Aminoanthracene	1 µg/pl	+ 453 478 534	488	23.9

T : thinning of the background lawn
 * : total lack of the background lawn
 MIC: microcolony

Study title/number: (b) (4): Bacterial Mutations Assay / PNET-16-09

Key Study Findings: Treatment with (b) (4) significantly increased the number of revertant colonies in the absence or presence of S9 metabolism, under the testing conditions.

GLP compliance: Yes

Conducting laboratory and location: [redacted] (b) (4)

Test system: See table below

Tester strain	S9	Dose level (µg/plate)
TA1535, TA1537, TA98, TA100	±	1000, 500, 250, 125, 62.5 and 31.3
WP2 <i>uvrA</i>	±	3000, 1500, 750, 375, 188 and 93.8

[redacted] (b) (4) / Batch no: N07Q

Study is valid: Yes

Test results are summarized in the sponsor’s table (taken from the study report).

SOLVENT: DMSO

Strain: TA1535

Titre: 232

Dose-level [µg/pl]	Without metabolic activation					With metabolic activation				
	Plate counts					Plate counts				
	Mean	S. E.				Mean	S. E.			
Untreated	18	17	21	19	1.2	17	13	18	16	1.5
0.00	18	15	16	16	0.9	16	15	15	15	0.3
31.3	17	18	18	18	0.3	19	15	18	17	1.2
62.5	17	20	22	20	1.5	17	18	19	18	0.6
125	23	20	23	22	1.0	28	34	26	29	2.4
250	25	31	36	31	3.2	32	29	32	31	1.0
500	37	39	39	T 38	0.7	47	39	40	T 42	2.5
1000	46	35	37	T 39	3.4	51	62	56	T 56	3.2

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	4.028	0.0062	0.69382	2.5490	0.03816
1 - 4	-	4.052	0.0053	0.82839	4.6766	0.00087
1 - 5	-	4.025	0.0059	0.91020	7.9240	0.00000
1 - 6	-	4.135	0.0044	0.94659	11.7425	0.00000
1 - 7	-	4.400	0.0023	0.85346	7.1383	0.00000
1 - 3	+	3.942	0.0052	0.68573	2.4926	0.04144
1 - 4	+	3.779	0.0119	0.90454	6.7085	0.00005
1 - 5	+	3.987	0.0071	0.88829	6.9734	0.00001
1 - 6	+	4.143	0.0051	0.91979	9.3758	0.00000
1 - 7	+	4.342	0.0035	0.93005	11.0333	0.00000

Positive and negative controls

Treatment	S9	Plate counts	Mean	S. E.
Untreated	-	18 17 21	19	1.2
Sodium Azide	1 µg/pl -	564 532 479	525	24.8
DMSO	100 µL/pl +	16 15 15	15	0.3
2-Aminoanthracene	1 µg/pl +	142 133 92	122	15.4

T: thinning of the background lawn

SOLVENT: DMSO

Strain: TA1537											Titre: 286										
Dose-level [µg/pl]	Without metabolic activation						With metabolic activation														
	Plate counts			Mean	S. E.	Plate counts			Mean	S. E.											
Untreated	22	21	18	20	1.2	18	15	18	17	1.0											
0.00	15	17	13	15	1.2	16	18	15	16	0.9											
31.3	13	14	14	14	0.3	19	18	16	18	0.9											
62.5	14	16	14	15	0.7	19	14	18	17	1.5											
125	16	15	13	15	0.9	18	17	15	17	0.9											
250	17	15	16	16	0.6	14	15	16	15	0.6											
500	19	23	26	T 23	2.0	14	20	20	T 18	2.0											
1000	14	14	15	T 14	0.3	17	18	21	T 19	1.2											

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	3.817	-0.0006	-0.09925	0.2639	0.79947
1 - 4	-	3.799	0.0001	0.02666	0.0843	0.93445
1 - 5	-	3.768	0.0008	0.41008	1.6211	0.12898
1 - 6	-	3.685	0.0019	0.83668	6.1107	0.00002
1 - 7	-	3.897	0.0002	0.21668	0.9675	0.34546
1 - 3	+	4.080	0.0012	0.14862	0.3976	0.70276
1 - 4	+	4.110	0.0000	-0.00860	0.0272	0.97883
1 - 5	+	4.150	-0.0010	-0.41037	1.6225	0.12868
1 - 6	+	4.071	0.0001	0.07798	0.3129	0.75841
1 - 7	+	4.055	0.0002	0.31375	1.4403	0.16605

Positive and negative controls

Treatment		S9	Plate counts			Mean	S. E.
DMSO	100 µL/pl	-	15	17	13	15	1.2
9-Aminoacridine	50 µg/pl	-	176	129	201	169	21.1
DMSO	100 µL/pl	+	16	18	15	16	0.9
2-Aminoanthracene	1 µg/pl	+	96	107	102	102	3.2

T: thinning of the background lawn

SOLVENT: DMSO

Strain: WP2 uvrA		Titre: 437									
Dose-level [µg/pl]	Without metabolic activation					With metabolic activation					
	Plate counts		Mean	S. E.		Plate counts		Mean	S. E.		
Untreated	29	34	22	28	3.5	38	40	35	38	1.5	
0.00	31	28	27	29	1.2	31	35	32	33	1.2	
93.8	27	25	25	26	0.7	32	31	27	30	1.5	
188	29	26	35	30	2.6	36	31	30	32	1.9	
375	38	32	33	34	1.9	39	45	52	45	3.8	
750	40	31	35	35	2.6	50	46	45	47	1.5	
1500	53	46	45	48	2.5	44	46	50	47	1.8	
3000	66	53	49	T 56	5.1	51	58	52	T 54	2.2	

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	5.237	0.0006	0.16895	0.4535	0.66390
1 - 4	-	5.159	0.0017	0.64627	2.6781	0.02317
1 - 5	-	5.244	0.0010	0.68010	3.3448	0.00527
1 - 6	-	5.226	0.0011	0.89258	7.9183	0.00000
1 - 7	-	5.355	0.0008	0.90167	9.0891	0.00000
1 - 3	+	5.639	-0.0002	-0.05813	0.1541	0.88192
1 - 4	+	5.410	0.0030	0.74982	3.5837	0.00498
1 - 5	+	5.547	0.0019	0.81449	5.0617	0.00022
1 - 6	+	5.777	0.0009	0.72333	4.1902	0.00069
1 - 7	+	5.911	0.0005	0.76567	5.1886	0.00005

Positive and negative controls

Treatment	S9	Plate counts	Mean	S. E.
Untreated	-	29 34 22	28	3.5
MMS	500 µg/pl	- 174 201 197	191	8.4
DMSO	100 µL/pl	+ 31 35 32	33	1.2
2-Aminoanthracene	10 µg/pl	+ 195 173 216	195	12.4

T: thinning of the background lawn

 SOLVENT: DMSO

Strain: TA98

Titre: 306

Dose-level [µg/pl]	Without metabolic activation					With metabolic activation				
	Plate counts			Mean	S. E.	Plate counts			Mean	S. E.
Untreated	32	28	24	28	2.3	40	37	40	39	1.0
0.00	28	25	23	25	1.5	35	33	37	35	1.2
31.3	30	27	29	29	0.9	34	37	38	36	1.2
62.5	25	25	23	24	0.7	40	43	37	40	1.7
125	25	32	26	28	2.2	44	41	59	48	5.6
250	37	37	37	37	0.0	48	57	54	53	2.6
500	37	39	38	38	0.6	59	53	51	T 54	2.4
1000	63	64	59	T 62	1.5	74	77	74	T 75	1.0

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	5.153	-0.0015	-0.17030	0.4573	0.66134
1 - 4	-	5.095	0.0009	0.15519	0.4968	0.63008
1 - 5	-	4.959	0.0040	0.79320	4.6963	0.00042
1 - 6	-	5.069	0.0025	0.83376	6.0404	0.00002
1 - 7	-	5.031	0.0028	0.95982	14.9086	0.00000
1 - 3	+	5.884	0.0065	0.70796	2.6522	0.03284
1 - 4	+	5.842	0.0082	0.76903	3.8045	0.00346
1 - 5	+	5.951	0.0057	0.84035	5.5898	0.00009
1 - 6	+	6.158	0.0030	0.78263	5.0290	0.00012
1 - 7	+	6.211	0.0025	0.91154	9.6626	0.00000

Positive and negative controls

Treatment		S9	Plate counts			Mean	S. E.
DMSO	100 µL/pl	-	28	25	23	25	1.5
2-Nitrofluorene	2 µg/pl	-	115	113	112	113	0.9
DMSO	100 µL/pl	+	35	33	37	35	1.2
2-Aminoanthracene	1 µg/pl	+	414	374	346	378	19.7

T: thinning of the background lawn

SOLVENT: DMSO

Strain: TA100					Titre: 258					
Dose-level [µg/pl]	Without metabolic activation				With metabolic activation					
	Plate counts	Mean	S. E.		Plate counts	Mean	S. E.			
Untreated	156	165	160	160	2.6	180	176	186	181	2.9
0.00	166	139	126	144	11.8	177	167	183	176	4.7
31.3	177	181	197	185	6.1	248	203	213	221	13.6
62.5	195	190	202	196	3.5	266	247	281	265	9.8
125	251	256	247	251	2.6	268	371	311	317	29.9
250	347	361	386	365	11.4	431	485	480	465	17.2
500	572	551	574	T 566	7.4	738	614	674	T 675	35.8
1000	658	605	603	T 622	18.0	651	683	657	T 664	9.8

Regression analysis:

Points	S9	Intercept	Slope	Corr. coeff.	t	P-value
1 - 3	-	12.172	0.0323	0.83880	4.0763	0.00471
1 - 4	-	12.245	0.0294	0.94418	9.0632	0.00000
1 - 5	-	12.331	0.0274	0.98147	18.4684	0.00000
1 - 6	-	12.652	0.0231	0.98908	26.8392	0.00000
1 - 7	-	13.911	0.0131	0.91805	10.0935	0.00000
1 - 3	+	13.286	0.0482	0.93392	6.9118	0.00023
1 - 4	+	13.597	0.0354	0.90114	6.5730	0.00006
1 - 5	+	13.752	0.0319	0.96489	13.2450	0.00000
1 - 6	+	14.283	0.0247	0.97150	16.3948	0.00000
1 - 7	+	15.829	0.0125	0.86591	7.5458	0.00000

Positive and negative controls

Treatment	S9	Plate counts	Mean	S. E.
Untreated	-	156 165 160	160	2.6
Sodium Azide	1 µg/pl	596 527 589	571	21.9
DMSO	100 µL/pl	177 167 183	176	4.7
2-Aminoanthracene	1 µg/pl	1216 829 1174	1073	122.6

T: thinning of the background lawn

An in vitro chromosome aberration test was conducted with (b) (4) (PNET-15-37) and the result was negative.

8 Carcinogenicity

N/A

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title/Number: Pronetupitant Phosphate IV Fertility and Early Embryonic Development to Implantation Study in Rats / PNET-13-64

Key Study Findings: The high dose of 39.47 mg/kg/day was the NOAEL, with no effects observed in mating, fertility, or embryonic development.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing: See table below

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: Wistar Hannover rats

Number/Sex/Group: 24

Satellite groups: None

Study design: See table below

Deviation from study protocol affecting interpretation of results: None

Group	Treatment (mg/kg/day)		Dose Volume	Number of rats
	Pronetupitant Phosphate ^a	Netupitant ^b (mL/kg)		
1	0	0	5	24 males and 24 females
2	3.95	3	5	24 males and 24 females
3	13.16	10	5	24 males and 24 females
4	39.47	30	5	24 males and 24 females

^ain terms of Pronetupitant Phosphate corrected for purity

^bin terms of Netupitant

Note: Netupitant column indicates the equivalent dose derived from 100% conversion of fosnetupitant.

Treatment of females was initiated at 2 weeks prior to mating, and treatment of males was initiated at 4 weeks prior to mating. Treatment continued throughout the mating period and through day 7 post-coitum. Both males and females were sacrificed on day 15 post-coitum.

Observations and Results

Parameters	Major findings
Mortality	1 control male found dead, one HD female cannibalized
Clinical Signs	None
Body Weights	Slight decreased BW noted in treatment groups
Necropsy findings	None
Mating Index	None
Fertility Index	None
Corpora lutea	None
Implantations	None
Uterine deaths	None
Pre- and Post-implantation loss	None

Toxicokinetics were not performed.

9.2 Embryonic Fetal Development

Study title/ number: Pronetupitant Phosphate Intravenous Embryo-Foetal Development Study in Rats with Toxicokinetics /PNET-13-56

Key Study Findings: One high-dose fetus (39.47 mg/kg/day) had a malrotated hindlimb and 6 high-dose fetuses from 3 different litters had no ossification of pubis. One high-dose fetus was found dead. Maternal bodyweight was decreased in the high-dose group. In pregnant rats treated with 3.95 or 13.16 mg/kg/day, there were no effects on litter parameters, including the number of viable fetuses, fetal weight, resorptions, or malformations (skeletal or visceral). The NOAEL was 13.16 mg/kg/day.

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing: See table below (taken from study report)

Route of administration: IV
Formulation/Vehicle: 5% glucose
Species/Strain: Wistar Hannover rats
Number/Sex/Group: 24
Satellite groups: See table below
Study design: See table below

Fosnetupitant was given to pregnant rats by IV injection at 0 (vehicle), 3.95, 13.16, and 39.47 mg/kg/day during gestation days 6-17. The females were sacrificed on day 20 post coitum and assessment of embryo-fetal development was conducted.

Deviation from study protocol affecting interpretation of results: None

Treatment (mg/kg/day)				
Main Group	Pronetupitant Phosphate ^a	Netupitant ^b	Level	Number of Females
1	0	0	Control	24
2	3.95	3	Low	24
3	13.16	10	Medium	24
4	39.47	30	High	24

Treatment (mg/kg/day)				
Satellite Group	Pronetupitant Phosphate ^a	Netupitant ^b	Level	Number of Females
5	0	0	Control	3
6	3.95	3	Low	6
7	13.16	10	Medium	6
8	39.47	30	High	6

^ain terms of Pronetupitant Phosphate corrected for purity

^bin terms of Netupitant

Note: Netupitant column indicates the equivalent dose derived from 100% conversion of fosnetupitant.

Observations and Results

Parameters	Major findings
Mortality	One high dose fetus found dead
Clinical Signs	None

Body Weights	Decreased in HD
Necropsy findings Cesarean Section Data [Implantation Sites, Pre- and Post-Implantation Loss, etc.]	No significant findings
Necropsy findings Offspring [malformations, variations, etc]	Unossified pubis was noted in 6 HD fetuses in 3 litters Malrotated hindlimb was found in 1 HD fetus (see sponsor's table below)

LD: low dose; MD: mid dose; HD: high dose

Data for litter parameters is shown in the table below (taken from the study report).

Reproductive and developmental toxicity Report Title: Segment II: Fosnetupitant intravenous- Embryo-Fetal Development studies in the Rat with toxicokinetics
 Test Item: Fosnetupitant Study Number: PNET-13-56 (b) (4) Study no.: 96160

Daily Dose (mg/kg)	0 (Control)	3.95	13.16	39.47
Number of animals – Main groups	24	24	24	24

Litters:				
No. Litters Evaluated	20	23	18	24
No Live Foetuses	11.80±1.44	11.70±2.90	12.50±1.89	11.75±2.95^
Mean No. Resorption (total)	0.45±0.60	0.52±0.95	0.22±0.43	0.38±0.65
No. of Litters with Dead Foetuses	0	0	0	1
Mean % Post-implantation Loss	3.60±4.92	5.30±10.13	1.73±3.37	3.36±5.91
Mean Foetal Body Weight (g)	3.72±0.20	3.78±0.21	3.86±0.21	3.70±0.27
Foetal Sex Ratios (males %)	49.40±15.56	53.18±18.77	55.77±9.78	47.13±11.07
Foetal Malformations:				
- External examination				
<i>Hindlimb malrotated</i>				
No. Foetuses (%)	0	0	0	1 (0.4%)
No. Litters (%)	0	0	0	1 (4.2%)
- Skeletal examination				
<i>Pubis no ossification</i>				
No. Foetuses (%)	0	0	0	6 (4.0%)
No. Litters (%)	0	0	0	3 (12.5%)
- Visceral examination				
	-	- n/a	- n/a	-

^ = Including dead foetuses.

- = No noteworthy findings

n/a = not applicable

TK data for fosnetupitant, netupitant, and metabolites M1, M2, and M3 are presented in the following tables (taken from the study report).

Reproductive and developmental toxicity
toxicokinetics
Test Item: Fosnetupitant

Report Title: Segment II: Fosnetupitant intravenous- Embryo-Fetal Development studies in the Rat with
Study Number: PNET-13-56 (b) (4) Study no.: 96160

Dose (mg/kg/day) Toxicokinetic Data	3.95		13.16		39.47		
Fosnetupitant (204-NETU)	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	
	t_{max} (h)	0.25	0.25	0.25	0.25	0.25	0.25
	C_{max} (ng/mL)	29.27±43.88	102.9±128.1	120.0±75.34	46.2±27.48	168.5±76.02	137.1±119.4
AUC (0-last) (ng·h/mL)	n.c	n.c	n.c	n.c	n.c	n.c	
NETUPITANT	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	
	t_{max} (h)	0.25	0.25	0.25	3	0.25	0.25
	C_{max} (ng/mL)	727.4±139.5	2723±561.0	3386±1461	3952±557.7	3809±420.1	4787±246.8
AUC (0-last) (ng·h/mL)	3971	10036	12774	24504	17366	35815	

pc = post coitum
n.c. = not computable

Reproductive and developmental toxicity
toxicokinetics
Test Item: Fosnetupitant

Report Title: Segment II: Fosnetupitant intravenous- Embryo-Fetal Development studies in the Rat with
Study Number: PNET-13-56 (b) (4) Study no.: 96160

Daily Dose (mg/kg)	0 (Control)	3.95	13.16	39.47
Number of animals – Main groups	24	24	24	24
– Satellite groups	3	6	6	6

Dose (mg/kg/day) Toxicokinetic Data (Males)	3.95		13.16		39.47		
M1	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	
	t_{max} (h)	8	8	8	0	8	3
	C_{max} (ng/mL)	72.56±22.91	457.6±172.0	243.1±184	904.2±88.49	222.2±49.02	1591±323.0
AUC _(0-last) (ng·h/mL)	356	3022	991	6744	1250	12144	
M2	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	
	t_{max} (h)	0.25	0.25	0.25	3	0.25	3
	C_{max} (ng/mL)	16.37±2.08	22.63±6.79	104.9±48.96	48.50±4.346	139.6±27.54	118.5±17.03
AUC _(0-last) (ng·h/mL)	2.05	150	327	313	604	813	
M3	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	Day 6 pc	Day 17 pc	
	t_{max} (h)	n.c	0.25	8	0	8	0.25
	C_{max} (ng/mL)	0	22.26±1.105	5.523±9.567	77.80±7.691	13.03±3.203	171.9±8.591
AUC _(0-last) (ng·h/mL)	0	161.2	13.8	495	32.6	1149	

pc = post coitum
n.c. = not computable

Study title and number: Pronetupitant Phosphate Intravenous Embryo-Foetal Development Study in Rabbits / PNET-13-71

Key Study Findings: The high dose of 12.5 mg/kg/day is considered the NOAEL for maternal toxicity. An increase in resorptions occurred at doses of 6.25 and 12.5 mg/kg/day. No other litter parameters were affected at these doses. In pregnant rabbits treated with 3.13 mg/kg/day, there were no effects on litter parameters, including the number of viable fetuses, fetal weight, resorptions, or malformations (skeletal or visceral).

Conducting laboratory and location: [REDACTED] (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing: See table below (taken from study report)

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: New Zealand White Rabbits

Number/Sex/Group: 20

Satellite groups: Four additional groups of 4 females each were included for toxicokinetic evaluation.

Study design: See table below (taken from study report)

Main Group	Treatment (mg/kg/day) ^a	Level	Number of Females
1	0 (vehicle)	Control	20
2	3.13	Low	20
3	6.25	Medium	20
4	12.5	High	20

^ain terms of Pronetupitant Phosphate corrected for the purity

All animals were given the test drug by intravenous injection starting from Day 6 through Day 19 post coitum. The females were sacrificed on day 29 post coitum and assessment of embryo-fetal development was conducted.

Deviation from study protocol affecting interpretation of results: None

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	None
Body Weights	None
Necropsy findings Cesarean Section Data [<i>Implantation Sites, Pre- and Post-Implantation Loss, etc.</i>]	Increase in resorptions in MD and HD groups (see sponsor's table below)

Necropsy findings Offspring [malformations, variations,	None

LD: low dose; MD: mid dose; HD: high dose

Data for litter parameters is shown in the table below (taken from the study report).

Reproductive and developmental toxicity
Test Item: Fosnetupitant

Report Title: Segment II: Fosnetupitant intravenous - Embryo-Fetal Development study in rabbits
Study Number: PNET-13-71
Study no.: 96190

Daily Dose (mg/kg)	0 (Control)	3.13	6.25	12.5
Number of animals – Main groups	20	20	20	20
Necropsy Observations	-	-	-	-
Mean No. Corpora Lutea	9.47±2.29	9.05±1.93	9.79±2.15	10.83±2.33
Mean No. Implantations	8.06±1.64	7.68±2.24	8.53±2.63	9.61±2.00*
Mean % Pre-implantation Loss	13.45±10.65	15.71±12.86	13.50±18.95	11.02±10.14
Litters:				
No. Litters Evaluated	17	19	19	18
No Live Foetuses	7.94±1.56	7.11±2.21	7.42±2.17	8.94±1.89
Mean No. Resorption (total)	0.12±0.33	0.58±0.96	1.11±1.15*	0.67±0.77*
No. of Litters with Dead Foetuses	0	0	1	1
Mean % Post-implantation Loss	1.24±3.51	7.54±12.22	11.52±12.25	6.55±7.72
Mean Foetal Body Weight (g)	41.91±3.82	42.95±6.41	43.31±5.33	39.73±4.38
Fetal Sex Ratios (males %)	45.79±11.53	58.41±22.33	45.95±20.27	43.57±17.19
Fetal Malformations				
- External examination				
<i>Ablepharia</i>				
No. Foetuses (%)	1 (0.74%)	0	0	0
No. Litters (%)	1 (5.88%)	0	0	0
<i>Hindlimb malrotated</i>				
No. Foetuses (%)	0	1 (0.74%)	0	0
No. Litters (%)	0	1 (5.26%)	0	0
<i>Paw malrotated</i>				
No. Foetuses (%)	0	0	1 (0.70%)	0
No. Litters (%)	0	0	1 (5.26%)	0
- Skeletal examination	-	n/a	n/a	-
- Visceral examination	-	n/a	n/a	-

- No noteworthy findings; n/a = not applicable; * - p<0.05 by Kruskal-Wallis/William's test

TK data for fosnetupitant, netupitant, and metabolites M1, M2, and M3 are presented in the following tables (taken from the study report).

Reproductive and developmental toxicity
Test Item: Fosnetupitant

Report Title: Segment II: Fosnetupitant intravenous - Embryo-Fetal Development study in rabbits
Study Number: PNET-13-71 (b) (4) Study no.: 96190

Dose (mg/kg) Toxicokinetic Data	3.13		6.25		12.5	
	Day 6 pc	Day 19 pc	Day 6 pc	Day 19 pc	Day 6 pc	Day 19 pc
Fosnetupitant (204-NETU)						
T _{max} (h)	0.017	0.017	0.017	0.017	0.017	0.017
C _{max} (ng/mL)	15278	30929	43203	51138	109870	98138
AUC _(0-last) (ng·h/mL)	8099	15929	22123	27382	56367	50784
Netupitant (14-NETU)						
T _{max} (h)	0.017	0.75	0.017	0.017	0.017	0.017
C _{max} (ng/mL)	353	915	552	1601	948	2435
AUC _(0-last) (ng·h/mL)	1467	4739	2480	4586	3511	8705

pc = post coitum
n.c. = not computable

Dose (mg/kg)	3.13		6.25		12.5	
	Day 6 pc	Day 19 pc	Day 6 pc	Day 19 pc	Day 6 pc	Day 19 pc
M1						
T _{max} (h)	8	0.75	8	8	8	8
C _{max} (ng/mL)	57.1	105.8	65.9	124.1	128.1	206.5
AUC _(0-last) (ng·h/mL)	313	628	423	782	811	1322
M2						
T _{max} (h)	1	0.75	1	1	1	1
C _{max} (ng/mL)	31.5	88.4	83.7	267.8	149.3	510.3
AUC _(0-last) (ng·h/mL)	15.5	391	45.7	1268	435	2371
M3						
T _{max} (h)	8	2.5	4.5	5.67	8	4.5
C _{max} (ng/mL)	19.3	70.0	26.4	104	41.9	178
AUC _(0-last) (ng·h/mL)	85.4	437	171.8	775	278.3	1212

pc = post coitum
n.c. = not computable

9.3 Prenatal and Postnatal Development

Study title and number: Fosnetupitant Intravenous Pre- and Postnatal Toxicity Study in Rats, Including Maternal Function / PNET-15-85

Key Study Findings: The high dose (39.47 mg/kg/day) produced a reduction in body weight gain in F0 and F1 rats (birth through maturation), and increases in pre-birth loss, missing pups or pups found dead (particularly males), and clinical signs such as cold to touch, absence of milk intake, small size, and pale appearance. The mid-dose of 13.16 mg/kg/day was the NOAEL for dams and their offspring (F0 and F1 generations, respectively).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing: See sponsor's table below

Route of administration: IV

Formulation/Vehicle: 5% glucose

Species/Strain: Wistar Hannover rats

Number/Sex/Group: 24

Satellite groups: None

Study design: See table below

F0 generation:

Group Number	Treatment (mg/kg/day)		Number of females
	Fosnetupitant	Netupitant	
1	0	0	24
2	3.95	3	24
3	13.16	10	24
4	39.47	30	24

F1 generation:

Group Number		Males		Females	
1	Not dosed	24	24	24	24
2	Not dosed	24	24	24	24
3	Not dosed	24	24	24	24
4	Not dosed	24	24	24	24

Note: Netupitant column indicates the equivalent dose derived from 100% conversion of fosnetupitant.

Female rats were given fosnetupitant by intravenous injection from implantation (Day 6 post-coitum) through weaning (Day 20 postpartum). The F0 females were allowed to deliver and rear their offspring (F1 generation) to weaning, at which time one male and one female per litter were randomly selected, mated, and allowed to produce their offspring (F2 generation) which were sacrificed on Day 21 postpartum.

Deviation from study protocol affecting interpretation of results: None

Observations and Results:

Generation	Major Findings

F0 Dams ^a	Mortality: 1 LD, 1 HD Clinical signs: local irritations in HD group Lower body weight and food consumption: HD group Increased pre-birth loss in HD group Lower pup body weight in HD group
F1 Generation ^a	Mortality: 2 LD group Lower body weight in HD group Failure in Y-Maze test in some rats in HD group
F2 Generation ^a	Increased mean number of days needed to reach the completion of the pre-weaning test in HD group

LD: low dose; MD: mid dose; HD: high dose, a = the results are summarized in the sponsor's tables.

Study Number: **PNET-15-85**

Location in CTD: Section 4.2.3.5.3

GLP Compliance: GLP

Test Article: Fosnetupitant

Duration of Dosing: F0 generation from Day 6 *post coitum* to Day 20 *post partum*

(b) (4) Study No.: X0270

Day of Mating: 0 pc (G)

Test Facility: RTC (Italy)

Species/Strain: Rat/Wistar Hannover

Initial Age: At least 6 weeks

Method of Administration: Intravenous route

Date of First Dose: 21 December 2015

Vehicle/Formulation: 5% glucose (in softened water by reverse osmosis)

Special Features: None

No Observed Adverse Effect Level in F0 and F1 generation: 13.16 mg/kg/day

Daily Dose (mg/kg)/Group	0 (Control)1	3.95/2	13.16/3	39.47/4
Number of F0 females allocated to groups	24	24	24	24
Dams:				
No. Pregnant	24	24	23	24
No. of Not pregnant	0	0	1	0
No. Unilateral implantation	0	2	1	0
Total litter loss	0	0	0	1
Humanic kill, pregnant	0	0	0	1
Found dead, pregnant	0	1	0	0
Total resorption	0	0	0	1
Mean Duration of Gestation (mean days)	22.3	22.3	22.0	21.9 [†]
No. with live pups on Day 21 <i>post partum</i>	24	23	23	21

- No noteworthy findings. * - p<0.05 ** - p<0.01 (§) = Modified t test if group variances are inhomogeneous

G = Gestation day pc = *post coitum* day pp = *post partum*

Reproductive and developmental toxicity Report Title: Segment III Intravenous pre- and postnatal toxicity study in rats including maternal function
 Test Item: Fosnetupitant Study Number: PNET-15-85 (b) (4) Study no.: X0270

Daily Dose (mg/kg)/Group	0 (Control)/1	3.95/2	13.16/3	39.47/4
Number of F0 females allocated to groups	24	24	24	24
Dams:				
Clinical signs/observations (%)				
- Scab	-	-	-	54.2
- Swelling	-	-	-	16.7
- Piloerection	-	-	-	37.5
- Ulceration	-	-	-	20.8
- Pale	-	-	-	12.5
- Abrasion/tail desquamation	-	-	-	4.2
Body weight (g) ^a				
- Day 12 pc	248.89	-	-	-5*
- Day 15 pc	263.40	-	-	-6**
- Day 20 pc	315.24	-	-	-7**
Body weight (g) ^a				
- Day 1 pp	246.95	-	-	-9**
- Day 4 pp	258.29	-	-	-8**
- Day 7 pp	268.80	-	-	-5*
Body weight gain per day (g) ^a				
- Day 9 pc	2.295	-	-	-101**
- Day 12 pc	4.038	-	-	-56**(\$)
- Day 15 pc	4.837	-	-	-28**(\$)
Food consumption (g/animal/day) ^a				
- Day 15 pc	21.03	-	-12**	-28**
- Day 20 pc	23.79	-	-8**(\$)	-20**(\$)

- No noteworthy findings. * - p<0.05 ** - p<0.01 (\$) = Modified t test if group variances are inhomogeneous
^a = For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
 G = Gestation day pc = post coitum pp = post partum

Reproductive and developmental toxicity Report Title: Segment III Intravenous pre- and postnatal toxicity study in rats including maternal function
 Test Item: Fosnetupitant Study Number: PNET-15-85 (b) (4) Study no.: X0270

Daily Dose (mg/kg)/Group	0 (Control)/1	3.95/2	13.16/3	39.47/4
Number of F0 females allocated to groups	24	24	24	24
Litter data of F0 generation				
Number of litters evaluated ^a	24	23	23	23
- Pre-birth loss	7.8	-	-	+38
- Litter weight (g) - Day 1 pp	68.4	-	-	-14*
- Mean pup weight (g) - Day 1 pp	6.8	-	-	-16*
- Litter weight (g) - Day 4 pp	103.2	-	-	-22*
- Mean pup weight (g) - Day 4 pp	10.3	-	-	-23*
- Litter weight (g) - Day 7 pp	135.5	-	-	-20*
- Mean pup weight (g) - Day 7 pp	15.21	-	-	-22*
- Litter weight (g) - Day 14 pp	252.7	-	-	-16*
- Mean pup weight (g) - Day 14 pp	28.26	-	-	-15*
- Litter weight (g) - Day 21 pp	402.7	-	-	-16*
- Mean pup weight (g) - Day 21 pp	44.88	-	-	-15*
- Cumulative loss% - Day 4 pp	1.5	-	-	+747
- Pup Sex Ratios on Day 21 pp	42.38	45.96	53.33	50.69
Necropsy Observations				
Thymus	0	2	4	2
Abnormal size (reduced) - (number of females affected)				

- No noteworthy findings. * - p<0.05 ** - p<0.01 (\$) = Modified t test if group variances are inhomogeneous
^a = For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
 G = Gestation day pc = post coitum pp = post partum

FOSNETUPITANT: INTRAVENOUS PRE- AND POSTNATAL TOXICITY STUDY IN RATS, INCLUDING MATERNAL FUNCTION

LITTER DATA AT BIRTH AND ON DAY 1 AND ON DAY 4 POST PARTUM (BEFORE CULLING) OF F0 FEMALES WITH LIVE PUPS AT DAY 1 POST PARTUM - GROUP MEAN

STUDY NO.: X0270

Group		At birth			On Day 1 post partum			On Day 4 post partum			
		Total litter size	Live litter size	Pup loss (%)	Live litter size	Litter weight (g)	Mean pup weight (g)	Live litter size	Cumulative loss (%)	Litter weight (g)	Mean pup weight (g)
1	Mean	10.3	10.3	0.0	10.1	68.4	6.8	10.1	1.5	103.2	10.3
	SD	2.9	2.9	0.0	2.8	18.1	0.6	2.8	3.4	25.6	1.0
	N	24	24	24	24	24	24	24	24	24	24
2	Mean	10.3	10.3	0.0	10.3	69.3	6.9	10.3	0.0	103.8	10.3
	SD	2.1	2.1	0.0	2.1	10.9	0.8	2.1	0.0	16.2	1.2
	N	23	23	23	23	23	23	23	23	23	23
3	Mean	10.3	10.3	0.0	10.3	66.6	6.5	10.3	0.5	97.4	9.6
	SD	2.2	2.2	0.0	2.2	12.2	0.7	2.2	2.6	18.0	1.1
	N	23	23	23	23	23	23	23	23	23	23
4	Mean	10.8	10.7	0.6	10.0	58.8*	5.7*	9.6	12.7	80.2*	7.9*
	SD	3.0	2.9	2.8	3.1	14.4	0.7	3.3	24.6	22.4	1.3
	N	23	23	23	23	22	22	23	23	22	22

Statistical analysis: Kruskal Wallis test

William's test if group mean differences are different from control at p < 0.05

* = mean value of group is significantly different from control

FOSNETUPITANT: INTRAVENOUS PRE- AND POSTNATAL TOXICITY STUDY IN RATS, INCLUDING MATERNAL FUNCTION

LITTER DATA FROM DAY 7 (AFTER CULLING) THROUGH DAY 21 POST PARTUM OF F0 FEMALES - GROUP MEAN DATA

STUDY NO.: X0270

Group		On Day 7				On Day 14				On Day 21				Lactation index (%)
		Live litter size	Cumul- active loss %	Litter wt. (g)	Mean pup wt. (g)	Live litter size	Cumul- active loss %	Litter wt. (g)	Mean pup wt. (g)	Live litter size	Cumul- active loss %	Litter wt. (g)	Mean pup wt. (g)	
1	Mean	8.96	0.00	135.5	15.21	9.17	0.00	252.7	28.26	9.17	0.00	402.7	44.88	100.0
	SD	1.90	0.00	28.19	1.45	1.71	0.00	54.39	2.19	1.71	0.00	89.02	3.74	0.00
	N	24	24	24	24	24	24	24	24	24	24	24	24	24
2	Mean	9.22	0.00	137.7	15.10	9.22	0.00	254.1	27.80	9.22	0.00	399.7	44.23	100.0
	SD	1.24	0.00	14.37	1.68	1.24	0.00	28.82	2.80	1.24	0.00	56.62	5.02	0.00
	N	23	23	23	23	23	23	23	23	23	23	23	23	23
3	Mean	9.17	0.00	129.1	14.27	9.17	0.00	248.7	27.41	9.13	0.43	389.1	43.03	99.57
	SD	1.59	0.00	17.63	1.58	1.59	0.00	37.80	2.81	1.58	2.09	60.22	4.06	2.09
	N	23	23	23	23	23	23	23	23	23	23	23	23	23
4	Mean	9.05	0.00	108.0*	11.86*	8.90	1.43	213.0*	23.94*	8.90	1.43	339.4*	37.93*	98.57
	SD	1.75	0.00	26.05	1.81	1.70	3.59	49.87	2.85	1.70	3.59	77.08	4.70	3.59
	N	21	21	21	21	21	21	21	21	21	21	21	21	21

Statistical analysis: Kruskal Wallis test

William's test if group mean differences are different from control at p < 0.05

* = mean value of group is significantly different from control

Reproductive and developmental toxicity Report Title: Segment III Intravenous pre- and postnatal toxicity study in rats including maternal function
 Test Item: Fosnetupitant Study Number: PNET-15-85 (b) (4) Study no.: X0270

Daily Dose (mg/kg)	0 (Control)/1	3.95/2	13.16/3	39.47/4
Litter data of F1 generation				
Number of litters evaluated ^a	24	23	23	23
Pre-weaning clinical signs of F1 pups				
- Missing pups	3	-	3	24
- Found dead pups	1	-	-	4
Pre-weaning development of F1 pups (days)				
- Pinna detachment	2.83	-	-	3.36*
- Startle response to sound	13.96	-	-	15.10*
- Eye opening	14.88	-	-	15.76*
Necropsy of F1 pups	-	-	-	-
Daily Dose (mg/kg) – Not dosed	Control	2	3	4
Number of F1 selected animals – Males	24	24	24	24
- Females	24	24	24	24
F1 Males – Mortality				
Found dead	0	1	0	0
F1 Females				
- No. of Not pregnant	3	1	2	3
- No. With Total Resorption	0	0	1 ^b	0
- No. With Unilateral implantation	2	2	1 ^b	1
- Killed humanely	0	1	0	0
- No. of pregnant females	21	23	22	21
- No. With live pups on <i>post partum</i> Day 21	21	22	21	21

- No noteworthy findings. * - p<0.05 ** - p<0.01 (\$) = Modified t test if group variances are inhomogeneous
^a = For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
 G = Gestation day pc = *post coitum* pp = *post partum*
^b = Same female

Reproductive and developmental toxicity Report Title: Segment III Intravenous pre- and postnatal toxicity study in rats including maternal function
 Test Item: Fosnetupitant Study Number: PNET-15-85 (b) (4) Study no.: X0270

Daily Dose (mg/kg) – Not dosed	Control	2	3	4
Number of F1 selected animals – Males	24	24	24	24
- Females	24	24	24	24
Clinical Observations – F1 Males and F1 Females	-	-	-	-
F1 Males				
Body weight (g) ^a				
- Day 28	84.61	-	-	-14**
- Day 35	133.24	-	-	-11**
- Day 42	181.04	-	-	-10**
- Day 49	226.79	-	-	-10**
- Day 56	276.46	-	-	-10**
- Day 63	310.44	-	-	-8**
- Day 70	340.06	-	-	-8**
- Day 78	364.27	-	-	-7**
- Day 85	385.85	-	-	-7**
F1 Females				
Body weight (g) ^a				
- Day 28	76.81	-	-	-11*
- Day 35	115.25	-	-	-9**
- Day 42	143.78	-	-	-7**
- Day 49	163.98	-	-	-5*

- No noteworthy findings. * - p<0.05 ** - p<0.01 (\$) = Modified t test if group variances are inhomogeneous
^a = For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
 G = Gestation day pc = *post coitum* pp = *post partum*

Reproductive and developmental toxicity Report Title: Segment III Intravenous pre- and postnatal toxicity study in rats including maternal function
 Test Item: Fosnetupitant Study Number: PNET-15-85 (b) (4) Study no.: X0270

Daily Dose (mg/kg) – Not dosed	Control		2		3		4	
Number of F1 selected animals	24		24		24		24	
– Males	24		24		24		24	
– Females								
F1 Males								
Body weight gain per day (g) ^a								
- Day 35	6.946		-		-		-7**	
- Day 42	6.829		-		-7*		-7*	
- Day 49	6.536		-		-		-11**	
- Day 56	7.096		-8*		-8*		-8*	
F1 Females								
Body weight gain per day (g) ^a	-		-		-		-	
Preputial Separation (days)	41.29		42.13		42.58		43.42*	
Vaginal opening	32.29		32.96		33.50		33.83	
Motor activity (COUNT)	M	F	M	F	M	F	M	F
	1055.9	1404.1	1492.7**	1678.1	1263.8	1555.8	1304.7	1441.1
Y-Maze test (sec)	M	F	M	F	M	F	M	F
Time 1	23.3	20.5	16.9*	9.9	22.8	7.8	26.5	8.2
Time 2	9.5	20.3	7.7	12.1	10.7	9.3	14.0	10.1
Time 3	11.4	24.6	11.1	13.0	9.0	13.0*	9.5	11.6
Time 4	10.7	23.2	10.1	12.8	8.0	10.8	10.8	12.0

- No noteworthy findings. * - p<0.05 ** - p<0.01 (\$) = Modified t test if group variances are inhomogeneous
^a = For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
 G = Gestation day pc = post coitum pp = post partum
 M = Male F = Females

Reproductive and developmental toxicity Report Title: Segment III Intravenous pre- and postnatal toxicity study in rats including maternal function
 Test Item: Fosnetupitant Study Number: PNET-15-85 (b) (4) Study no.: X0270

Daily Dose (mg/kg) – Not dosed	Control		2		3		4	
Number of F1 selected animals – Males	24		24		24		24	
– Females	24		24		24		24	
Mean No. Days Prior to Mating	2.83		2.75		2.33		3.88	
No. of Males that Mated	24		24		24		24	
No. of Fertile Males	21		23		22		21	
No. of Females Sperm-Positive	24		24		24		24	
F1 Females								
Mean No. Corpora Lutea	12.1		12.5		12.9		12.7	
Mean No. Implantations	12.1		12.5		12.9		12.7	
% Preimplantation Loss	0.0		0.3		0.0		0.0	
Terminal body weight (g) - Males	388.1		-		-6*		-7**	
Terminal body weight (g) – Females	-		-		-		-	
Absolute organ weight - F1 Males and F1 Females	-		-		-		-	
Relative organ weight - F1 Males and F1 Females	-		-		-		-	
Macroscopic observations of F1 animals	-		-		-		-	
F2 GENERATION								
Pre-weaning development of F2 pups (days)								
- Startle response to sound	13.52		15.55		15.38		16.05 (+18.7) *	
Necropsy of F2 pups	-		-		-		-	

- No noteworthy findings. * - p<0.05 ** - p<0.01 (\$) = Modified t test if group variances are inhomogeneous
^a = For controls group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
 G = Gestation day pc = post coitum pp = post partum

Toxicokinetics were not performed.

10 Special Toxicology Studies

Local Tolerance Studies:

The local tolerance of fosnetupitant and palonosetron combination was evaluated following single intravenous, para-venous, and intra-arterial doses in male New Zealand White rabbits (NEPA-14-33). Study design is summarized in the following table (taken from the study report).

Fosnetupitant + Palonosetron

Group Number	Treatment Site*	Treatment	Route of admin.	Dose Volume (mL/site/animal)	Animal Numbers
1	Right ear	Control Item	Intravenous	0.5	2, 4, 6, 8
2	Right ear	Control Item	Intra-arterial	0.5	10, 12, 14, 16
3	Right ear	Control Item	Paravenous	0.2	18, 20, 22, 24
4	Right ear	Test Item	Intravenous	0.5	26, 28, 30, 32
5	Right ear	Test Item	Intra-arterial	0.5	34, 36, 38, 40
6	Right ear	Test Item	Paravenous	0.2	42, 44, 46, 48

* Each animal served as its own control. The left ear remained untreated and acted as control.

The final drug product contained 260 mg of fosnetupitant and 0.25 mg of palonosetron as a lyophilized powder, and was reconstituted prior to administration. The final concentration was 13 mg/ml and 0.0125 mg/mL of fosnetupitant and palonosetron, respectively.

No histopathological change was observed following intravenous or intra-arterial administration; however inflammation occurred at the injection site following para-venous injection. Ulceration of cutis, necrosis, and hemorrhage of dermis were also noted following para-venous injection in one rabbit.

The local tolerance of fosnetupitant alone was evaluated following single intravenous, para-venous, and intra-arterial doses in male New Zealand White

rabbits (PNET-14-12). The study design is summarized in the following table (taken from the study report).

Fosnetupitant

Group Number	Treatment Site	Treatment	Route of admin.	Dose Volume (mL/site/ animal)	Animal Numbers
1	Right ear	Control item	Intravenous	0.5	2, 4, 6, 8
2	Right ear	Control item	Intra-arterial	0.5	10, 12, 14, 16
3	Right ear	Control item	Paravenous	0.2	18, 20, 22, 24
4	Right ear	Test item	Intravenous	0.5	26, 28, 30, 32
5	Right ear	Test item	Intra-arterial	0.5	34, 36, 38, 40
6	Right ear	Test item	Paravenous	0.2	42, 44, 46, 48

The final drug product contained 130 mg of fosnetupitant in 10 ml vehicle (13 mg/ml).

Intravenous injection resulted in perivascular and/or vascular minimal chronic inflammation in two treated rabbits, with minimal perivascular necrosis in one of these two rabbits. Treatment-related changes including scab formation, epidermal hyperplasia, chronic inflammation, focal minimal hemorrhage, and edema of dermis were noted following para-venous injection at the injection site. No histopathological change was observed following intra-arterial administration.

Application of 0.5 mL solution containing fosnetupitant at 13 mg/mL to the prepared dorsal skin of New Zealand White female rabbits for 4 hours resulted in slight erythema (PNET-13-44).

Fosnetupitant at 13 mg/mL did not produce eye irritation in bovine corneas (PNET-13-65).

Skin Sensitization Tests:

Intradermal injection of fosnetupitant (20%) did not induce a sensitization response in guinea pigs (PNET-13-46).

Fosnetupitant did not induce anaphylaxis in the active systemic anaphylaxis test in guinea pigs (PNET-14-10).

Fosnetupitant did not induce anaphylaxis in the passive cutaneous anaphylaxis test in guinea pigs (PNET-14-11).

In Vitro Hemolysis Study:

Fosnetupitant and netupitant at concentrations up to 500 µg/ml did not have hemolytic effects in human blood (NETU-09-18).

Phototoxicity:

Fosnetupitant tested positive in the in vitro phototoxicity test using Balb/c 3T3 cells (PNET-13-66). The biological relevance of this finding is uncertain.

11 Integrated Summary and Safety Evaluation

AKYNZEO injection is a fixed-dose combination of two active drug substances, fosnetupitant chloride hydrochloride and palonosetron HCl. Fosnetupitant is quickly converted in vivo to netupitant, an NK1 receptor antagonist. Palonosetron is a 5-HT₃ receptor antagonist. Oral AKYNZEO® (capsules) was approved in 2014 as a fixed-dose combination of 300 mg netupitant and 0.5 mg palonosetron (free base equivalent) under NDA 205718 for the prevention of chemotherapy-induced nausea and vomiting (CINV). Palonosetron hydrochloride is an approved drug that is available as Aloxi® Injection (approved in 2003). An oral formulation, Aloxi® Capsules, was approved in 2008 but was later withdrawn from marketing. Aloxi® Injection is indicated for prevention of CINV and prevention of PONV (postoperative nausea and vomiting). The approved IV dose is 0.25 mg and the approved oral dose is 0.5 mg (doses expressed as the free base equivalent). The sponsor seeks approval of AKYNZEO injection for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in adults.

Given the rapid conversion of fosnetupitant to netupitant in humans and in most animal species, the in vivo pharmacological profile for fosnetupitant is assumed to be highly similar to that of netupitant. Fosnetupitant at 10 and 30 µM slightly inhibited the delayed rectifier potassium current (I_{Kr}) mediated by the hERG channel in stably transfected human embryonic kidney (HEK293) cells. Repeated intravenous dosing of fosnetupitant at doses up to 13.2 mg/kg/day for 2 weeks did not have any effects on cardiovascular function, including blood pressure, heart rate, and ECG in conscious dogs. Repeated intravenous combination doses of fosnetupitant and palonosetron at 1.32/1, 3.95/3, and 13.2/6 mg/kg/day for 2 weeks had no effects on blood pressure, heart rate, or body temperature in conscious dogs. However, at a dose of 13.2/6 mg/kg/day, the combination of fosnetupitant and palonosetron prolonged PR, PQ, and QT intervals, and QRS complex duration.

Following intravenous administration, fosnetupitant was quickly converted to netupitant in rats, dogs, and monkeys. The human plasma protein binding of

fosnetupitant was approximately 92-95%. Netupitant exhibits high protein binding (>99%) in plasma in rats, dogs, and humans. Three major metabolites (M1, M2, and M3) were identified in rats, dogs, and humans. Following IV administration of radiolabeled fosnetupitant, elimination of radioactivity was mainly found in the bile and feces, with only a very small fraction in urine for both rats and dogs. The excretion pattern of fosnetupitant is similar to that of netupitant. The administered dose of fosnetupitant was quickly converted to netupitant, which was eliminated mainly by biliary excretion.

Given the rapid metabolic conversion of fosnetupitant to netupitant, the Agency accepted the sponsor's proposal to conduct intravenous toxicity studies of fosnetupitant alone and the combination of fosnetupitant + palonosetron using a maximum duration of 4 weeks. It is noted that the toxicology program for oral Akynzeo included oral studies of up to 6 months in rats and 9 months in dogs using netupitant alone, and 3-month studies of the combination of netupitant + palonosetron in rats and dogs. The toxicity studies of fosnetupitant alone and the combination of fosnetupitant + palonosetron did not produce any novel findings, as compared to the toxicology program for oral Akynzeo.

Fosnetupitant alone was tested in intravenous toxicity studies of up to 4 weeks in rats and in dogs. In the 4-week intravenous toxicity study in rats, fosnetupitant was tested at 0, 3.95, 13.16, and 39.47 mg/kg/day (equivalent to 3, 10 and 30 mg/kg/day of netupitant, respectively). The high dose of 39.47 mg/kg/day is considered as the NOAEL.

In the 4-week intravenous toxicity study in dogs, fosnetupitant was tested at 0, 1.32, 3.95, and 13.16 mg/kg/day. The high dose of 13.16 mg/kg/day was the NOAEL.

4-Week intravenous toxicity studies with the combination of palonosetron and fosnetupitant were conducted in rats and dogs. In the 4-week intravenous toxicity study in rats, fosnetupitant was tested at 3.95, 13.16, and 39.47 mg/kg/day in combination with palonosetron at 1, 3, and 10 mg/kg/day, respectively. The high dose of 39.47/10 mg/kg/day was the NOAEL.

Fosnetupitant in combination with palonosetron was tested at 1.316 + 1 mg/kg/day, 3.95 + 3 mg/kg/day, and 13.16 + 10 / 6 mg/kg/day in dogs. The dose of 10 mg/kg/day palonosetron was reduced to 6 mg/kg/day on day 15 due to convulsion. The treatment resulted in convulsion, salivation, and swelling at the injection site in high dose group. The test article increased heart rate and prolonged the QT_c intervals in mid- and high-dose groups. The dose of 1.316 + 1 mg/kg/day was NOAEL.

Fosnetupitant was negative in the Ames test, in vitro chromosome aberration test using human lymphocytes, and the in vivo rat micronucleus test.

Long-term studies in animals to evaluate carcinogenic potential of fosnetupitant are not needed to support approval for the proposed indication; therefore no carcinogenicity studies with fosnetupitant were conducted.

In the segment I fertility and early embryonic development study in rats, male rats were treated with pronetupitant at 3.95, 13.16, or 39.47 mg/kg by IV administration for four weeks prior to mating, continuing throughout the mating period and up to day 7 post-coitum. Female rats were treated with the same IV doses for two weeks prior to mating, continuing throughout the mating period and up to day 7 post-coitum. Both males and females were sacrificed on day 15 post-coitum. The high dose of 39.47 mg/kg/day was the NOAEL.

In the segment II embryo-fetal development study in rats, fosnetupitant was given to pregnant rats by IV injection at 0 (vehicle), 3.95, 13.16, or 39.47 mg/kg/day during gestation days 6-17. One high-dose fetus showed hindlimb malrotation and 6 high-dose fetuses from 3 different litters had no ossification of pubis. One high-dose fetus was found dead. No malformations were detected in the control, low-, or mid-dose groups. The NOAEL was 13.16 mg/kg/day.

In the segment II embryo-fetal development study in rabbits, pregnant rabbits were treated with fosnetupitant at 3.13, 6.25, and 12.5 mg/kg/day by intravenous injection during Day 6 through Day 19 post-coitum. The high dose of 12.5 mg/kg/day was considered the NOAEL for maternal toxicity. The low dose of 3.13 mg/kg/day was the NOAEL for developmental toxicity based on the increased number of resorptions at doses of 6.25 mg/kg/day or higher. The embryo-fetal effects in this study differed from the effects of oral netupitant in rabbits, and this difference can be attributed to the minimal transformation of fosnetupitant to netupitant, in contrast to the rapid metabolism of fosnetupitant in rats and humans.

In the pre-/postnatal development study in rats, female rats were treated with fosnetupitant at 0, 3.95, 13.16, and 39.47 mg/kg/day by intravenous injection from implantation (Day 6 post-coitum) through weaning (Day 20 post-partum). The high dose reduced body weight gain in the F0 and F1 rats. The offspring had lower bodyweight at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). The mid-dose of 13.16 mg/kg/day was the NOAEL for dams and pups (F0 and F1 generations, respectively).

The table below summarizes the animal to human AUC multiples for fosnetupitant calculated from the animal AUC values associated with the NOAEL.

Fosnetupitant AUC Multiples of Human Exposure

Toxicity study	Species	NOAEL (mg/kg/day)	AUC at NOAEL (ng•hr/mL)	Multiples of Human exposure ^a
4-week IV	Rat	Male: 39.47 Female: 39.47	Male: 4385 Female: 3050	Male: 1.5 Female: 1.0
4-week IV	Dog	Male: 13.16 Female: 13.16	Male: 2858 Female: 2160	Male: 1.0 Female: 0.7
Segment 2 Reproductive	Rat Rabbit	Female: 13.16 Female: 3.13	Female: N/A Female: 15929	Female: N/A Female: 5.4

^a fosnetupitant AUC = 2943 ng•hr/mL at 260 mg fosnetupitant chloride hydrochloride IV in study PNET-12-23

The table below summarizes the animal to human AUC multiples for netupitant calculated from the animal AUC values associated with the NOAEL.

Netupitant AUC Multiples of Human Exposure

Toxicity study	Species	NOAEL (mg/kg/day)	AUC at NOAEL (ng•hr/mL)	Multiples of Human exposure ^a
4-week IV	Rat	Male: 39.47 Female: 39.47	Male: 43864 Female: 59329	Male: 3.7 Female: 4.94
4-week IV	Dog	Male: 13.16 Female: 13.16	Male: 85719 Female: 77957	Male: 7.1 Female: 6.5
Segment 2 Reproductive	Rat Rabbit	Female: 13.16 Female: 3.13	Female: 24504 Female: 4739	Female: 2.0 Female: 0.4

^a Netupitant AUC = 12014 ng•hr/mL at 260 mg fosnetupitant chloride hydrochloride IV in study PNET-12-23

The high doses tested in general toxicity studies in rats and dogs were NOAELs, and the animal to human AUC multiples for netupitant ranged from 3.7 to 7.1. These data support the recommended human dose with little safety concern. It is noted that oral administration of netupitant in repeated dose toxicity studies produced phospholipidosis, which was not seen in the intravenous toxicity studies with fosnetupitant (Pharmacology/Toxicology review of NDA 205718 by Dr. Ke Zhang, dated 06/19/2014).

In summary, fosnetupitant alone was tested intravenously for up to 4-weeks in rats and in dogs. No treatment-related changes were noted in these studies. Intravenous toxicity studies of 4-weeks duration with the combination of fosnetupitant and palonosetron were performed in rats and dogs. The combination of fosnetupitant and palonosetron did not produce additional toxicity as compared to either compound given alone, based on comparison to the intravenous toxicity studies with fosnetupitant alone or the intravenous toxicity studies previously conducted with palonosetron alone. Fosnetupitant was

negative in the Ames test, in vitro chromosomal aberration test, and in vivo rat micronucleus test.

Reviewer Signature _____

Ke Zhang, Ph.D.
Pharmacologist
Division of Gastroenterology and Inborn Errors Products

Supervisor Signature _____

David B. Joseph, Ph.D.
Lead Pharmacologist
Division of Gastroenterology and Inborn Errors Products

cc:
Orig NDA 210,493
DGIEP
DGIEP/PM
DGIEP/D. Joseph
DGIEP/K. Zhang

R/D Init.: 12/11/17

12 Appendix/Attachments

QSAR Assessments for Impurities:

Statistical-based and expert rule-based methods were used for the QSAR assessment of 19 potential impurities for the Ames test (DMF (b) (4), Section 3.2.S.3.2). The statistical-based QSAR method included three different models: ACD/Percepta statistical model, Leadscope Genetox QSAR Statistical Suite, and Vega Mutagenicity statistical model. The expert rule-based method also included three models: ACD/Percepta expert rule-based system, Leadscope Genetox Expert Alert Model, and Toxtree (a Benigni/Bossa rulebase for mutagenicity). The assessment for each method (statistical and expert-based) compared results across the three respective models in order to reach a consensus prediction. The QSAR analysis results are summarized in the sponsor's table below.

Table 3: In Silico Evaluation of Genotoxic Impurities

Name	QSAR Statistical-based weight of evidence prediction	Expert rule-based weight of evidence prediction	QSAR weight of evidence prediction
(b) (4)	POSITIVE (Borderline Reliable)	POSITIVE (Borderline Reliable)	POSITIVE (Borderline Reliable)
(b) (4)	NEGATIVE (High Reliable)	NEGATIVE (Moderate Reliable)	NEGATIVE (High Reliable)
(b) (4)	NEGATIVE (High Reliable)	NEGATIVE (Moderate Reliable)	NEGATIVE (High Reliable)
(b) (4)	NEGATIVE (High Reliable)	NEGATIVE (Moderate Reliable)	NEGATIVE (High Reliable)
(b) (4)	NEGATIVE (High Reliable)	NEGATIVE (Moderate Reliable)	NEGATIVE (High Reliable)
(b) (4)	NEGATIVE (High Reliable)	NEGATIVE (Borderline Reliable)	NEGATIVE (High Reliable)
(b) (4)	INCONCLUSIVE	POSITIVE (Borderline Reliable)	POSITIVE (Borderline Reliable)
(b) (4)	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)
(b) (4)	NEGATIVE (Moderate Reliable)	POSITIVE (Borderline Reliable)	POSITIVE (Borderline Reliable)
(b) (4)	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)

(b) (4)	NEGATIVE (Borderline Reliable)	POSITIVE (Borderline Reliable)	POSITIVE (Borderline Reliable)
	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)
	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)
	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)
	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)
	INCONCLUSIVE	NEGATIVE (na*)	NEGATIVE (na*)
	NEGATIVE (Borderline Reliable)	NEGATIVE (na*)	NEGATIVE (Borderline Reliable)
	NEGATIVE (Borderline Reliable)	NEGATIVE (Borderline Reliable)	NEGATIVE (Borderline Reliable)
	NEGATIVE (Moderate Reliable)	NEGATIVE (Moderate Reliable)	NEGATIVE (Moderate Reliable)

*na: not available

Because of the positive predictions for impurities (b) (4) Ames tests were conducted for both, and the results were negative (these studies are not presented in this review). Several impurities had a negative prediction with borderline reliability (see table above). Since each of the borderline negative impurities is (b) (4), a read-across study was performed to provide additional analysis in support of the negative predictions (see sponsor's table below). The impurities (b) (4) had positive predictions in the QSAR analysis, and both tested positive in the Ames test (see section 2.5 for information on the control strategy for these impurities).

Table 4: Read-across Study

Name	QSAR Statistical-based weight of evidence prediction	Expert rule-based weight of evidence prediction	Read-across prediction
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	INCONCLUSIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE
(b) (4)	NEGATIVE	NEGATIVE	NEGATIVE

Review of Leachables/Extractables

(b) (4)
 Extractables Risk Assessment Report
 (3.2.P.2.3 Annex 2)

The (b) (4) was evaluated for extractables, and several extractables were identified. The calculated maximum dose for each identified extractable following administration of Akynzeo for injection is lower than the Permitted Daily Exposure (PDE, calculated in accordance with ICH guidance Q3C) (see sponsor's table below). The estimated worst case exposure for each extractable is also below the TTC of 1.5 mcg/day (ICH guidance M7). The sponsor calculated the worst case exposure based on the batch volume of (b) (4) and an assumed production of about (b) (4) vials of drug product from a single batch. The CMC product reviewer, Dr. Caroline Strasinger, confirmed the validity of sponsor's calculation.

Identified Compounds	Total Compound for # of filters / batch [mg]	Conc. total extractable in 300 L [$\mu\text{g/L}$]	Exposure Patient (20 mL) [ng/patient]	Below PDE?
(b) (4)				yes
				yes
				yes
				yes
				yes
				yes
				yes
				yes

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

/s/

KE ZHANG
12/19/2017

DAVID B JOSEPH
12/20/2017
I concur.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 210-493

Drug Name: AKYNZEO® (fosnetupitant and palonosetron) for injection

Indication(s): The prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic chemotherapy.

Applicant: Helsinn Healthcare SA

Date(s): Stamp date: 04/20/2017
PDUFA Goal date: 04/20/2018

Review Priority: Standard

Biometrics Division: DBIII

Statistical Reviewer: Min Min, Ph.D.

Concurring Reviewers: Yeh-Fong Chen, Ph.D.

Medical Division: Division of Gastrointestinal and Inborn Error Products (DGIEP)

Clinical Team: Medical Officer: Charles Line, M.D.
Medical Team Leader: Anil Rajpal, M.D.

Project Manager: Mary Chung

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1 EXECUTIVE SUMMARY

The applicant submitted one phase 3 efficacy study with IV palonosetron in cancer patients (PALO-15-17) and one phase 3 safety study with fosnetupitant-palonosetron FDC (NEPA-15-18) to support the use of IV fosnetupitant-palonosetron FDC in preventing acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

Before conducting these two phase 3 studies, the applicant also conducted three phase 1 studies (two PK and safety studies in healthy volunteers, i.e., PNET-12-23 and PNET-13-63, with fosnetupitant administration, and one PK and safety study in cancer patients, i.e., NEPA-15-19, with fosnetupitant-palonosetron FDC administration). Based on the FDA's advice after negotiation, the ultimate requirements for the IV NEPA FDC clinical development program should include a bioequivalence trial (PNET-12-23), a non-inferiority (NI) efficacy trial on the palonosetron component (PALO-15-17), a clinical safety trial (NEPA-15-18) and two clinical pharmacology trials (i.e., PNET-13-63, drug-drug interaction in healthy volunteers; NEPA-15-19, PK in cancer patients).

The statistical reviewer had carefully evaluated this application and successfully confirmed the applicant's efficacy findings in Study PALO-15-17. The applicant had successfully demonstrated the efficacy of IV palonosetron component in preventing acute nausea and vomiting associated with initial and repeat courses of HEC. However, the rate of complete response (CR) in the delayed phase for IV NEPA FDC arm was observed to be 9% more lower than that for the concurrent oral Akynzeo arm in the safety Study NEPA-15-18. In addition, the observed CR rate in the delayed phase was 12% more lower than that for oral Akynzeo in Study NETU-07-07. Whether the data supported the efficacy of delayed phase for IV fosnetupitant-palonosetron is deferred to the clinical pharmacology reviewer's evaluation.

In conclusion, data of Study PALO-15-17 indeed supported the efficacy of IV Akynzeo in preventing the nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) only for the acute phase.

2 INTRODUCTION

2.1 OVERVIEW

The applicant is seeking the following indication for AKYNZEO® (fosnetupitant and palonosetron) for injection, for intravenous use, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. In the US, oral Akynzeo® (netupitant + palonosetron HCl) capsules were approved (NDA 205718) in October 2014 for the prevention of both the acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy, including but not limited to highly emetogenic chemotherapy (HEC). Fosnetupitant is a neputitant prodrug. In Europe, Akynzeo® was approved in May 2015. The therapeutic indication is also the prevention

of acute and delayed nausea and vomiting but associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy.

Nausea and vomiting are among the side effects associated with cancer treatment that patients and their families fear the most (Laslo J, 1981; Griffin AM, 1996; De Boer-Dennert M, 1997; Hofman M, 2004; Basch E, 2010). The negative aspects of nausea and vomiting can influence all facets of a patient's life. If nausea and vomiting are not controlled in a cancer patient, serious metabolic problems such as fluid and electrolyte balance disturbances and nutritional status deficiencies can develop. Psychological problems associated with nausea and vomiting may include anxiety and depression. In addition, uncontrolled nausea and vomiting may also lead to the decision by the physician to reduce chemotherapy dose intensity or to the wish by the patient to stop potentially beneficial cancer therapy (Oo T.H., 2005). CINV is classified as either acute, i.e., occurring within the first 24 hours after chemotherapy, or delayed, i.e., occurring after the first 24 hours, extending until the fifth day. The development of acute emesis is known to largely depend on serotonin (5-HT). CINV mainly occurs due to input from the chemoreceptor trigger zone (CTZ).

The 5-HT₃ receptor has been demonstrated to selectively participate in the emetic response, thus providing a physiologic explanation for the demonstrated and clinically useful antiemetic effects of 5-HT₃ receptor antagonists (RAs). The 5-HT₃ and NK1 Receptor Antagonists (RA) are among the drugs of choice for an optimal antiemetic prophylaxis in cancer patients receiving chemotherapy; clinical practice guidelines in oncology (Navari et al, 2016) recommend that patients receiving HEC or MEC regimens should be treated with a combination of a 5-HT₃ RA, NK1 RA and a systemic corticosteroid. 5-HT₃ RAs are designed to block one or more of the signals that cause nausea and vomiting. The most sensitive signal during the first 24 hours after chemotherapy appears to be 5-HT₃ mediated. Approved 5-HT₃ inhibitors include: ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®) and palonosetron (Aloxi®). Aprepitant (Emend®) was the first selective NK1 RA approved for CINV in the US (2003), in combination with other antiemetic agents, with a subsequent IV formulation (fosaprepitant, prodrug of aprepitant) approved. In 2015, oral rolapitant (Varubi®) was approved and marketed in the US for prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to highly emetogenic chemotherapy.

Helsinn developed an oral NEPA fixed-dose combination (FDC), which includes a 5-HT₃ receptor antagonist (palonosetron, 0.5 mg) and an NK1 receptor antagonist (netupitant, 300 mg) in the form of a hard-gelatin capsule to be administered as a single dose 1 hour (h) prior to chemotherapy. In the US, oral NEPA FDC (Akynzeo® capsules) was approved in October 2014 for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy, including but not limited to highly emetogenic chemotherapy (HEC). In Europe, Akynzeo® was approved in May 2015. The therapeutic indication is the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy.

An IV formulation (IV NEPA FDC) was developed as a benefit for patients who are not able to tolerate an oral formulation. The IV NEPA FDC development program was initially designed and proposed based on a bioequivalence approach, with the concept that IV NEPA FDC was a line extension of oral NEPA FDC and the precedent being the approval of fosaprepitant (Emend®).

After negotiating with FDA, the ultimate requirements of the IV NEPA FDC clinical development program were to include a bioequivalence trial (PNET-12-23), a non-inferiority efficacy trial on the palonosetron component (PALO-15-17), a clinical safety trial (NEPA-15-18) and two clinical pharmacology trials (PNET-13-63, drug-drug interaction in healthy volunteers; NEPA-15-19, PK in cancer patients).

Although the focus of this NDA is the IV NEPA FDC data, much of the information is derived from the oral Akynzeo® development program (ref. NDA 205718) which comprised 23 phase 1 trials (20 in healthy volunteers, 2 in patients with cancer and 1 in patients with hepatic impairment), one phase 2 dose-ranging efficacy trial and 3 phase 3 efficacy and safety trials in cancer patients. In addition, additional supportive safety information from the 2 studies conducted (b) (4) was included.

Overall, the applicant submitted reports and results for three phase 1 studies (two PK and safety studies in healthy volunteers, PNET- 12-23 and PNET-13-63, with fosnetupitant administration, one PK and safety study in cancer patients, NEPA-15-19, with fosnetupitant-palonosetron FDC administration), one phase 3 efficacy study with IV palonosetron in cancer patients (PALO- 15-17) and one phase 3 safety study with fosnetupitant-palonosetron FDC (NEPA-15-18) to support their prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (see Table 1). In this statistical review, we only focus on the efficacy Study PALO-15-17.

Table 1: Overview of Clinical Trials Providing Key Efficacy and Safety Data for the IV NEPA FDC Program

PALO-15-17 phase 3 study in cancer patients (HEC) Single-cycle	Double-blind, randomized (1:1) active controlled parallel group study; Provide demonstration of the efficacy contribution of the palonosetron component to the IV NEPA FDC, by establishing non-inferiority [CR acute period (0-24 hr)] of the palonosetron IV infusion vs. IV bolus	PALO IV 30 min infusion (225/225/225) vs. PALO IV 30 sec bolus (216/215/215) 441 randomized patients total
PNET-12-23 phase 1 study in healthy subjects SAD administration on Day 1 of each period	Three-part double-blind (within dose cohorts) study Convey netupitant acute and delayed phase HEC efficacy from oral Akynzeo® to fosnetupitant in the I.V. FDC by identifying the IV fosnetupitant dose that yields a netupitant exposure equivalent to that provided by a 300 mg dose of oral netupitant.	SAD/ SAD-CO; P-CO; F-CO. 160 randomized subjects total (SAD/SAD-CO: 80, P-CO: 40, F-CO: 40)
NEPA-15-18* phase 3 study	Double-blind, randomized (1:1) active controlled	IV NEPA FDC (203/203/203)

in cancer patients (HEC) Multiple cycles (up to 4)	parallel group study Provide safety information and descriptive efficacy information of the IV NEPA FDC	vs. Oral Akynzeo® (202/201/201) 405 randomized patients total
NEPA-15-19* Single-cycle	Open-label full sample PK study Provides safety information and PK in the patient population	IV NEPA FDC (36/24^/36)

IV NEPA FDC = Fosnetupitant/Palonosetron Fixed Dose Combination - (fosnetupitant 260 mg/palonosetron 0.25 mg)

Oral Akynzeo®= Netupitant/Palonosetron Fixed Dose Combination (netupitant 300 mg/palonosetron 0.5 mg)

PALO= Palonosetron;

SAD: single ascending dose; SAD-CO: single ascending dose crossover; P-CO: pilot crossover; F-CO: final crossover,

Frel IV: relative availability factor (based on AUC_{0-inf}); ^ PK population, not FAS

*Dexamethasone is included in all dose regimens for studies PALO-15-17, NEPA-15-18 and NEPA-15-19

Source: the applicant's Table 1 of clinical-overview.pdf

2.1.1 Regulatory History

The following listed important communications between the applicant and the FDA:

12/09/2014 meeting minutes:

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.

FDA recommended the application “conduct an additional study with a non-inferiority 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, defined as no emetic episodes and no rescue medication, in the acute phase, and the primary objective should be to demonstrate non-inferiority of the efficacy of the new proposed infusion time compared to the approved rapid infusion”.

Type B teleconference minutes on 2/4/2015:

Clinical program

The favorable PK, safety and efficacy data from PNET-12-23, NEPA-15-18 and PALO-15-17 studies collectively comprise the IV NEPA FDC NDA clinical development program as agreed with FDA and are considered adequate to support the proposed indication cited above.

- Fosnetupitant (Netupitant) acute and delayed phase HEC efficacy and safety data supporting the proposed IV NEPA FDC indication.
- Palonosetron (30- minute infusion) HEC acute phase efficacy and safety data supporting the proposed IV NEPA. FDC indication.

NI margin (FDA response to Question 1)

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 intravenous 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 the applicant agreed that the NI margin of 15% is acceptable based on the applicant's plan to use a two-sided 99% confidence interval for the PALO-15-XX study.**

2/27/2015 teleconference:

Design, population and primary endpoint, PALO-15-XX (which became PALO-15-17). "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 (b) (4)

(b) (4)
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. (b) (4)

(b) (4) with a limitation of use stating that it has not been studied in the setting of anthracycline plus cyclophosphamide chemotherapy."

"We agree with the design of study NEPA-15-YY (which became NEPA-15-18) 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, because (b) (4)

(b) (4) Should a safety signal be found, additional studies and/or patients may be required."

The overall I.V. FDC NDA clinical program was proposed to be comprised of the following five studies to support the target indication: "prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Akynzeo is an intravenous (b) (4) combination of palonosetron and pronetupitant: palonosetron prevents

nausea and vomiting during the acute phase and pronetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.”

1. PALO-15-17: a phase 3 noninferiority study of I.V. palonosetron 0.25 mg given as a 30 minute infusion versus FDA-approved I.V. palonosetron 0.25 mg given as a 30 second bolus, to support efficacy of the I.V. palonosetron 30 minute infusion in the I.V. FDC.
2. NEPA-15-18: a phase 3 HEC clinical safety study to assess the safety of the I.V. pronetupitant/palonosetron (260 mg/0.25 mg) FDC infused over 30 minutes compared to approved oral Akynzeo (netupitant/palonosetron 300/0.5 mg) capsules for the prevention of HEC chemotherapy-induced nausea and vomiting in four repeated consecutive chemotherapy cycles. The intent is to assess the safety of the I.V. FDC which has a higher Cmax than Akynzeo capsules.
3. PNET-13-63: a clinical drug-drug interaction study in healthy volunteers to assess the effect of I.V. pronetupitant infused over 30 minutes on the PK of oral dexamethasone.
4. PNET-12-23: a phase 1, double-blind, single ascending dose study in healthy subjects to assess safety and define the maximum tolerated dose of I.V. pronetupitant. An FDA-requested BE analysis from this trial demonstrated that the 260 mg pronetupitant dose is BE for AUClast and AUCinf to oral netupitant 300 mg from the approved FDC capsule. Netupitant Cmax for I.V. pronetupitant 260 mg was greater and not bioequivalent to netupitant 300 mg from the approved oral FDC thereby requiring HEC safety study NEPA-15-18.
5. NEPA-15-19: a phase 1, open label study to evaluate the PK profile and safety of the I.V. pronetupitant/palonosetron (260 mg/0.25 mg) FDC administered for the prevention of HEC in cancer patients receiving a single cycle of HEC chemotherapy. The intent is to obtain PK data in cancer patients to support labeling the planned I.V. FDC NDA.

“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.”

FDA Biostatistics Written Replies on 6/06/2016

1. Please provide justification for the assumptions used to calculate the sample size, including the response rates and the anticipated dropout rates.
2. Since you intend to enroll 440 adult patients from approximately 88 sites worldwide for Study PALO-15-17, county/region effect should be taken into consideration for both studies. Moreover, based on the anticipated number of patients in the study, it is possible that there will only be about 5 patients, on average, from each site. To ensure the blinding of the study, you should use centralized randomization.
3. To assess the impact of the dropouts on the final analysis, the statistical analysis plan (SAP) should include several missing data strategies for the primary endpoint. For example, one sensitivity analysis is to impute dropouts as responders or non-responders. In addition, you should consider other approaches that can handle data missing at random (MAR) such as the MI (i.e., multiple imputations). Furthermore, since the missing data can be informative [i.e., missing not at random (MNAR)], you should also consider approaches such as pattern mixture models or selection models.
4. For the proposed non-inferiority (NI) study, we expect that the NI analysis based on the per-protocol (PP) needs to be consistent with the analysis based on the FAS population. Any analysis of the secondary endpoints (i.e., ‘Key’ secondary endpoint) for which the

results are intended to be described in the labeling need to be pre-specified and agreed upon with the review division. In addition, you need to propose a valid multiplicity procedure in order to control the overall type I error for the primary and key secondary endpoints.

5. Please submit your revised phase 3 protocols and SAP for review prior to starting your studies. Note that key features of your statistical plan, including primary and secondary endpoints and analyses, type I error control, missing data handling strategy, etc., should be pre-specified in your protocol and not introduced in the SAP after start of study.”

Pre NDA meeting on 11/30/2016

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.

2.2 DATA SOURCES

The applicant’s original NDA submission including the data sets is stored in the following link: <\\CDSESUB1\evsprod\NDA210493\0001\>.

3 STATISTICAL EVALUATION

3.1 DATA and ANALYSIS QUALITY

The statistical reviewer confirmed the applicant’s analysis results for the pivotal study. Overall, the data and analysis quality of this NDA submission are acceptable.

3.2 EVALUATION of EFFICACY

The following sections contain the study description, where mostly was extracted directly from the applicant’s Clinical Study Report (CSR). If there is any major discrepancy between the CSR and the study protocol or amendments, the detailed discussion will be included in the Section of Reviewer’s Findings and Conclusions. The two studies, PALO-15-17 and NEPA-15-18 had

different designs and statistical methods; the former was a non-inferiority efficacy study and the later was a safety study with secondary efficacy assessments (descriptive statistics only).

3.2.1 Study PALO-15-17

Study PALO-15-17 is titled “A phase 3, single-dose, multicenter, randomized, double-blind, parallel group study to assess the efficacy and safety of palonosetron 0.25 mg administered as a 30-minute IV infusion compared to palonosetron 0.25 mg administered as a 30-second IV bolus for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic chemotherapy.” It was conducted from September 30 2015 through March 09 2016 in 76 study centers in 9 countries (Belarus, Bosnia and Herzegovina, Bulgaria, Georgia, Greece, Hungary, Lithuania, Romania, and Russia).

3.2.1.1 Study Objective and Study Design

This was a phase 3, single-dose, multicenter, randomized, double-blind, parallel group study to assess the efficacy and safety of palonosetron 0.25 mg administered as a 30-minute IV infusion compared to palonosetron 0.25 mg administered as a 30-second IV bolus for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic chemotherapy. A total of 440 patients, stratified by country and gender, are to be randomized to receive one of the two treatment regimens in a 1:1 randomization ratio according to specific procedures using the interactive web response system (IWRS). Before the start of the reference HEC administration on study Day 1, patients will be randomly allocated to receive one of the two treatment regimens for prevention of chemotherapy induced nausea and vomiting:

- Test group - IV PALO 0.25 mg administered as a 30-minute infusion on Day 1.
 - Control group - IV PALO 0.25 mg administered as a 30-second bolus on Day 1.
- Oral

Oral dexamethasone administration is open-label, 20 mg (5 tablets of 4 mg) given as single dose 30 minutes before the start of the reference HEC at Day 1 and 8 mg bid (2 tablets of 4 mg bid) on Days 2 to 4. Identical dosages and posology will be applied in both treatment groups. The blinding of the study medication will be guaranteed by the use of placebo of the alternative treatments (double-dummy technique). A placebo matching the IV PALO 0.25mg administered as 30-minute infusion and a placebo matching the IV PALO 0.25 mg administered as a 30-second bolus will be prepared and administered.

The primary objective of Study PALO-15-17 was to demonstrate the non-inferiority of a single intravenous (IV) dose of palonosetron 0.25 mg administered as a 30-minute (min) infusion with oral dexamethasone versus a single IV dose of palonosetron 0.25 mg administered as a 30-second (sec) bolus with oral dexamethasone, in terms of proportion of patients with complete response (CR), defined as no emetic episodes and no rescue medication, in the acute phase (0-24 h after start of reference highly emetogenic chemotherapy [HEC]).

The target population consisted of chemotherapy naïve patients. A naïve patient is defined as a patient having no history of cytotoxic chemotherapy when entering the present study. Adult

chemotherapy naïve male and female patients with a diagnosis of malignant solid tumor scheduled to receive their first course of HEC (cisplatin administered as a single IV dose of ≥ 70 mg/m², cyclophosphamide ≥ 1500 mg/m², carmustine (BCNU) > 250 mg/m², dacarbazine (DTIC), mechlorethamine (nitrogen mustard)) are to be enrolled in this study.

3.2.1.2 Efficacy Endpoints and Analyses

Three phases are defined for the efficacy evaluation. The acute phase starts at ‘time 0’, which is the start of the reference HEC administration and lasts for the first 24 hours. The delayed phase starts at > 24 hours after the start of reference HEC administration and lasts until 120 hours. The overall phase lasts from time 0 till 120 hours after the start of HEC administration.

Primary efficacy endpoint is the proportion of patients with CR, defined as no emetic episodes and no rescue medication, in the acute phase of CINV.

Secondary efficacy endpoints are:

- the proportion of patients with CR during the delayed and overall phases of CINV;
- the proportion of patients with no emetic episodes during the acute, delayed, and overall phases of CINV;
- the proportion of patients with no rescue medication during the acute, delayed, and overall phases of CINV.

Blinding

The blinding of the study medication will be guaranteed by the use of identical placebos to the respective active drugs (double-dummy technique). When the 30-minute IV palonosetron 0.25 mg infusion will be administered, a 30-second IV placebo bolus will be also administered (Group 1). Oppositely, when the 30-second IV palonosetron 0.25 mg bolus, a 30-minute placebo infusion will be also administered (Group 2). Therefore, each patient will receive a 30-second IV bolus and a 30-minute IV infusion. No blinding is required for dexamethasone, which is administered at the same dose and posology in both treatment groups.

Analysis populations

There are three analysis populations:

1. All Randomized Patients
This population includes all patients who have been randomized to treatment. Patients will be assigned to the study treatment group according to the treatment to which they have been randomized. Tables displaying patients’ disposition will be based on all patients randomized.
2. Full Analysis Set
The Full Analysis Set (FAS) includes all patients who have been randomized to treatment and received HEC regimen and active study drug (including partial infusion). Following the intent-to-treat principle, patients will be assigned to the study treatment group according to the treatment to which they have been randomized.
FAS will be used for demography, other baseline characteristics, for primary efficacy analysis and all efficacy analyses.
3. Per Protocol (PP) population

The Per-Protocol Population includes all patients from the FAS, who have completed the 0-24 hours study period and with no major protocol violations i.e. those affecting the primary efficacy endpoint. All the protocol violations (e.g., wrong inclusion, poor compliance, missing diaries, forbidden concomitant medications, mis-randomizations) will be reviewed and discussed case by case during the BDRM and decisions described in the blind data review document/minutes which will be finalized prior to database lock. Patients will be assigned to study treatment groups according to the actual treatment received.

PP Population will be used for demography, other baseline characteristics and for the primary efficacy analysis.

Rationale for the choice of non-inferiority margin

Palonosetron 0.25 mg given intravenously as a 30-second bolus is the active control drug proposed for this trial since it is approved for CINV in HEC setting in the acute phase. The efficacy of this therapy has been clearly established and quantified in study PALO-99-05 (conducted worldwide enrolling overall 680 patients) that served as the pivotal efficacy trial to support approval of IV palonosetron 0.25 mg bolus. In this study, the proportion of patients with CR in the acute phase in the IV palonosetron 0.25 mg group was 59.2% (95% CI: 52.4% to 65.6%).

The meta-analysis database was comprised of 78 treatment arms from published trials and included data from 7,274 patients (the above mentioned studies using placebo were part of the database as well). Using this database, a logistic regression was performed to identify which covariates were predictive of CR. Using the relevant covariates from the meta-analysis, an equation was produced to determine the predicted CR rate for any given patient population (i.e., any given combination of relevant covariates). Relevant covariates from PALO-99-05 were entered into this equation (model) to produce the predicted historical placebo CR in the acute phase for the patient population of that study.

PALO-99-05: CR in the acute phase for IV palonosetron 0.25 mg (Intention-To-Treat population) and modeled historical placebo

	IV palonosetron 0.25 mg (N=223)	Modeled historical placebo
Proportion of patients with CR (95% CI)	59.2% (52.4% to 65.6%)	11.8% (8.7% to 15.8%)

The entire effect of the active control drug assumed to be present in this non-inferiority trial (M1) is estimated by the difference between the lower limit of the 95% CI for the IV palonosetron 0.25 mg (i.e., 52.4%) and the upper limit of the 95% CI for the modeled historical placebo (i.e., 15.8%). As a consequence, the non-inferiority margin for the current study should not exceed 36.6% (M1).

Based also on clinical judgment, it is considered that a substantial portion of M1 (at least 50%) should be preserved, leading to a value of about 18%. In order to be as conservative as possible, a further additional adjustment is applied to reflect uncertainties and the non-inferiority margin is

reduced to 15% (M2, the largest clinically acceptable difference of the test drug compared to the control drug). The proposed non-inferiority margin of 15% is the same as that used for HEC pivotal efficacy trial PALO-99-05. A 15% non-inferiority margin was also considered adequate for pivotal CINV studies for other 5-HT3 antagonists. Studies which formed the basis for approval of dolasetron used a non-inferiority margin of 15% versus active control drug treatments (study MCPR0031 versus ondansetron and study 73147-3-S-093 versus granisetron).

Efficacy analysis

Since the only difference between test and control groups is the duration of infusion (30 minutes versus 30 seconds), it is expected that, a single dose of IV PALO 0.25 mg administered as a 30-minute infusion will not decrease the percentage of patients with CR in the acute phase (0-24h after the start of chemotherapy).

The null hypothesis can be written as: $H_0 : \pi_T - \pi_C \leq -\Delta$

H_0 will be tested against the alternative hypothesis: $H_1 : \pi_T - \pi_C > -\Delta$

Where π_T is the proportion of patients with CR in the test group (PALO IV 30-minute infusion), π_C is the proportion of patients with CR in the control group (PALO IV 30-second bolus) and Δ is the non-inferiority margin which is fixed at 15%.

All efficacy analyses will be performed on the FAS. The primary efficacy endpoint, i.e. CR in the acute phase will also be summarized on PP Population. The primary efficacy analysis will be performed on both the FAS and the PP Populations. All missing data will be considered as failures. For the non-inferiority of IV 30-minute palonosetron 0.25 mg infusion vs. I.V. 30-second palonosetron 0.25 mg bolus, both populations will have equal importance and the analyses will conclude on the basis of the coherence between the results obtained in both populations. To test the null hypothesis, the lower limit of the two-sided 99% CI for the difference in proportion of patients with CR in the acute phase between palonosetron IV 30-minute infusion and palonosetron IV 30-second bolus will be compared to the pre-set non-inferiority margin set at -15%.

Calculations will be based on stratum-adjusted Cochran-Mantel-Haenszel (CMH) for the risk difference, 99% CI for the risk difference will be calculated. The model will include gender and country as strata. P-value for non-inferiority testing will be computed.

To calculate confidence intervals for CMH statistics the below quantities are needed. The calculations and the following notation are listed below.

Let K be the number of strata.

For the kth stratum we denote with:

n_k the number of patients in the test group

m_k the number of patients in the control group

x_k the number of patients with CR in the acute phase in the test group

y_k the number of patients with CR in the acute phase in the control group

$N_k = n_k + m_k$ the total number of patients.

With these quantities the CMH estimator for risk difference is given by:

$$d_{CMH} = \frac{\sum W_{CMH,k} d_k}{\sum W_{CMH,k}}$$

Where

$$W_{CMH,k} = n_k m_k / N_k$$

and

$$d_k = \frac{x_k}{n_k} - \frac{y_k}{m_k}$$

The variance of d_{CMH} is $\frac{\sum L_k}{(\sum W_{CMH,k})^2}$ with

$$L_k = [x_k(n_k - x_k)m_k^3 - y_k(m_k - y_k)n_k^3] / (n_k m_k N_k^2)$$

Finally the 100(1- α)% level confidence interval for the risk difference is

$$d_{CMH} \pm z_{1-\frac{\alpha}{2}} (\sum L_k)^{1/2} / \sum W_{CMH,k}$$

where $z_{1-\frac{\alpha}{2}}$ is the $1 - \frac{\alpha}{2}$ quantile of standard normal distribution.

Multiplicity

No adjustment for multiplicity is foreseen in the study since there is only one single primary efficacy endpoint, which is the CR in the acute phase. All secondary efficacy endpoints are intended to provide supportive evidence related to the primary objective or additional clinical characterization of treatment effect, the results on these will be interpreted in only a descriptive manner.

Sample Size

The sample size and power estimation were based upon CR (complete response) in the acute phase (0-24h after the start of chemotherapy), the primary efficacy endpoint of the study. CR rate in the acute phase was estimated to be 80%. The non-inferiority margin is set at – 15%. For a two-sided test of difference using Type I error equal to 0.01, a sample size of 212 evaluable patients per group is needed to ensure 90% power (nQuery + nTerim 3.0, module PTEO-1). The number of patients was increased up to 220 per group for a total of 440 to ensure an adequate number of evaluable patients.

Subgroups that will be explored include:

- Gender (Male, Female)
- Country (Belarus, Bosnia and Herzegovina, Bulgaria, Georgia, Greece, Hungary, Lithuania, Romania, Russia)

Interaction Analysis:

Treatment by factor (gender and country) interactions will be explored but not included in the primary analysis model. In case significant interactions (i.e. $p\text{-value} \leq 0.100$) are found, additional investigational analyses may be run in order to understand the reason for the heterogeneity. As mentioned in the protocol, as exploratory analysis, the following full model will be fitted with logistic regression using the available data to investigate the interactions between treatment (Trt) and factors (Gender or Country)

Interim Analysis: Not applicable

Missing Values and Imputation Methods

Due to the short observation period (24 hours for the primary efficacy endpoint and a maximum of 120 hours for all the other efficacy assessments) and based on a previous the applicant's studies with a very similar design and in the same setting (HEC), a very low number of drop-outs and minimal missing data is expected. Minimizing the withdrawal and missing data is particularly important in the context of a non-inferiority trial. The procedure for handling missing data will be applied to the FAS and PP Population.

Any patients who do not provide data about occurrence of emetic episodes and rescue medication intake or do not provide a full set of these data throughout the 24 hours after HEC administration will be considered as treatment failures (i.e., non-responders) for the primary efficacy analysis. For consistency, the same approach for handling missing data as described for the primary efficacy analysis will be also applied to emetic episodes and rescue medication intake. The same approach described above for the primary efficacy analysis will be applied also to CR in the delayed and overall phases.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 441 patients were randomized, and 440 (99.8%) received study treatment. The number of patients randomized into each treatment group, patient disposition, and the reasons for early withdrawal from the study are summarized in Table 2, at 88 sites in Russian Federation (30.4%), Hungary (22.2%), Romania (20.6%), and the Republic of Georgia (9.5%). Table 2 displays the number of patients randomized into each treatment group, patient disposition and the reasons for early discontinuation.

Patient retention was excellent; 96.1% of the randomized patients and 96.4% of the treated patients completed the study. Of the 17 (3.9%) patients who withdrew from the study prematurely, 13 (2.9%) patients died while on study (6 [2.7%] patients in the infusion group, and 7 [3.2%] in the bolus group); 2 (0.5%) patients were lost to follow-up (one patient in each treatment group); and 2 (0.5%) patients chose to withdraw (both patients in the bolus group).

Table 2 Patient Disposition for Study PALO-15-17

Palonosetron 0.25 mg IV	30-min Infusion n (%)	30-sec Bolus n (%)
FAS / Safety Population	225 (100)	215 (99.5)
Per-Protocol population	214 (95.1)	211 (97.7)
Reason for exclusion from PP population		
Major protocol deviation	11 (4.9)	4 (1.9)
Not in FAS	0 (0.0)	1 (0.5)
Randomized	225 (100)	216 (100)
Never treated	0 (0.0)	0 (0.0)
Treated	225 (100)	216 (100)
Completed the study	218 (96.9)	206 (95.4)
Primary reason for withdrawal		
Death	6 (2.7)	7 (3.2)
Lost to follow up	1 (0.4)	1 (0.5)
Withdrawal by patient	0 (0.0)	2 (0.9)

Source: the applicant's Table 3 of palo-15-17-study-report.pdf

Table 3 Patients' Baseline Demographics based on Randomized Subjects for Study PALO-15-17

Palonosetron 0.25 mg IV	30-min Infusion n (%)	30-sec Bolus n (%)
Gender		
Male	151 (67.1)	144 (67.0)
Female	74 (32.9)	71 (33.0)
Age (years), mean (SD)	59.9 (8.7)	58.9 (8.5)
Age (years), median	61.0	59.0
Age (years), min, max	25, 78	34, 79
Weight (kg), mean (SD)	73.9 (16.5)	74.4 (17.4)
Race		
White	225 (100.0)	215 (100.0)

Source: the applicant's Table 6 of palo-15-17-study-report.pdf

3.2.1.4 The applicant’s Efficacy Results & Conclusions

The applicant’s results for non-inferiority analyses of CR in the acute phase for both FAS and PP populations in Table 4.

Table 4 The applicant’s Results for Non-Inferiority Analyses of Complete Response (CR) Rate in the Acute Phase for both FAS and PP Populations

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Full Analysis Set	N=225	N=215
Responder, n (%)	186 (82.7)	186 (86.5)
[95% confidence interval] *	[77.2, 87.1]	[81.3, 90.4]
CMH risk difference % (Infusion-Bolus)	-3.8 [-12.2; 4.7]	
[99% CI] **		
P-value **	<.001	
Per Protocol Population	N=214	N=211
Responder, n (%)	177 (82.7)	182 (86.3)
[95% confidence interval] *	[77.2, 87.1]	[81.3, 90.4]
CMH risk difference % (Infusion-Bolus)	-3.4 [-12.0; 5.2]	
[99% CI] **		
P-value **	<.001	

Source: the applicant’s Table 11 of palo-15-17-study-report.pdf

*: Wilson score method confidence interval

**: CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O’Gorman et al. The non-inferiority margin is set to 15%. P-value associated with non-inferiority testing.

The applicant’s summary is that “this study demonstrated non-inferiority of palonosetron 0.25 mg administered as a 30-min IV infusion compared with administration as a 30-sec IV bolus, in terms of the proportion of patients reporting CR (defined as no emetic episodes and no rescue medication intake) in the acute phase.”

Secondary efficacy analyses

Results of secondary efficacy endpoints supported well the conclusion of non-inferiority of the 30-min IV infusion versus the 30-sec IV bolus. These secondary endpoints included CR in the delayed and overall phases; the proportion of patients with no emetic episodes in the acute, delayed, and overall phases; and the proportion of patients with no use of rescue medication in the acute, delayed, and overall phases.

3.2.2 Statistical Reviewer’s Findings and Comments

- (Efficacy Findings for Study PALO-15-17)** The statistical reviewer confirmed the applicant’s analysis results for the primary endpoint. We concluded that the study data support non-inferiority of palonosetron 0.25 mg administered as a 30-min IV infusion compared with administration as a 30-sec IV bolus, in terms of the proportion of patients reporting CR (defined as no emetic episodes and no rescue medication intake) in the acute phase.

- 2. (Efficacy Results for Study NEPA-15-18)** The rate of complete response (CR) in the delayed phase for IV NEPA FDC arm was observed to be 9% more lower than that for the concurrent oral Akynzeo arm in the safety Study NEPA-15-18. In addition, the observed CR rate in the delayed phase was 12% more lower than that for oral Akynzeo in Study NETU-07-07. Whether the data supported the efficacy of delayed phase for IV fosnetupitant-palonosetron is deferred to the clinical pharmacology reviewer's evaluation.

The statistical reviewer found that the study was not powered to demonstrate the efficacy of IV NEPA FDC in delayed phase by comparing with oral NEPA FDC. As shown on the Tables 8 and 9 in the appendix, we noted that when NI margin for NETU 300mg is very small (1%), the sample size will be huge. The size of NEPA-15-18 study can only provide 4% power. Note that 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. The descriptive analysis results for the efficacy endpoints cannot be claimed in the labeling.

- 3. (Efficacy Results for Study NETU-07-07)** In order to address previous issues (#2 above), the efficacy of the oral 100 mg netupitant/0.5 mg palonestron group by comparing with 0.5 mg palonestron group in delayed phase was assessed. According to the FDA's statistical review for the oral Akynzeo, it was noted that Study NETU-07-07 had the needed information; 100 mg netupitant/0.5 mg palonestron is indeed superior to 0.5 mg palonestron group in delayed phase based on the CR rate difference (see Appendix Table 9).

3.3 Evaluation of Safety

The safety evaluation is not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

1.1. Gender, Age, and Geographic Region

1.1.2 For Study PALO-15-17

The following Tables 5 to 6 present the applicant's subgroup (gender and geographic region) analysis results for the primary efficacy endpoint. Table 7 presents the statistical reviewer's age subgroup analysis results for the primary efficacy endpoint. Of note, all of the patients were Caucasians; thus the subgroup analysis for race was not performed. According to the results from Tables 5 to 7, we noted that except Male, Russia and Age <65 subgroups, none of the lower limit of the 99% C.I. for females is greater than -15, i.e., the defined margin for the entire patient population. Since all of these subsets had small number of patients (<80/arm) comparing with their counterparts and their confidence intervals overlapped, we do not think this is an issue for being concerned.

Table 5 Exploratory Analysis of Complete Response Rate in the Acute Phase by Gender (Population: Full Analysis Set)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Male (N)	N=151	N=144
Responder, n (%)	134 (88.7)	129 (89.6)
[95% confidence interval] *	[82.7, 92.9]	[83.5, 93.6]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-0.8 [-7.8; 6.2]	
Female (N)	N=74	N=71
Responder, n (%)	52 (70.3)	57 (80.3)
[95% confidence interval] *	[59.1, 79.5]	[69.6, 87.9]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-9.8 [-23.2; 3.6]	

Source: the applicant's Table 18 of palo-15-17-study-report.pdf

*: Wilson score method confidence interval

** : CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O'Gorman et al. The non-inferiority (NI) margin is set to 15%. P-value associated with non-inferiority testing.

Table 6 Exploratory Analysis of Complete Response Rate in the Acute Phase by Country (Population: Full Analysis Set)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus
Bulgaria (N)	N=19	N=19
Responder, n (%)	16 (84.2)	17 (89.5)
[95% confidence interval] *	[62.4, 94.5]	[68.6, 97.1]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-5.3 [-25.5; 15.0]	
Georgia (N)	N=21	N=21
Responder, n (%)	19 (90.5)	20 (95.2)
[95% confidence interval] *	[71.1, 97.3]	[77.3, 99.2]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-5.2 [-20.8; 10.4]	
Hungary (N)	N=50	N=48
Responder, n (%)	39 (78.0)	42 (87.5)
[95% confidence interval] *	[64.8, 87.2]	[75.3, 94.1]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-9.8 [-23.9; 4.3]	
Romania (N)	N=46	N=45
Responder, n (%)	40 (87.0)	37 (82.2)
[95% confidence interval] *	[74.3, 93.9]	[68.7, 90.7]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-4.7 [-10.0; 19.5]	
Russian Federation (N)	N=68	N=65
Responder, n (%)	53 (77.9)	56 (86.2)
[95% confidence interval] *	[66.7, 86.2]	[75.7, 92.5]
CMH risk difference % (Infusion-Bolus) [99% CI] **	-8.1 [-20.7; 4.6]	

Source: the applicant's Table 18 of palo-15-17-study-report.pdf

*: Wilson score method confidence interval

***: CMH stratum-adjusted method for difference in proportions, stratified by gender and country according to Koch et al. and O’Gorman et al. The non-inferiority margin is set to 15%. P-value associated with non-inferiority testing.

Table 7 Statistical Reviewer’s Age Subgroup Analysis Results for Complete Response Rate in the Acute Phase by Age (Population: Full Analysis Set)

Palonosetron 0.25 mg IV	30-min Infusion	30-sec Bolus	Difference Infusion-Bolus
Age < 65 (N)	N=156	N=157	
Responder, n (%)	123 (78.9)	134 (85.4)	-6.5
Age ≥ 65 (N)	N=69	N=58	
Responder, n (%)	63 (91.3)	52 (89.7)	1.6

5 SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

The applicant submitted one phase 3 efficacy study with IV palonosetron in cancer patients (PALO-15-17) and one phase 3 safety study with fosnetupitant-palonosetron FDC (NEPA-15-18) to support the use of IV fosnetupitant-palonosetron FDC in preventing acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

In addition to these two phase 3 studies, the applicant also conducted three phase 1 studies (two PK and safety studies in healthy volunteers, PNET- 12-23 and PNET-13-63, with fosnetupitant administration, one PK and safety study in cancer patients, NEPA-15-19, with fosnetupitant-palonosetron FDC administration). Based on the FDA’s advice after negotiation, the ultimate requirements for the IV NEPA FDC clinical development program should include a bioequivalence trial (PNET-12-23), a non-inferiority efficacy trial on the palonosetron component (PALO-15-17), a clinical safety trial (NEPA-15-18) and two clinical pharmacology trials (i.e., PNET-13-63, drug-drug interaction in healthy volunteers; NEPA-15-19, PK in cancer patients).

Regarding the efficacy study with IV palonosetron, although data support the use of IV fosnetupitant-palonosetron FDC in preventing acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC); we noted that the observed CR rate (delayed phase) for IV NEPA FDC arm was 9% lower than the CR rate in the delayed phase for the concurrent oral Akynzeo arm in Study NEPA-15-18, and was 12% lower than the CR in the delayed phase for oral Akynzeo in Study NETU-07-07. Whether the data supported the efficacy of delayed phase for IV fosnetupitant-palonosetron is deferred to the clinical pharmacology reviewer’s evaluation.

5.2. Conclusions and Recommendations

Study PALO-15-17 is positive and support the indication of preventing acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC).

The statistical reviewer had carefully evaluated this application and successfully confirmed the applicant's efficacy findings in Study PALO-15-17. Even though the applicant had successfully demonstrated the efficacy of IV palonosetron component, efficacy in preventing delayed nausea and vomiting associated with initial and repeat courses of HEC has not yet been demonstrated; the rate of complete response (CR) in the delayed phase for IV NEPA FDC arm was observed to be 9% more lower than that for the concurrent oral Akynzeo arm in the safety Study NEPA-15-18. In addition, the observed CR rate in the delayed phase was 12% more lower than that for oral Akynzeo in Study NETU-07-07. Whether the data supported the efficacy of delayed phase for IV fosnetupitant-palonosetron is deferred to the clinical pharmacology reviewer's evaluation.

In conclusion, data of Study PALO-15-17 indeed supported the efficacy of IV Akynzeo in preventing the nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) only for the acute phase.

6 APPENDIX

Table 8 The applicant's Results for Non-Inferiority Analyses of Complete Response (CR) Rate in the Delayed Phase for NEPA-15-18 FAS Population

	IV NEPA FDC	Oral NEPA FDC
Full Analysis Set	N=203	N=201
Responder, n (%)	159 (78.3)	176 (87.6)
CMH risk difference % (Infusion-Bolus) [95% CI] *	-9.0 [-15.8; 2.2]	

Source: the applicant's Table 11 of nepa-15-18-study-report.pdf

*: CMH stratum-adjusted method for difference in proportions, stratified by gender and country.

Table 9 The applicant's Results for Complete Response (CR) Rate in the Delayed Phase, Acute Phase and Overall Phase based on MFAS Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=137)	PALO+NETU 300 mg (N=135)
Delayed phase (25-120 hours)				
Number (%) of Patients	109 (80.1)	122 (90.4)	125 (91.2)	122 (90.4)
Difference from Palo alone (%) with 95 CI		102 (1.9, 18.6)	11.1 (2.9, 19.3)	10.2 (1.9, 18.6)
p-value by logistic regression model*		0.018	0.010	0.018
p-value by CMH test**		0.017	0.008	0.016
Acute phase (0-24 hours)				
Number (%) of Patients	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)
Difference from Palo alone (%) with 95 CI		3.6 (-3.0, 10.2)	3.0 (-3.7, 9.7)	8.8 (3.3, 14.3)
p-value by logistic regression model*		0.278	0.383	0.007
p-value by CMH test**		0.278	0.383	0.002
Overall phase (0-120 hours)				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)
Difference from Palo alone (%) with 95 CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 21.9)
p-value by logistic regression model*		0.018	0.017	0.004
p-value by CMH test**		0.018	0.016	0.003

Source: Table 4 of Dr. Yeh-Fong Chen's statistical review for NDA205718

For the above table 9, the smallest p-value 0.008 for the comparison between PALO+NETU 200mg and PALO alone is less than 0.05/3, second smallest p-value 0.016 for the comparison between PALO+NETU 100mg and PALO alone is less than 0.05/2 and the largest p-value 0.017 for the comparison between PALO+NETU 300mg and PALO alone is less than 0.05. Based on the Holm-Bonferroni method to control the overall type I error rate due to the three study doses, we can conclude that statistically significant superiority to palonosetron alone was observed for each dose of netupitant.

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MIN MIN
12/18/2017

YEH FONG CHEN
12/18/2017

Office of Clinical Pharmacology Review

NDA or BLA Number	210493
Link to EDR	\\CDSESUB1\evsprod\NDA210493\210493.enx
Submission Date	4/20/2017
Submission Type	Original Submission
Brand Name	Akynzeo Injectable
Generic Name	Fosnetupitant/Palonosetron
Dosage Form and Strength	Lyophilized powder to be reconstituted for IV infusion (235 mg Fosnetupitant/0.25 mg Palonosetron)
Route of Administration	Intravenous Infusion
Proposed Indication	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of (b) (4) highly emetogenic chemotherapy
Applicant	Helsinn Healthcare SA
Associated IND	115191
OCP Review Team	Elizabeth Shang, Ph.D., R.Ph., Xinyuan Zhang, Ph.D. (PBPk primary review), Yuching Yang, Ph.D. (PBPk secondary review), Insook Kim, Ph.D.
OCP Final Signatory	Hae-Young Ahn, Ph.D.

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1. EXECUTIVE SUMMARY

The oral Akynzeo capsule, a fixed-dose combination (FDC) product containing 300 mg netupitant and 0.5 mg palonosetron, has been approved since 2014 for acute and delayed chemotherapy induced nausea and vomiting (CINV) associated with i) highly emetogenic chemotherapy (HEC) including cisplatin based chemotherapy and ii) anthracyclines and cyclophosphamide based chemotherapy and chemotherapy not considered highly emetogenic.

In this submission, the sponsor proposes a new FDC (Akynzeo, 235 mg fosnetupitant/0.25 mg palonosetron) injectable product for intravenous infusion over 30 minutes for acute and delayed CINV associated with HEC. While fosnetupitant itself does not have pharmacological activities, its hydrolytic metabolite netupitant, an NK-1 receptor antagonist, is the active drug. Netupitant is not registered as a single agent. Palonosetron (5-HT₃ receptor antagonist) injectable (Aloxi injectable 0.25 mg) is approved for the prevention of acute nausea and vomiting after HEC and acute and delayed nausea and vomiting after moderately emetogenic chemotherapy (MEC). Oral palonosetron (0.5 mg) had been approved for acute nausea and vomiting associated with MEC only. The oral palonosetron product has been discontinued not due to efficacy or safety.

The sponsor conducted three clinical trials to support the efficacy and safety of Akynzeo IV: a relative BA study between IV fosnetupitant and Akynzeo capsule, a non-inferiority efficacy trial between IV palonosetron infused over 30 min and Aloxi (palonosetron 0.25 mg) injection, and a safety study between Akynzeo injectable and Akynzeo oral capsules. The sponsor proposes to support the efficacy of fosnetupitant as a pro-drug following Akynzeo IV administration by relying on the Agency's findings on the efficacy of netupitant from the approved Akynzeo oral capsule (NDA 205718) owned by the same sponsor. A relative BA study was conducted to compare systemic exposures (C_{max} and AUC) of netupitant following single dose of 235 mg fosnetupitant IV and Akynzeo oral capsule. The results showed that the systemic exposure (AUC_{0-120h}) to netupitant was comparable. A phase 3 safety study was conducted to provide safety information for fosnetupitant following Akynzeo IV infusion because i) there is a 1.5-fold increase in C_{max} of netupitant and ii) fosnetupitant, a new molecular entity, had not been used in humans. This phase 3 safety study also provided safety data for administering fosnetupitant/palonosetron as an FDC product in patients.

For the palonosetron component of the product, the sponsor also relied on the Agency's findings on the safety of palonosetron IV (Aloxi; NDA 21372) owned by the same sponsor. Because Akynzeo IV is administered over 30 minutes while Aloxi is administered via IV push over 30 seconds, the C_{max} of Aloxi will be higher than that from Akynzeo IV while AUC will be comparable because the dose is the same. Therefore, safety of the 30-minute infusion of palonosetron is at least comparable if not better than Aloxi administered by IV push. On the other hand, the sponsor conducted a pivotal phase 3 study to evaluate the potential difference in efficacy due to the lower C_{max} and demonstrated that the efficacy of palonosetron IV administered over 30 minutes is not inferior to Aloxi injectable.

The effect of fosnetupitant IV on the systemic exposures to oral dexamethasone was evaluated and found to be comparable to the effect of Akynzeo oral capsules on dexamethasone both in terms of magnitude and duration. This supports the same reduction in the dosage of dexamethasone as that when given with Akynzeo oral capsules.

Recommendations

The Division of Clinical Pharmacology 3 has reviewed this application and found this NDA acceptable from a clinical pharmacology perspective.

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data from the pivotal BA/BE study (PNET-12-23) without on-site inspection as OSIS recently inspected the study sites with the inspectional outcome from the inspections classified as No Action Indicated (NAI).

Post-Marketing Requirements and Commitments

The following PMCs are recommended. The potential interaction between fosnetupitant, a new molecular entity, and the transporters has not been fully characterized. The in vitro study showed that palonosetron is an inhibitor of MATE1 and MATE2-K. Thus, the sponsor needs to address the in vivo drug interaction potential via these two transporters.

1. In vitro assessment of inhibition potential of fosnetupitant towards MATE2-K
2. In vitro assessment of fosnetupitant being a substrate of P-gp/MDR1, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OCT1, and OCT2.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Netupitant is a substance P/neurokinin 1 (NK1) receptor antagonist. Fosnetupitant, a pro-drug, is hydrolyzed to netupitant following the IV infusion. Palonosetron is a 5-HT₃ receptor antagonist. Chemotherapeutic agents exert their emetic stimulus via processes that involve the release of serotonin and substance P and subsequent activation of the 5-HT₃ and NK1 receptors. The release of substance P is considered to be associated with delayed emesis induced by chemotherapy while serotonin is considered to be associated with acute emesis induced by chemotherapy.

Following a single intravenous dose administration of 235 mg fosnetupitant (free base) to healthy subjects, the median time to C_{max} of fosnetupitant was at the end of infusion (i.e., 0.5 hour) and mean C_{max} was 6431 ng/mL (%CV:14%). The mean terminal half-life was about one hour. The median time to C_{max} of netupitant was 0.6 hours and the mean C_{max} was 812 ng/mL (%CV: 21%). The mean terminal half-life of netupitant following IV infusion of fosnetupitant in healthy subjects was not well estimated due to short sampling time (120 hours) in this NDA.

Following a single intravenous dose administration of the proposed product Akynzeo to cancer patients, the median time to C_{max} of fosnetupitant was at the end of infusion (i.e., 0.5 hour) and mean C_{max} was 3478 ng/mL (%CV: 45%). The mean terminal half-life was about 0.75 hours. The median time to C_{max} of netupitant was 0.56 hours and the mean C_{max} was 590 ng/mL (%CV: 28%). The mean terminal half-life of netupitant was 144 hours with sampling time up to 192 hours. The median time to C_{max} of palonosetron was also close to the end of infusion (i.e., 0.58 hour) and mean C_{max} was 823 ng/mL (%CV: 35%). The mean terminal half-life was about 58 hours.

2.1.1. Comparison of systemic exposures (C_{max} and AUC) comparison to netupitant and its major metabolites following 235 mg fosnetupitant IV and Akynzeo capsule

A relative BA study between single dose of 235 mg fosnetupitant injectable intravenously infused over 30 minutes and single dose of oral Akynzeo capsule (300 mg netupitant/0.5 mg palonosetron) showed that the systemic exposure (AUC_{0-120h}) of netupitant met the bioequivalence criteria. The C_{max} of netupitant from fosnetupitant IV administration was 1.5-fold that of oral Akynzeo.

The AUC_{0-120h} of major metabolites, M1, M2, and M3 after IV administration of fosnetupitant were 29%, 25%, and 16% lower than those from Akynzeo oral administration.

The C_{max} of the major metabolites M1, M2, and M3 after IV administration of fosnetupitant were 39%, 34%, and 25% lower those from Akynzeo oral administration.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen with Akynzeo IV is shown below. The proposed dose for fosnetupitant is presented as fosnetupitant free base. The dose of 235 mg fosnetupitant as free base is equivalent to 260 mg fosnetupitant chloride hydrochloride. The rationale of using reduced dexamethasone dose is discussed in Section 3.3.4 of the review.

Table 1. Proposed antiemetic treatment regimen using Akynzeo IV or oral capsules

(b) (4)



Source Data: Sponsor's proposed product label

Hereafter, the fosnetupitant dose refers to the salt form unless otherwise specified since that was the designation used by the sponsor during their drug development. In addition, the sponsor had used pro-netupitant (or pronetupitant) early on during its drug development. Hereafter, fosnetupitant and pro-netupitant are used interchangeably in the review document.

2.2.2 Therapeutic individualization

Similar to the approved oral Akynzeo, avoid use of Akynzeo IV in patients with severe hepatic impairment, severe renal impairment or end-stage renal disease.

2.3 Outstanding Issues

Two PMCs will be issued. Refer to Section 1 of this review

2.4 Summary of Labeling Recommendations

We recommend the following areas to be added to Section 12.3 of the product label:

- Added PK data of fosnetupitant in healthy subjects (absorption part)
- Added palonosetron infusion PK data in cancer patients
- Described the difference in systemic exposure to fosnetupitant between healthy subjects and patients
- Added Drug-drug interaction in regard to co-administration with warfarin
- Added QT study results to Section 12.2.

Labeling revisions are ongoing. Please refer to the final approved labeling when available.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Proposed product

AKYNZEO (235 mg fosnetupitant (free base)/0.25 mg palonosetron) for injection is a (b) (4) combination product of fosnetupitant, a prodrug of netupitant which is a substance P/neurokinin 1 (NK1) receptor antagonist, and palonosetron hydrochloride, a serotonin-3 (5-HT3) receptor antagonist.

AKYNZEO is supplied as a sterile, lyophilized powder for injection in single-use vials of 235 mg fosnetupitant (free base)/0.25 mg palonosetron. The inactive ingredients are edetate disodium (6.4 mg), mannitol (760 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

Each vial must be reconstituted in 50 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP.

Clinical development program and relevant regulatory background

The clinical program consisted of five studies including three phase 1 clinical pharmacology studies. No PK data were collected from the two phase 3 studies.

- Three phase 1 trials (two PK and safety studies in healthy volunteers, PNET-12-23 and PNET-13-63, with fosnetupitant administration, one PK and safety study in cancer patients, NEPA-15-19, with fosnetupitant-palonosetron fixed dose combination (FDC) administration);
- One phase 3 efficacy study with IV palonosetron in cancer patients (PALO-15-17): palonosetron IV push (30 seconds infusion) using Aloxi vs. palonosetron 30-minute IV infusion;
- One phase 3 safety study with fosnetupitant-palonosetron FDC (NEPA-15-18) using oral Akynzeo as a comparator.

The objectives and designs of these clinical studies are shown below.

Study Type Study No.	Study Objective(s)	Study Design	Key inclusion criteria	Sample Size Gender Age Range (yrs)	Treatment
Comparative bioavailability and bioequivalence					
PNET-12-23	Safety/ Fosnetupitant / netupitant Frel IV	Three-part double-blind (within dose cohorts) study	Healthy subjects	160 HVs SAD/SAD-CO; 80 P-CO; 40 F-CO: 40 18-45 yrs 158 subjects (94M, 64F) received treatment (Safety and PK Set)	Part 1: parallel group single ascending dose (SAD) with a crossover extension (SAD CO) (where applicable); Part 2: a pilot crossover part (P- CO), Part 3: final crossover part (F- CO). All parts were performed under
Patient PK and initial tolerability study reports					
NEPA-15-19	PK/safety study	Open label, multicenter study with single administration of IV fosnetupitant/palonosetr on (260 mg/0.25 mg) fixed-dose combination, in association with oral dexamethasone, in cancer patients prior to receiving a cycle of HEC	Cancer patients (HEC)	24 (11M, 13F) 42-76 yrs	Single IV IV NEPA FDC 260 mg/0.25 mg
Extrinsic factor PK study reports					
PNET-13-63	PK/Safety drug interaction study with dexamethasone	Single-centre phase 1 open label, 3-period, 4- treatment, cross-over study using an incomplete block design. Pro-Netu administered at 3 dose levels (130 mg, 195 mg and 260 mg) with increasing drug concentration in the infusion solution (2.6 mg/ml, 3.9 mg/ml and 5.2 mg/ml, respectively) to healthy male and female subjects receiving concomitant administration of oral dexamethasone	Healthy subjects	30 (20M, 10F) 23-45 yrs	Trt A: oral dex regimen + IV 50 ml 5% glucose infusion over 30 min Trt B: oral dex regimen + IV 50 ml fosnetupitant 130 mg infusion over 30 min (2.6 mg/mL) Trt C: oral dex regimen + IV 50 ml fosnetupitant 195 mg infusion over 30 min (3.9 mg/mL) Trt D: oral dex regimen + IV 50 ml fosnetupitant 260 mg infusion over 30 min (5.2 mg/mL). The dex regimen was: 20 mg/day on Day 1, then 8 mg twice a day (b.i.d.) [16 mg/day] on Days 2, 3 and 4.

Phase 3 studies

PALO-15-17	Provide demonstration of the efficacy contribution of the palonosetron component to the IV NEPA FDC, by establishing non-inferiority [CR acute period (0-24 hr)] of the palonosetron IV infusion vs. IV bolus	Double-blind, randomized (1:1) active-controlled parallel group study	Cancer patients (HEC)	440 (295 M, 145 F) 25-79 yrs	PALO IV 30 min infusion vs. PALO IV 30 sec bolus
NEPA-15-18	Provide safety information and descriptive efficacy information of the IV NEPA FDC	Double-blind, randomized (1:1) active-controlled parallel group study	Cancer patients (HEC)	404 (214 M, 190 F) 25-82 yrs	IV NEPA FDC vs. Oral Akynzeo

F=female; FDC=fixed dose combination; HEC= highly emetogenic chemotherapy; IV=intravenous; M=male; MEC=moderately emetogenic chemotherapy; PD=pharmacodynamic; PK=pharmacokinetic; PO=oral.

No pivotal phase 3 clinical trial with efficacy as a primary endpoint was conducted. Fosnetupitant is a prodrug of netupitant. The sponsor is relying on the Agency's findings on netupitant from the approved Akynzeo oral capsule (NDA 205718), a fixed-dose combination product containing netupitant and palonosetron, owned by the same sponsor. Netupitant is not registered as a single agent. A relative BA study was conducted to show systemic exposures (C_{max} and AUC) of netupitant following single dose of 260 mg fosnetupitant IV and Akynzeo oral capsule. The relative BA study results were summarized in Section 2.1. A phase 3 safety study was conducted to provide safety information on fosnetupitant following Akynzeo IV infusion (Study NEPA-15-18).

Since Akynzeo IV is an FDC product containing palonosetron, the sponsor also relied on the Agency's findings on palonosetron IV (Aloxi; NDA 21372). Aloxi is also owned by the same sponsor. Because Akynzeo IV is administered over 30 minutes while Aloxi is administered via IV push, the C_{max} of Aloxi will be higher than that from Akynzeo IV. Therefore, safety is not an issue. The sponsor conducted a pivotal phase 3 study demonstrating that the efficacy (acute phase CINV associated with HEC) contribution of palonosetron from Akynzeo IV is not inferior to Aloxi (Study PALO-15-17).

3.2 General Pharmacology and Pharmacokinetic Characteristics

The mechanism of action, absorption, distribution, metabolism, and excretion information of netupitant can be found in the product label of approved Akynzeo oral capsule.

The mechanism of action, absorption, distribution, metabolism, and excretion information of palonosetron can be found in the product label of approved Akynzeo oral capsule and Aloxi IV.

Fosnetupitant is a new molecular entity (NME). Below is a brief summary of the PK characteristics and ADME of fosnetupitant.

Absorption

The mean (CV%) C_{max} and AUC_{0-inf} of fosnetupitant following single IV dose of 260 mg fosnetupitant in healthy subjects reached 6431 ng/mL (14%) and 2938 h×ng/mL (12%), respectively.

The median [min to max] time to C_{max} (T_{max}) is 0.5 [0.25 -0.52] hour. The median T_{max} is at the end of the 30-minute infusion.

Fosnetupitant exhibited dose-proportional linear pharmacokinetics over the dose ranging from 19.5 to 390 mg.

Distribution

The mean (%CV) apparent volume of distribution (V_d) following single IV dose of 260 mg fosnetupitant in healthy subjects was 124 L (61%).

The human plasma protein binding of fosnetupitant measured by equilibrium dialysis was 92.1% at 1 μM and 94.9% at 10 μM. The free fraction was in the range of 5 - 8%.

The mean blood to plasma concentration ratio in humans was in the range of 0.4 - 0.6 with fosnetupitant concentrations of 0.1, 1, and 10 μM.

Metabolism

Fosnetupitant is hydrolyzed to netupitant by non-CYP450 enzymes. The proposed metabolic pathway is shown in Figure 1 in Section 3.3.4.

In vitro fosnetupitant is converted to netupitant in human hepatocytes and S9 preparations from human livers, kidney, lung, and intestine indicating that the conversion of fosnetupitant to netupitant occurs in liver and extrahepatic tissues.

Following a single intravenous dose administration of 260 mg fosnetupitant to healthy subjects, the median time to C_{max} of fosnetupitant was at the end of infusion (i.e., 0.5 hour) while the median time to C_{max} of netupitant was 0.6 hours indicating a rapid conversion of fosnetupitant to netupitant upon administration. The mean C_{max} was 812 ng/mL (%CV: 21%). The mean terminal half-life of netupitant following IV infusion of fosnetupitant in healthy subjects was not well estimated due to short sampling time (120 hours) in this NDA.

Similarly, following a single intravenous dose administration of the proposed product Akynzeo to cancer patients, the median time to C_{max} of fosnetupitant was at the end of infusion (i.e., 0.5 hour) while the median time to C_{max} of netupitant was 0.56 hours indicating a rapid conversion of

fosnetupitant to netupitant. The mean C_{max} was 590 ng/mL (%CV: 28%). The mean terminal half-life of netupitant was 144 hours with sampling time up to 192 hours. The median time to C_{max} of palonosetron was also close to the end of infusion (i.e., 0.58 hour) and mean C_{max} was 823 ng/mL (%CV: 35%). The mean terminal half-life was about 58 hours.

Elimination

After IV administration of fosnetupitant, its plasma concentrations declined biexponentially. The mean terminal t_{1/2} following single IV dose of 260 mg fosnetupitant in healthy subjects was about an hour. Except for the lower doses where many PK samples of the first 24 hours were below BLOQ, the mean t_{1/2} did not change with the increase in dose.

Cross-study comparison of systemic exposure to fosnetupitant and its metabolites in cancer patients and healthy subjects

The values for C_{max} of fosnetupitant were about 53% to 58% lower in the cancer patient population. The values for AUC_{0-inf} were also 56% to 58% lower in the cancer patient population.

Table 2. C_{max} and AUCs of fosnetupitant following either Akynzeo or fosnetupitant 260 mg IV infusion

Study ID (subjects)	Drug (IV)	Descriptive Statistics	AUC _{0-last} (hr×ng/mL)	AUC _{0-inf} (hr×ng/mL)	C _{max} (ng/mL)
NEPA-15-19	Akynzeo	N	24	23	24
Cancer Patients		Mean	1398	1401	3478
		SD	635	649	1558
		CV%	45.4	46.3	44.8
		GeoMean	1216	1214	3018
PNET-12-23	Fosnetupitant	N	30	30	30
Healthy Subjects		Mean	2934	2938	6431
		SD	362	362	911
		CV%	12.3	12.3	14.2
		GeoMean	2910	2914	6363
PNET-13-63	Fosnetupitant	N	17	17	17
Healthy Subjects		Mean	2852	2855	7367
		SD	662	663	1737
		CV%	23.2	23.2	23.6
		GeoMean	2773	2777	7159

Source data: Reviewer's summary based upon sponsor's submission data

The AUC_{0-120h} of netupitant in patients was 26% lower than that in the healthy subjects (Table 3). The AUC_{0-120h} of netupitant, M1, M2, and M3 are shown in the table below. The reason for choosing AUC_{0-120h} as a key PK parameter for comparison is provided in Section 3.3.1. As this is a cross-study comparison, the differences in systemic exposures to fosnetupitant, netupitant, and its metabolites may not have clinical significance.

Table 3. Comparison of AUC_{0-120h} of netupitant, M1, M2, and M3 in healthy subjects given single dose of 260 mg fosnetupitant IV and patients given single dose of Akynzeo IV

Summary Statistics	AUC _{0-120hr} (h*ng/mL) after 260mg IV fosnetupitant		
	Healthy subjects (PNET-12-23)	Healthy subjects (PNET-13-63)	Patients (NEPA-15-19)
NETUPITANT			
n	30	17	24
Mean	12012	12305.6	8921.8
SD	2339	3817.4	1921.8
CV (%)	19.47	31.02	21.54
GeoMean	11785	11796.2	8709.3
M1			
n	30	17	24
Mean	2326.42	2224.11	1849.14
SD	352.08	571.67	547.00
CV (%)	15.13	25.70	29.58
GeoMean	2298.36	2166.97	1772.82
M2			
n	30	17	20
Mean	2588.3	2002.61	2302.94
SD	1247.7	909.13	792.75
CV (%)	48.20	45.40	34.42
GeoMean	2314.6	1859.96	2181.20
M3			
n	30	17	24
Mean	3454.6	3675.40	2620.81
SD	739.5	1396.41	680.19
CV (%)	21.41	37.99	25.95
GeoMean	3376.8	3476.49	2533.19

Source data: Response to IR of 10/20/2017, Table 2

PK characteristics of palonosetron in patients from Akynzeo IV

The key PK parameters of single dose Akynzeo IV infusion over 30 minute in cancer patients are shown in Table 4.

Table 4. Key PK parameters of palonosetron following single IV dose of Akynzeo in the cancer patients

Analyte	Mean Cmax (ng/mL) (%CV)	Median Tmax (hr) [min-max]	Mean AUC _{0-inf} (hr×ng/mL) (%CV)	Mean t _{1/2} (hr) (%CV)
Palonosetron	823 (35)	0.58 [0.52-6]	36066 (30)	58 (47)

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Adequacy of the bridging

The sponsor relied on the efficacy and safety findings of oral Akynzeo for CINV. The efficacy of Akynzeo IV formulation was supported by the results from the pivotal BA/BE study (PNET-12-23) in which BE criteria were met for AUC of netupitant between fosnetupitant IV and oral Akynzeo.

A relative BA study between the IV formulation of 260 mg fosnetupitant and approved oral Akynzeo capsules showed that the systemic exposures (AUC_{0-120h}) to netupitant met bioequivalence criteria. The Agency focused on AUC_{0-120h} instead of AUC_{0-inf} for the following two reasons:

1. The sampling time for netupitant was only up to 120 hours while its mean terminal half-life in patients is 80 hours. The reported AUC_{0-inf} in the study could not be reliably estimated.
2. For the indication of CINV, the ideal duration of a drug effect is 5 days (120 hours). Thus, comparison of AUC_{0-120h} is clinically relevant.

The C_{max} of netupitant from fosnetupitant 260 mg IV administration was 1.5-fold the oral Akynzeo capsules. In addition, the AUC_{0-120h} of netupitant from fosnetupitant IV administration were comparable to those from oral Akynzeo administration in the pivotal BA/BE study. For details, see Section 4.2.1.

The AUC_{0-120h} of metabolites M1, M2, and M3 from fosnetupitant IV were 29%, 25%, and 16% lower than that from oral Akynzeo, respectively. Similarly, the C_{max} of metabolites M1, M2, and M3 from fosnetupitant IV administration were 39%, 34%, 25% lower than that from oral Akynzeo administration, respectively.

Whether metabolites M1, M2, and M3 carry functional pharmacological activity is not clear at the time of this review. All three bind to NK1 receptor with equal affinity based upon pKi values. Netupitant inhibited NK-1 receptor agonist-induced foot-tapping behavior in gerbils in a dose-dependent manner. The metabolites M1, M2, and M3, also blocked the foot tapping activity in this study. However, the relevance of the effect on foot-tapping activity to the pharmacodynamic activity for the proposed indication is unknown. There is no data in animals to evaluate whether the metabolites have anti-emetic activity unlike what was done for netupitant. Refer to Pharm/Tox review of Akynzeo oral capsules (NDA 205718). The potential therapeutic contribution of these metabolites could not be evaluated. Therefore, for the review of pivotal BA study (PNET-12-23), focus was made on the comparison of systemic exposures (Cmax and AUC) of netupitant.

The safety and tolerability profile of Akynzeo IV is supported by a phase 1 study in cancer patients (NEPA-15-19) and a phase 3 safety study in cancer patients (NEPA-15-18). Refer to Dr. Charles Line's Clinical Review for the safety of Akynzeo IV.

Although the final proposed product is a combination product of fosnetupitant and palonosetron while fosnetupitant as a single agent was used in the pivotal BA study, the presence of palonosetron does not affect the PK of fosnetupitant. This determination was made based upon the following facts:

1. No chemical interaction has occurred between fosnetupitant and palonosetron following reconstitution from the lyophilized vial.
2. The infusion time was fixed at 30 minutes. Thus, the difference in concentrations between fosnetupitant used in the pivotal BA study (2.6 mg/mL) and the final proposed product (5.2 mg/mL) is not an issue.
3. Effect of palonosetron on fosnetupitant: Fosnetupitant is not metabolized by CYP450 enzymes. Fosnetupitant is a substrate of OATP transporters. However, palonosetron is not an inhibitor of OATP transporter.
4. Effect of palonosetron on netupitant (Clinical Pharmacology Review of oral Akynzeo NDA 205718 and approved label of Akynzeo oral capsules):
 - a. Netupitant and is mainly metabolized by CYP3A4. In vitro studies showed that palonosetron does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 or induce CYP1A2, CYP2D6 or CYP3A4/5 although CYP2C19 was not investigated.
 - b. An in vivo study showed that oral dose of palonosetron 0.75 mg did not affect the systemic exposure to netupitant (450 mg PO). In addition, in vivo interaction with netupitant being a substrate for BCRP, OATP1B1, OATP1B3, and OCT1 is unlikely.
5. The human plasma protein binding of fosnetupitant phosphate is 93.5% while the binding of palonosetron to human plasma protein is 62%. Neither drug is highly protein bound. Thus, no competition for plasma protein binding sites with potential displacement of bound drugs is expected.

Effect of fosnetupitant on palonosetron was minimal based upon the following facts:

1. Palonosetron is metabolized by CYP2D6 and, to a minor extent, by CYP3A4 and CYP1A2. In vivo inhibition of CYP2D6, CYP3A and CYP1A2 by fosnetupitant is unlikely given their in vitro IC₅₀ values being at least 20-fold the in vivo values of C_{max} following 260 mg fosnetupitant IV (CYP2D6: IC₅₀ = 217.2 μM; CYP3A4: IC₅₀ = 196.8 - 299.2 μM; and CYP1A2: IC₅₀ = 208.4 μM). The R values ($R = 1 + [I]/K_i$ where $[I] = C_{max} = 9.2 \mu M$; $K_i = IC_{50}/2$) were all < 1.1.
2. Palonosetron was a MDR1/P-gp substrate based upon in vitro studies. However, in vivo drug interaction between a P-gp substrate and fosnetupitant in liver is unlikely based upon basic model estimation. P-gp is also located on the blood-brain barrier (BBB). Theoretically, fosnetupitant may increase the uptake of palonosetron by inhibiting P-gp on BBB. The safety of Akynzeo IV is evaluated in a phase 3 study and is acceptable.
3. Interaction at plasma protein level would be minimal as indicated in Bullet 4 of the “Effect of palonosetron on fosnetupitant.”

Evidence supporting effectiveness

It is noteworthy that for the delayed phase nausea and vomiting, the proportion of patients with Complete Response rate at Cycle 1 was 78.3% in the IV Akynzeo (fosnetupitant 260 mg/palonosetron 0.25 mg) group and 87.6% in the oral Akynzeo (netupitant 300 mg/palonosetron 0.5 mg) group (Study NEPA-15-18). The caveat is that efficacy assessment in this study was the secondary objective (i.e., no statistical power to detect difference). However, the dose-response relationship for efficacy and magnitude of systemic exposure achieved following Akynzeo IV provided sufficient evidence to support effectiveness.

The dose-response curve was flat in the dose range of 100, 200, and 300 mg oral netupitant in combination with 0.5 mg oral palonosetron (Clinical Pharmacology Review of NDA 205718 oral Akynzeo). In a dose-ranging phase 2 study (Study NETU-07-07, NDA 205718), both 100 mg and 300 mg oral netupitant in combination with 0.5 mg oral palonosetron showed statistical superiority in the primary endpoint of Complete Response Rate in the delayed phase compared to 0.5 mg oral palonosetron alone (Biometrics Review of NDA 205718 Akynzeo oral capsules). Even though systemic exposures to netupitant was not measured in this phase 2 study, the AUCs of netupitant, M1, M2, and M3 following a single oral dose of 100 mg netupitant in healthy subjects from a separate study were much lower than those from Akynzeo IV (Table 5). In addition, there is dose-proportional increase in systemic exposures (C_{max} and AUC) to fosnetupitant with fosnetupitant IV dose increase from 19.5 mg to 390 mg and greater than dose-proportional increase in systemic exposure to netupitant with oral netupitant dose increase from 100 mg to 300 mg. Taken together, the totality of the data supports the effectiveness of Akynzeo IV for the proposed indication of

delayed phase CINV. The effectiveness of Akynzeo IV for acute phase CINV was supported by a pivotal phase 3 efficacy study. Refer to Dr. Charles Lines' Clinical Review of this NDA.

Table 5. Cross-study comparison of AUC_{0-120h} (hr×ng/mL) following single oral dose of 100 mg netupitant in healthy subjects* and Akynzeo IV in cancer patients.

	AUC _{0-120hr} (h*ng/mL) after 260mg IV fosnetupitant			AUC _{0-120hr} (h*ng/mL) after 100 mg netupitant PO			
	Healthy subjects (PNET-12-23)	Healthy subjects (PNET-13-63)	Patients (NEPA-15-19)	Healthy subjects	Fold increase compared to 100 mg netupitant (PNET-12-23)	Fold increase compared to 100 mg netupitant (PNET-13-63)	Fold increase compared to 100 mg netupitant (NEPA-15-19)
NETUPITANT							
n	30	17	24	4			
GeoMean	11785	11796	8709	3887	3.0	3.0	2.2
M1							
n	30	17	24	4			
GeoMean	2298	2167	1773	889	2.6	2.4	2.0
M2							
n	30	17	20	4			
GeoMean	2315	1860	2181	308	7.5	6.0	7.1
M3							
n	30	17	24	4			
GeoMean	3377	3476	2533	1298	2.6	2.7	2.0

Source data: Reviewer's summary table.

Fold increase was calculated by the GeoMean of AUC_{0-120hr} after 260 mg IV fosnetupitant divided by the GeoMean of AUC_{0-120hr} after 100 mg netupitant PO.

* from Study NP16603 submitted to NDA 205718 for Akynzeo oral capsules

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Not applicable.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interactions

Since Akynzeo is administered by IV infusion, food-effect study was not conducted as food-drug interactions are not anticipated or applicable.

Drug-drug interactions

In vivo evaluation

Inhibition potential of dexamethasone (CYP3A4 substrate)

The effects of single dose fosnetupitant IV on dexamethasone, a CYP3A4 substrate was evaluated since Akynzeo is given in combination of with a corticosteroid, dexamethasone.

The results are summarized below. For details of the study results, refer to Section 4.2.3.

Table 6. Summary of the effects of single doses of fosnetupitant IV infusion on dexamethasone (CYP3A4 substrate)

Fosnetupitant Dose (mg)	Fold Change in Cmax		Fold Change in AUC _{0-24hr}	
	Day 1	Day 4	Day 1	Day 4
130 mg	1.11	1.40	1.27	1.73
195 mg	1.03	1.58	1.49	2.21
260 mg*	0.97	1.70	1.50	2.42

Fold change: ratio of geometric mean of Cmax and AUC of each substrate (dexamethasone) when dexamethasone was co-administered with fosnetupitant vs dexamethasone administered alone
Day 1: Co-administration of fosnetupitant IV and a substrate drug; Day 4: administration of a substrate drug alone
*Proposed fosnetupitant dose in Akynzeo IV

The mean Cmin was also increased across the doses on Day 1 and Day 4. The Mean Cmin increased 5-fold on Day 1 and 3-fold on Day 4 following 260 mg IV dose of fosnetupitant.

The magnitude of the increase in the systemic exposure to dexamethasone following 260 mg IV infusion on Day 1 and Day 4 was similar to that following 300 mg single oral dose of netupitant.

Table 7. Cross-study comparison of the systemic exposures to dexamethasone administered with or without oral netupitant / IV fosnetupitant

	Fold Change in Cmax		Fold Change in AUC _{0-24hr}	
	Day 1	Day 4	Day 1	Day 4
260 mg IV Fosnetupitant	0.97	1.70	1.50	2.42
300 mg Oral Netupitant*	1.11	1.75	1.72	2.38
Oral Akynzeo†	1.0	1.5	1.6	2.4

Fold change: ratio of geometric mean of Cmax and AUC of each substrate (dexamethasone) when dexamethasone was co-administered with fosnetupitant or netupitant vs dexamethasone administered alone
*Based upon NDA 205718 Review, Table 44; Summary by the reviewer
† NEPA-14-39 PMC study results submitted to NDA 205718

As fosnetupitant is converted to netupitant quickly and with similar magnitude of inhibition between oral netupitant and IV fosnetupitant, it is likely that the inhibition of CYP3A4 is caused by netupitant and metabolite M1, both previously shown as CYP3A4 inhibitors.

In a post-marketing commitment study conducted for oral Akynzeo NDA program, the sponsor has shown that the inhibition of CYP3A decreased on Day 8 and ended from Day 8 to Day 10. The current label for oral Akynzeo states, “A single oral dose of netupitant 300 mg significantly inhibits CYP3A4 for 6 days.” Given that the inhibition of CYP3A on Day 4 was similar between 300 mg oral netupitant and 260 mg IV fosnetupitant, it is reasonable to assume that fosnetupitant single dose will inhibit CYP3A for 6 days as well. It is also reasonable to assume that the inhibition of CYP3A by fosnetupitant will decrease on Day 8 and end from Day 8 to Day 10.

The effect of dexamethasone on the systemic exposures to fosnetupitant, netupitant and its metabolites was not evaluated. However, the systemic exposures to fosnetupitant and netupitant following co-administration of fosnetupitant 260 mg IV and oral dexamethasone (Study PNET-13-63) are comparable to those from Study PNET-12-23 where fosnetupitant 260 mg IV were administered in healthy subjects. See Table 3 and Table 4 in Section 3.2 for the descriptive statistics of C_{max} and AUCs from these studies.

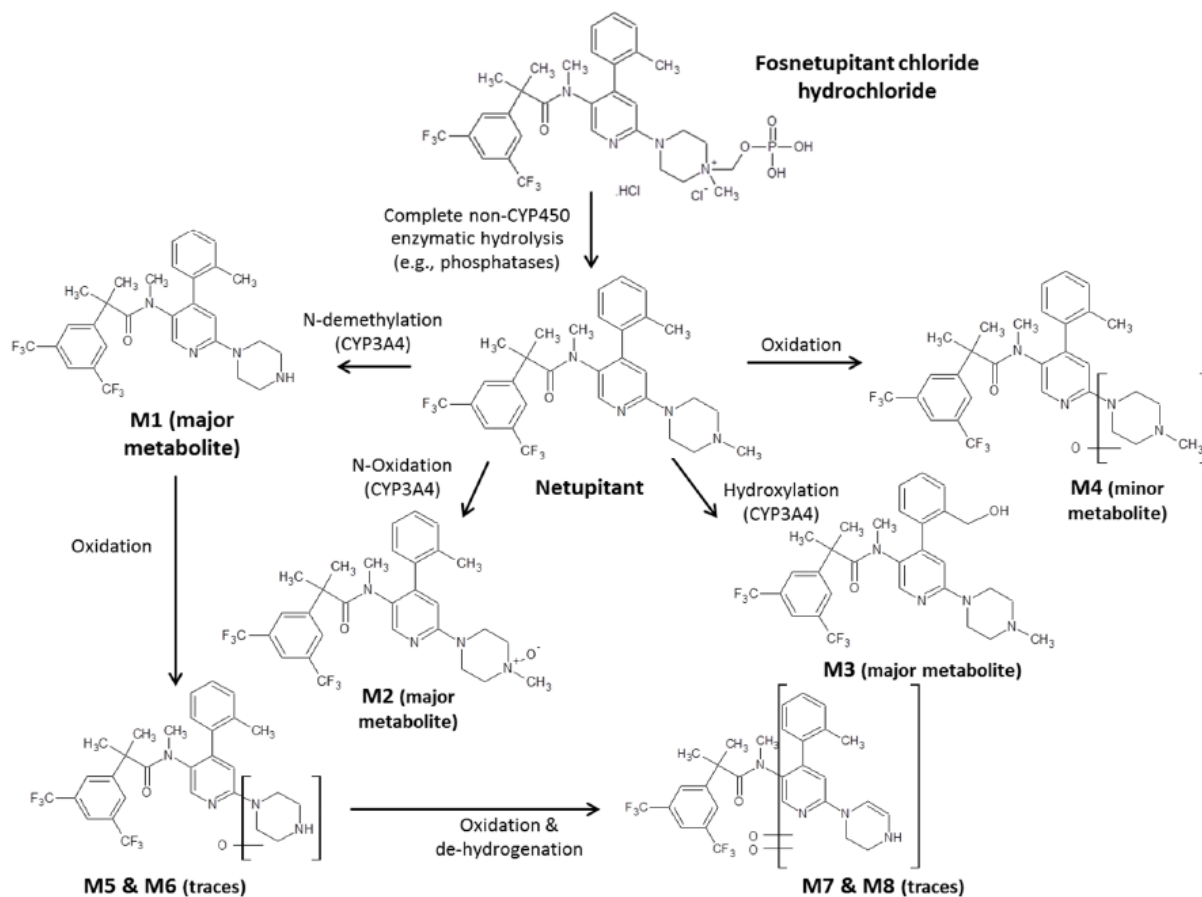
[In vitro and in silico evaluation](#)

Fosnetupitant metabolism

Fosnetupitant is hydrolyzed to netupitant by non-CYP450 enzymes. Therefore, it is unlikely to be affected by CYP450 inhibitors and inducers.

The proposed metabolism pathway is shown in Figure 1. The metabolism pathway of netupitant is reviewed in the original NDA 205718 for Akynzeo oral capsules.

Figure 1. Proposed metabolic Pathway of fosnetupitant in humans



Source data: Section 2.7.2 Summary of Clinical Pharmacology, Figure 22

Fosnetupitant is a substrate for both OATP1B1 and OATP1B3 uptake transporters. However, because fosnetupitant is quickly hydrolyzed to netupitant following the single dose administration, the effect of OATP1B1 and OATP1B3 inhibitors upon systemic exposures to fosnetupitant will be small.

Fosnetupitant as a CYP450 inhibitor

In the range of concentrations tested (0.3-1000 μM), fosnetupitant showed inhibition towards CYP2C9 ($\text{IC}_{50} = 27.9 \mu\text{M}$), CYP2C19 ($\text{IC}_{50} = 46.1 \mu\text{M}$), CYP2C8 ($\text{IC}_{50} = 56.7 \mu\text{M}$), CYP2B6 ($\text{IC}_{50} = 106.8 \mu\text{M}$), CYP1A2 ($\text{IC}_{50} = 208.4 \mu\text{M}$), CYP2D6 ($\text{IC}_{50} = 217.2 \mu\text{M}$) and CYP3A4 ($\text{IC}_{50} = 196.8 \mu\text{M}$ and $299.2 \mu\text{M}$ with midazolam and testosterone substrates, respectively). The in vitro study was conducted using human liver microsomes.

Time-dependent inhibition (TDI)

In the concentration range from 0.3 to 300 μM with up to 30 minutes of pre-incubation time, fosnetupitant did not show TDI potential towards CYP3A4 and CYP2C9.

At the concentration of 1000 μM , fosnetupitant showed a significant TDI effect, with an activity loss of 63% for CYP3A4 and 98% for CYP2C9. The concentration of 1000 μM is about 100-fold the C_{max} (9.2 μM) following 260 mg single IV dose.

In silico evaluation of in vivo inhibition potential of CYP2C9 and CYP2C19 enzymes

The PBPK modeling approach suggested no significant effects of fosnetupitant on the systemic exposure to S-warfarin (CYP2C9 substrate) as well as omeprazole (CYP2C19 substrate) at the recommended dose level (260 mg IV infusion for 30 min). Refer to Section 4.3 “Review of Physiologically Based Pharmacokinetic Modeling (PBPK): PNET-16-29”.

No significant in vivo inhibition of other CYP450 enzymes is expected because no significant in vivo inhibition potential of CYP2C9 and CYP2C19 is expected. Fosnetupitant has the lowest IC_{50} values towards CYP2C9 and CYP2C19.

Fosnetupitant as a transporter inhibitor

Vesicular transporters

Fosnetupitant is an inhibitor of the MDR1-mediated NMQ transport in vesicular assay with a maximum inhibition of 47 % at 50 μM .

Fosnetupitant did **not** inhibit the BSEP-mediated taurocholate and BCRP-mediated E3S accumulation in vesicular transport inhibition assays up to 20 and 50 μM , respectively.

Hepatic uptake transporters

Fosnetupitant is an inhibitor of the OATP1B1-mediated E217 β G transport (IC_{50} : 19.01 μM) and the OATP1B3-mediated CCK-8 transport (IC_{50} : 17.37 μM).

Renal uptake transporters

Fosnetupitant is an inhibitor of the MATE1-mediated metformin transport (IC_{50} : 29.48 μM).

Fosnetupitant is an inhibitor of OCT1-mediated metformin transport, with a maximum inhibition of 44 % at 300 μM .

Fosnetupitant did **not** inhibit the OAT1-mediated tenofovir transport, the OAT3-mediated methotrexate transport and the OCT2-mediated metformin transport up to 300 μM .

In silico evaluation of in vivo inhibition potential of transporters

For OATP1B1 and OATP1B3 inhibition potential estimation, the calculated R values were slightly below the cutoff value of 1.1¹.

The DDI potential between fosnetupitant and P-gp substrates in the GI tract is minimal because fosnetupitant is administered intravenously and eliminated quickly from the systemic circulation. The ratio of the estimated $[I_{u,in,max}]$ and reported IC_{50} for P-gp was less than 0.1, where $I_{u,in,max}$ is the estimated maximum unbound concentration of fosnetupitant at the inlet to the liver, suggesting no DDI potential between fosnetupitant and P-gp substrates in the liver.

4. APPENDICES

4.1. Summary of Bioanalytical Method Validation and Performance

The analytical methods for plasma netupitant and its major metabolites M1, M2, and M3 were the same as those used to support oral Akynzeo approval. These methods were deemed to be acceptable. Refer to the Clinical Pharmacology Review of NDA 205718 for oral Akynzeo.

Fosnetupitant was measured by a validated liquid chromatographic-tandem mass spectrometric method (LC/MS/MS).

The summary of the analytical methods of fosnetupitant, netupitant, M1, M2, and M3 is shown below. All the parameters were within the specifications according to the FDA Guidance for Industry Bioanalytical Method Validation (Draft Guidance 2013).

¹ Draft guidance for industry (2017) In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>

Table 8. Summary of Bioanalytical Methods for plasma fosnetupitant, netupitant and its metabolites

Method	Lower Limit of Quantification (LLOQ)	Study No.	Bioanalytical Study Report	Method Validation
LC/MS/MS (b) (4)	Fosnetupitant: LLOQ 2 ng/mL	PNET-12-23	(b) (4) study No. 038/12-032.NT (b) (4)	(b) (4) study No. 047/12 05.NT (b) (4)
		PNET-13-63	(b) (4) study No. 230/13-03.NT-Part 2 (b) (4)	
	Netupitant: LLOQ 2 ng/mL M1: LLOQ 2 ng/mL M2: LLOQ 2 ng/mL M3: LLOQ 2 ng/mL	PNET-12-23	(b) (4) study No. 038/12-032.NT. (b) (4)	Netupitant, M1, M3: (b) (4) study No. 047/11-052.NP (b) (4) M2: (b) (4) study No. 244/11-05.NT (b) (4) (ref. to NDA 205718)
		PNET-13-63	(b) (4) study No. 230/13-03.NT-Part 2 (b) (4)	Netupitant, M1, M2, M3: (b) (4) study No. 047/11-052/NP (b) (4) with partial revalidation in (b) (4) study No. 230/13-03.NT-Part 1 (b) (4)
LC/MS/MS (b) (4)	Fosnetupitant: LLOQ 2 ng/mL	NEPA-15-19	(b) (4) study No. 15151 (b) (4)	(b) (4) study No. 15150 (b) (4)
	Netupitant: LLOQ 2 ng/mL M1: LLOQ 2 ng/mL M2: LLOQ 2 ng/mL M3: LLOQ 2 ng/mL		(b) (4) study No. 15152 (b) (4)	(b) (4) study No. 15056 (b) (4)

^a Assay performed at (b) (4)

^b Assay performed at (b) (4)

^c Complete validation tests are reported in (b) (4) report No. 15150 - (b) (4) (fosnetupitant) and No. 15056 - (b) (4) (netupitant and metabolites), including long-term stability data up to 6 months. Long-term stability study of analytes in human plasma samples at -18°C and -70°C, part of the validation and documented up to 1+ year storage as of December 2016, is ongoing and will be fully complete after 2.5 year storage.

Summary of the bioanalytical validation method (047/12 05.NT) performance for fosnetupitant is shown below. As shown in Table 8, this method was used to measure samples from the pivotal BA/BE study PNET-12-23 and in vivo drug-drug interaction study PNET-13-63.

Table 9. Summary of validation parameters for plasma fosnetupitant (validation report 047/12 05.NT) for Studies PNET-12-23 and PNET-13-63

Bioanalytical matrix:	Human K₃-EDTA plasma
Analyte/s:	Pro-netupitant
Internal standard:	(b) (4)
Short description of the method:	Internally standardized LC-MS/MS
Calibration range [ng/mL]:	2.000 – 1000.000
LLOQ [ng/mL]:	2.000
Between-run Accuracy / Precision at LLOQ [%]:	0.6 / 7.8 (API 4000)
QC concentrations [ng/mL]:	2.000 (LLOQ), 6.000, 200.000, 800.000, 1000.000 (ULOQ)
QC Between-run accuracy [%]:	-4.6 – 0.6 (API 4000)
QC Between-run precision [%]:	3.1 – 7.8 (API 4000)
QC Within-run accuracy [%]:	-8.4 – 8.5 (API 4000) -1.7 – 11.3 (API 5000)
QC Within-run precision [%]:	0.8 – 9.9 (API 4000) 5.1 – 13.2 (API 5000)
Selectivity:	Proven
Carry-over [% of LLOQ]:	194% (1 st blank sample, API 4000) 18% (4 th blank sample, API 4000) 348% (1 st blank sample, API 5000) 21% (5 th blank sample, API 5000) API 5000 was not used for routine analysis
Influence of concomitant analytes:	No effect

Stability of pro-netupitant in human plasma at 4°C and room temperature at the concentration of 800 ng/mL:	Stable for up to 24 h. No netupitant formed by pro-netupitant hydrolysis.
Stability of pro-netupitant in human plasma at 4°C and room temperature at the concentration of 5000 ng/mL:	Stable for up to 24 h. No netupitant formed by pro-netupitant hydrolysis.
Stability of pro-netupitant in human whole blood at 4°C and room temperature at the concentration of 800 ng/mL:	Stable for up to 4 h. No netupitant formed by pro-netupitant hydrolysis.
Recovery (analyte) [mean, %]:	100.1
Recovery (internal standard) [%]:	85.2
Matrix factor (CV, %) of low QC:	1.0 (12.2)
Matrix factor (CV, %) of high QC:	1.0 (11.9)
Hemolytic plasma:	No effect
Hyperlipidemic plasma:	No effect
Length of run assessment (maximal plasma sample number per sequence):	88
Dilution integrity:	No effect (dilution factor 10 and 15)
Bench-top stability of pro-netupitant in plasma at room temperature and influence of light (polypropylene vials):	Stable for at least 24 h
Freeze/thaw stability of pro-netupitant in plasma during 3 cycles (approx. -70°C to ambient temperature):	Stable
Freeze/thaw stability of pro-netupitant in plasma during 3 cycles (approx. -70°C to approx. 4°C):	Stable

Autosampler stability of pro-netupitant in plasma extract at approx. 4°C:	Stable for at least 182 h
Work-up stability of pro-netupitant in plasma at approx. 4°C:	Stable for at least 24 h
Long-term stability of pro-netupitant in plasma in polypropylene vials at approx. -20°C:	Stable for at least 182 days
Long-term stability of pro-netupitant in plasma in polypropylene vials at approx. -70°C:	Stable for at least 297 days
Stability of pro-netupitant in water/acetonitrile (1:1 v/v) at ambient temperature (polypropylene vials):	Stable for at least 6 h
Stability of pro-netupitant in water/acetonitrile (1:1 v/v) at approx. 4°C (polypropylene vials):	Stable for at least 224 days
Stability of repaglinide in acetonitrile at approx. 4°C (polypropylene vials):	Stable for at least 640 days

Carryover of pro-netupitant was observed for blank samples injected after the ULOQ sample for both detectors (API4000 and API5000). On the API5000 system the acceptance criteria for carry over were slightly exceeded, but since the API5000 system was not used for routine analysis, this was not investigated any further. It was concluded that for sample measurement, five blank samples need to be injected after a high concentrated sample and that study samples need to be sorted in an ascending order of pro-netupitant concentration.

No carryover was observed for the internal standard (IS) on both devices.

Table 10. Summary of validation parameters for plasma fosnetupitant (validation report (b) (4) 15150) for Study NEPA-15-19

Analyte	Pro-netupitant
Internal Standard	Pro-netupitant-d6
Calibration range	2.00 - 1000 ng/mL
Regression type	Linear, weighted (1/x ²)
Blank matrix evaluation	No significant interferences from endogenous compounds observed in six individual blank matrices
Matrix Effect	Normalized matrix factors: 6.9 % at level of 6.00 ng/mL 1.8% at level of 800 ng/mL
Hemolysed Plasma Effect Testing	No effect
Lipemic Plasma Effect Testing	No effect
Mutual interference between pro-netupitant and pro-netupitant-d6	No significant interferences observed between pro-netupitant and pro-netupitant-d6
Interference from coadministered drugs and metabolites	No significant interference from palonosetron (2000 pg/mL), M9 (500 pg/mL), netupitant (1000 ng/mL), M1 (500 ng/mL), M2 (500 ng/mL), M3 (500 ng/mL) and dexamethasone (500 ng/mL)
Carryover Evaluation	No carryover observed
Within-run Precision (%CV) and Accuracy (%Bias)	QC-LLOQ: %CV 2.0 and %Bias 11.8 QC-Low: %CV 3.5 and %Bias 7.6 QC-Medium: %CV 3.5 and %Bias 8.1 QC-High: %CV 2.4 and %Bias 7.2
Between-run Precision (%CV) and Accuracy (%Bias)	QC-LLOQ: %CV 2.7 and %Bias 10.2 QC-Low: %CV 4.4 and %Bias 6.3 QC-Medium: %CV 3.8 and %Bias 6.4 QC-High: %CV 3.3 and %Bias 5.5
Recovery in the concentration range from 6.00 ng/mL to 800 ng/mL for pro-netupitant and at the assay concentration for pro-netupitant-d6	Between 90.8% and 95.9% for pro-netupitant Between 92.3% and 95.9% for pro-netupitant-d6
Bench-top Stability	At least 18 hours at room temperature
Re-injection Stability	At least 53 hours at 2-8°C
Post-preparative Stability	At least 61 hours at 2-8°C
Freeze/thaw Stability	At least three additional F/T cycles after the first sample thawing
Stock Solution Stability	At least 195 days at ≤ -18°C
Spike Solution Stability	At least 70 days at 2-8°C
Whole Blood Stability	At least 1 hour at room temperature and at least 1 hour on melting ice
Long-term Frozen Sample Storage Stability	At least 187 days at ≤ -18°C At least 187 days at ≤ -70°C
Dilution Integrity	Up to 8000 ng/mL using a 10-fold dilution
Batch Size Determination	Up to (b) (4) injections

A summary of the in-study report of the pivotal BA/BE study (PNET-12-23) is shown below. This summary also applied to Study PNET-13-63.

Bioanalytical matrix:	Human K ₃ -EDTA plasma
Analyte:	Pro-netupitant
Internal standard:	(b) (4)
Short description of the method:	Internally standardized LC–MS/MS
Calibration range [ng/mL]:	2.000 through 1000.000
QC concentrations [ng/mL]:	6.000, 60.000, 100.000, 400.000, 800.000
QC Between-run accuracy [%]:	0.0 through 4.0
QC Between-run precision [%]:	7.9 through 14.8
Between-run accuracy of diluted QC samples (dilution factors 2, 2.5, 4, 5, 8, 10, 12, 15) [%]:	-4.1 through 6.8
Between-run precision of diluted QC samples (dilution factors 2, 2.5, 4, 5, 8, 10, 12, 15) [%]:	2.7 through 9.4
Received samples:	5646 (1 st aliquot) 5646 (backup)
Analyzed samples:	5646
Samples with valid results:	5646
Re-analyzed samples:	233
ISR samples:	246
ISR success rate [%]:	89
Analytical sequences:	250
Valid analytical sequences:	178

Bioanalytical matrix:	Human K ₃ -EDTA plasma
Analyte:	Netupitant
Internal standard:	Netupitant-D ₆
Short description of the method:	Internally standardized LC-MS/MS
Calibration range [ng/mL]:	2.000 through 500.000
QC concentrations [ng/mL]:	6.000, 60.000, 160.000, 280.000, 380.000
QC Between-run accuracy [%]:	3.9 through 8.3
QC Between-run precision [%]:	5.6 through 13.6
Between-run accuracy of diluted QC samples (dilution factors 2 and 4) [%]:	5.0 through 5.8
Between-run precision of diluted QC samples (dilution factors 2, 4) [%]:	5.5 through 11.4
Received samples:	5646 (1 st aliquot) 5646 (backup)
Analyzed samples:	5646
Samples with valid results:	5645
Re-analyzed samples:	586
Analytical sequences:	225
Valid analytical sequences:	186
Autosampler stability of sample extract at approximately 4°C/ Reinjection stability:	Stable for at least 192 h

Bioanalytical matrix:	Human K ₃ -EDTA plasma
Analyte:	M1
Internal standard:	(b) (4)
Short description of the method:	Internally standardized LC-MS/MS
Calibration range [ng/mL]:	2.000 through 500.000
QC concentrations [ng/mL]:	6.000, 60.000, 160.000, 280.000, 380.000
QC Between-run accuracy [%]:	-0.9 through 2.8
QC Between-run precision [%]:	4.2 through 6.5
Received samples:	5646 (1 st aliquot) 5646 (backup)
Analyzed samples:	5646
Samples with valid results:	5644
Re-analyzed samples:	107
Analytical sequences:	196
Valid analytical sequences:	180
Autosampler stability of sample extract at approximately 4°C:	Stable for at least 288 h
Reinjection stability at approximately 4°C:	Stable for at least 144 h

Bioanalytical matrix:	Human K ₃ -EDTA plasma
Analyte:	M2
Internal standard:	(b) (4)
Short description of the method:	Internally standardized LC–MS/MS
Calibration range [ng/mL]:	2.000 through 500.000
QC concentrations [ng/mL]:	6.000, 60.000, 160.000, 280.000, 380.000
QC Between-run accuracy [%]:	-1.3 through 4.3
QC Between-run precision [%]:	7.9 through 10.4
Between-run accuracy of diluted QC samples (dilution factors 2 and 4) [%]:	-1.5 through 0.5
Between-run precision of diluted QC samples (dilution factors 2, 4) [%]:	5.7 through 7.9
Received samples:	5646 (1 st aliquot) 5646 (backup)
Analyzed samples:	5646
Samples with valid results:	5636
Re-analyzed samples:	98
Analytical sequences:	261
Valid analytical sequences:	181
Autosampler stability of sample extract at approximately 4°C/ Reinjection stability:	Stable for at least 196 h

Bioanalytical matrix:	Human K ₃ -EDTA plasma
Analyte:	M3
Internal standard:	(b) (4)
Short description of the method:	Internally standardized LC-MS/MS
Calibration range [ng/mL]:	2.000 through 500.000
QC concentrations [ng/mL]:	6.000, 60.000, 160.000, 280.000, 380.000
QC Between-run accuracy [%]:	-1.5 through 2.3
QC Between-run precision [%]:	3.7 through 7.1
Received samples:	5646 (1 st aliquot) 5646 (backup)
Analyzed samples:	5646
Samples with valid results:	5646
Re-analyzed samples:	88
Analytical sequences:	193
Valid analytical sequences:	179
Autosampler stability of sample extract at approximately 4°C:	Stable for at least 288 h
Reinjection stability at approximately 4°C:	Stable for at least 144 h

Palonosetron

The LC-MS/MS bioanalytical method for measurement of palonosetron in human plasma was developed during the IV palonosetron program at (b) (4) and was based on previously validated methods for palonosetron during clinical development. The method was validated by (b) (4)

The summary of the analytical methods of palonosetron and metabolite M9 is shown below.

Table 11. Summary of Bioanalytical Methods for plasma palonosetron and metabolite M9

Method	Sensitivity of Method	Study No.	Bioanalytical Study Report	Validation Method
LC/MS/MS (b) (4)	Palonosetron LLOQ 50 pg/mL M9: LLOQ 50 pg/mL	NEPA-15-19	(b) (4) study No. 15153 (b) (4)	(b) (4) study No. 15059 (b) (4)

^a Assay performed at (b) (4)

^b Complete validation tests for palonosetron and metabolite M9 are reported in (b) (4) report No. 15059 – (b) (4) including long-term stability data up to 6 months. Long-term stability study of palonosetron and M9 in human plasma samples at -18°C and -70°C, part of the validation and documented up to 1+ year storage as of December 2016, is ongoing and will be fully complete after 2.5 year storage.

Table 12. Summary of validation parameters for palonosetron in plasma (validation report (b) (4) 15059) for Study NEPA-15-19

Analyte	palonosetron	M9
Internal Standard	Palonosetron-D3	Palonosetron-D3
Calibration range	50.0 - 2000 pg/mL	50.0 – 500 pg/mL
Regression type	Linear, weighted (1/x ²)	Linear, weighted (1/x ²)
Blank matrix evaluation	No significant interferences from endogenous compounds observed in six individual blank matrices	No significant interferences from endogenous compounds observed in six individual blank matrices
Matrix Effect	Normalized matrix factors: 5.0% at level of 150 pg/mL 2.1% at level of 1600 pg/mL	Normalized matrix factors: 3.3% at level of 150 pg/mL 5.2% at level of 400 pg/mL
Hemolysed Plasma Effect Testing	No effect	No effect
Lipemic Plasma Effect Testing	No effect	No effect
Mutual interference between palonosetron and M9 vs palonosetron-D3	No significant interferences observed between palonosetron and palonosetron-D3	No significant interferences observed between M9 and palonosetron-D3
Carryover Evaluation	No significant carryover observed	No significant carryover observed
Within-run Precision (%CV) and Accuracy (%Bias)	QC-LLOQ: %CV 5.3 and %Bias 6.0 QC-Low: %CV 5.0 % and Bias 5.6 QC-Medium: %CV 2.7 and %Bias 11.2 QC-High: %CV 1.9 and %Bias 10.4	QC-LLOQ: %CV 9.0 and %Bias -0.3 QC-Low: %CV 5.9 % and Bias 5.9 QC-Medium: %CV 6.5 and %Bias 4.0 QC-High: %CV 3.4 and %Bias 2.0
Between-run Precision (%CV) and Accuracy (%Bias)	QC-LLOQ: %CV 5.4 and %Bias 8.0 QC-Low: %CV 3.8 and %Bias 5.3 QC-Medium: %CV 2.1 and %Bias 11.7 QC-High: %CV 2.1 and %Bias 10.2	QC-LLOQ: %CV 9.3 and %Bias 0.8 QC-Low: %CV 7.3 and %Bias 3.1 QC-Medium: %CV 4.8 and %Bias 3.6 QC-High: %CV 3.2 and %Bias 3.8
Recovery	In the concentration range from 50.0 ng/mL to 2000 ng/mL (palonosetron) and at the assay concentration for palonosetron-D3 Between 86.8% and 91.5% for palonosetron Between 79.8% and 81.3% for palonosetron-D3	In the concentration range from 50.0 ng/mL to 500 ng/mL (M9) and at the assay concentration for palonosetron-D3 Between 80.0% and 84.6% for M9 Between 79.8% and 81.3% for palonosetron-D3
Bench-top Stability	At least 24 hours at room temperature	At least 24 hours at room temperature
Re-injection Stability	At least 57 hours	At least 57 hours
Processed sample stability	At least 55 hours	At least 55 hours
Freeze/thaw Stability	At least three additional F/T cycles after the first sample thawing	At least three additional F/T cycles after the first sample thawing
Stock Solution Stability	At least 169 days at ≤ -18°C	At least 169 days at ≤ -18°C
Spike Solution Stability	At least 134 days at 2-8°C	At least 134 days at 2-8°C
Whole Blood Stability	At least 1 hour at room temperature and at least 1 hour on melting ice	At least 1 hour at room temperature and at least 1 hour on melting ice
Long-term Frozen Sample Storage Stability	At least 174 days at ≤ -70°C At least 174 days at ≤ -18°C	At least 174 days at ≤ -70°C At least 174 days at ≤ -18°C
Dilution Integrity	5-fold	5-fold
Batch Size Determination	Up to (b) (4) injections	Up to (b) (4) injections

Long term stability (LTS) has been investigated up to approximately 6 months storage at $\leq -18^{\circ}\text{C}$ and $\leq -70^{\circ}\text{C}$. The stability assessment of all analytes is still ongoing and it will be accomplished on frozen plasma samples stored up to 2 years. The final report, including additional stability data at the planned time points, will be issued at the end of the LTS test period.

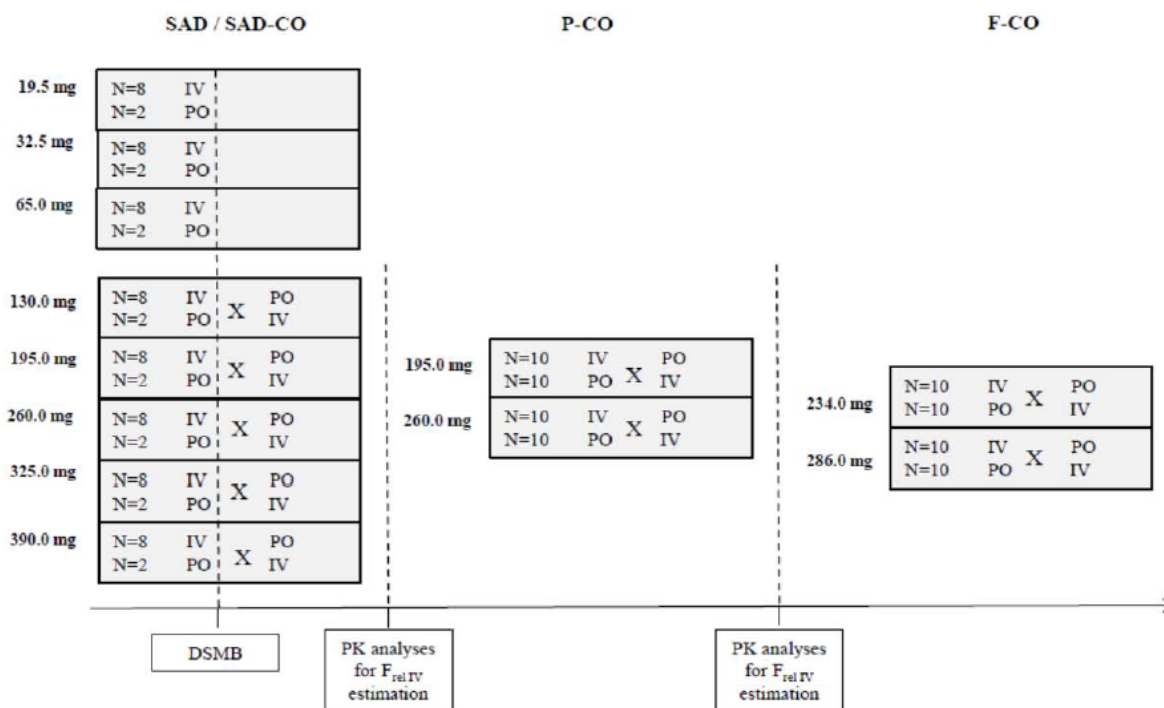
4.2. Review of Individual Studies

4.2.1. Pivotal BA/BE Study: PNET-12-23

Title: A Phase I, double-blind, controlled, parallel groups, unbalanced single ascending dose study to assess the safety of intravenously administered pro-netupitant combined with crossover study extensions to estimate the dose of intravenous pro-netupitant yielding equivalent drug exposure as oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination in healthy male and female volunteers.

Study Design: This is a randomized, single-dose, single-center, parallel group single ascending dose (SAD) part with a crossover extension (SAD-CO), a pilot crossover part (P-CO), and a final crossover part (F-CO) study (Figure 2). Single ascending dose administration on Day 1 of each period separated by a washout phase of at least 4 weeks. Crossover administrations in the same subject were separated by a washout phase of at least 4 weeks.

Figure 2. Schematic drawing of the study design



DSMB: Drug Safety Monitoring Board, F-CO: final crossover, IV: intravenous, N: number of subjects, P-CO: pilot crossover, PK: pharmacokinetics, PO: per os, SAD: single ascending dose, SAD-CO: single ascending dose crossover

Source data: Study PNET-12-3 CSR In-text Figure 9.1-1

Product information

Test product, dose and mode of administration, batch no.:

Fosnetupitant lyophilized powder

Dose: 19.5 mg, 32.5 mg, 65.0 mg, 130.0 mg, 195.0 mg, 260.0 mg, 325.0 mg, and 390.0 mg (SAD/SAD-CO part)

195.0 mg and 260.0 mg (P-CO part)

234.0 mg and 286.0 mg (F-CO part)

Mode of administration: intravenous infusion

Batch Nos.: 114921, 105679

Reference product, dose and mode of administration, batch no.:

Netupitant/palonosetron FDC capsules

Dose: 300 mg netupitant, 0.5 mg palonosetron (all study parts)

Mode of administration: oral

Batch No.: 105680

Placebo products, dose and mode of administration, batch no.:

Placebo solution (5% glucose solution)

Dose: not applicable

Mode of administration: intravenous infusion

Batch number: 14FH7104, 14FI7119, 14FG7105, 14GK7105

Placebo capsules

Dose: not applicable

Mode of administration: oral

Batch No.: 105680

PK sampling

Blood samples for fosnetupitant, netupitant and its metabolites (M1, M2, and M3) PK analysis were taken before start of infusion (predose) and at t_{mid} (15 min after start of infusion), t_{end} (30 min after start of infusion), and 40 min, 50 min, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 and 120 hours after the start of infusion after start of infusion.

Blood samples for netupitant and its metabolites (M1, M2, and M3) PK analysis were taken at predose, 15 min, 30 min, 40 min, 50 min, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 and 120 hours after oral dosing of Akynzeo capsule (reference product).

Pharmacokinetic Results

Demographics

Parameter		Overall IV N=147	Overall Oral N=129	Total N=153
Age [years]	n (available)	147	129	153
	n (missing)	0	0	0
	Mean	32.5	32.2	32.5
	SD	7.69	7.77	7.68
	CV	23.64	24.09	23.61
	Median	33.0	32.0	33.0
	Minimum	18	18	18
	Maximum	45	45	45
Height [cm]	n (available)	147	129	153
	n (missing)	0	0	0
	Mean	174.1	174.8	174.3
	SD	9.22	9.47	9.25
	CV	5.30	5.42	5.31
	Median	175.0	176.0	175.0
	Minimum	152	152	152
	Maximum	198	198	198
Weight [kg]	n (available)	147	129	153
	n (missing)	0	0	0
	Mean	74.80	75.98	75.07
	SD	12.275	12.667	12.469
	CV	16.410	16.671	16.610
	Median	76.80	78.50	77.50
	Minimum	50.3	50.3	50.3
	Maximum	113.2	113.2	113.2
BMI [kg/m ²]	n (available)	147	129	153
	n (missing)	0	0	0
	Mean	24.53	24.73	24.58
	SD	2.586	2.637	2.607
	CV	10.542	10.664	10.604
	Median	24.70	25.20	24.80
	Minimum	18.8	19.3	18.8
	Maximum	29.4 [#]	29.4 [#]	29.4 [#]
#: Acceptance window for upper limit of BMI: 29.0 to 29.4 kg/m² BMI: body mass index, CV: coefficient of variation, N: number of subjects in specified group, n (available): number of subjects with data available, n (missing): number of subjects with missing data, SD: standard deviation, PK-R: restricted pharmacokinetic data IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and placebo capsule Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) and placebo infusion Source: Table 14.1.2.1.2, Table 14.1.2.1.4				

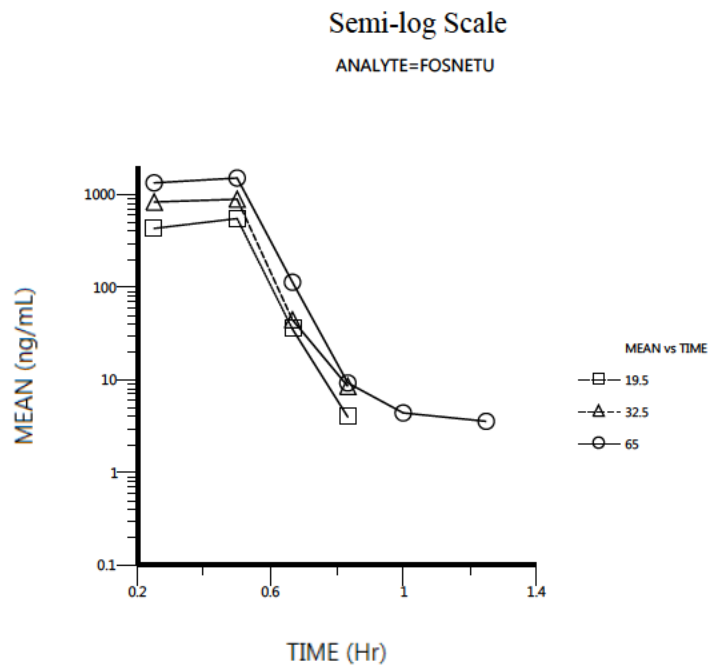
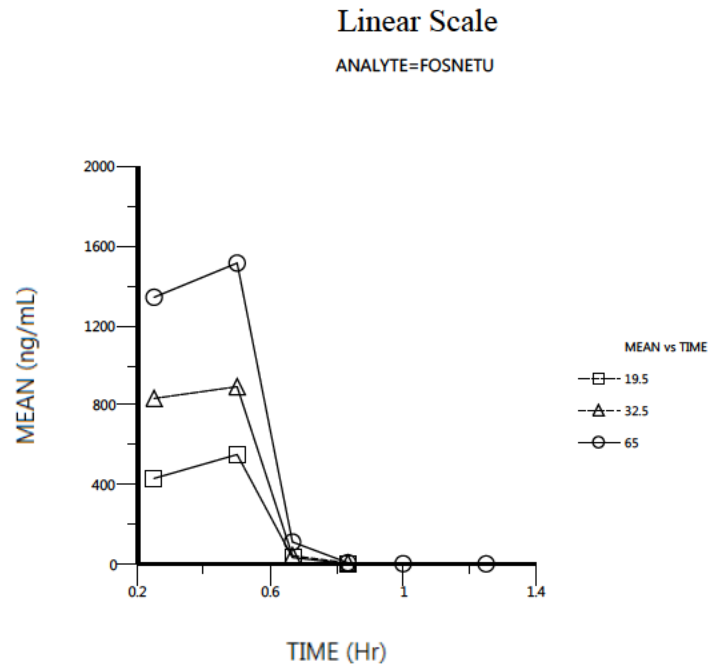
Source data: Study PNET-12-23 CSR, In-text Table 10.5-2

Over 90% of the subjects in the study are white. There were less than 10 subjects for each of following ethnic groups: Black, Asian, and Hispanic. Male subjects were ~50% more than the female subjects.

Summary of PK Parameters - Fosnetupitant

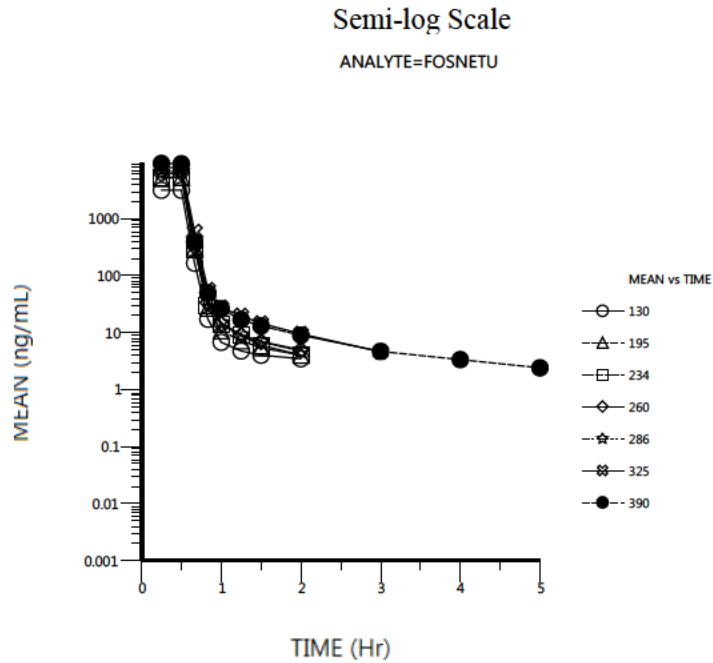
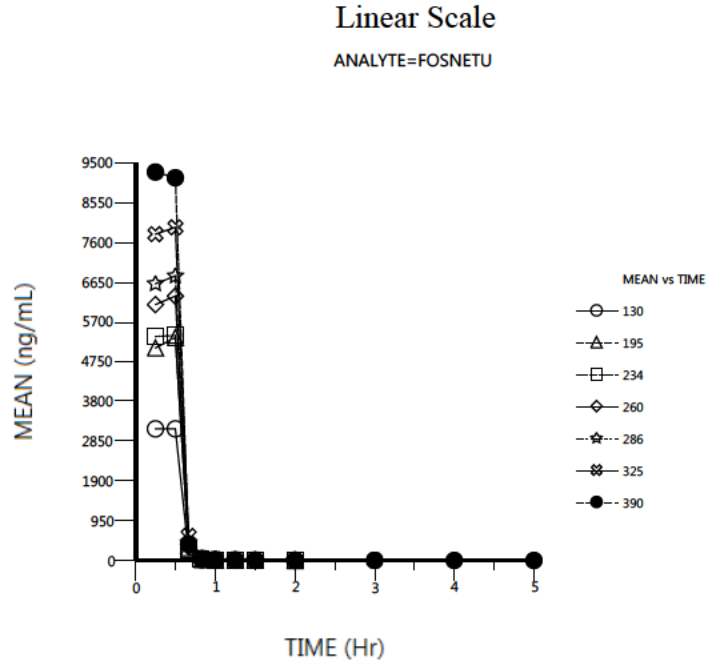
The mean concentration-time profiles of fosnetupitant are shown below. As across all the dose groups, fosnetupitant concentrations were below LLOQ at Hour 24, only first 24 hours concentration-time profiles were shown.

Figure 3. Mean Fosnetupitant Plasma Concentration-Time Profile: 19.5, 32.5, and 65 mg IV Single Dose Group



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28

Figure 4. Mean Fosnetupitant Plasma Concentration-Time Profile: 130, 195, 234, 260, 286, 325, 390 mg IV Single Dose Group



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28
For 195 mg and 260 mg dose groups, data were pooled from both SAD period and P-CO period

Descriptive summary of fosnetupitant PK parameters is shown below.

Table 13. Systemic exposures (AUC and Cmax) of fosnetupitant following single IV doses

Parameter	Statistics	19.5 mg N=8	32.5 mg N=8	65 mg N=8	130 mg N=10	S-195 mg N=10	P-195 mg N=18	S+P-195 mg N=28	F-234 mg N=19	S-260 mg N=10	P-260 mg N=20	S+P-260 mg N=30	F-286 mg N=18	325 mg N=9	390 mg N=9
AUC _{0-24h} [h·µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	222.0	403.3	676.2	1483	2317	2502	2436	2530	2922	2939	2934	3145	3794	4349
	SD	49.48	46.07	50.67	219.6	411.6	532.7	493.2	485.0	328.6	386.1	362.3	590.3	449.8	437.6
	CV [%]	22.29	11.42	7.494	14.81	17.76	21.30	20.25	19.16	11.25	13.13	12.35	18.77	11.86	10.06
	Geo. mean	216.7	401.2	674.6	1469	2284	2454	2392	2483	2905	2912	2910	3097	3769	4329
	Geo. SD	1.277	1.115	1.075	1.152	1.196	1.217	1.209	1.229	1.121	1.156	1.143	1.196	1.132	1.106
	Minimum	132.3	358.0	613.8	1248	1690	1865	1690	1579	2363	1853	1853	2350	3072	3624
Median	215.2	388.4	665.1	1409	2256	2341	2287	2554	2917	2991	2966	2937	3849	4286	
Maximum	285.9	497.7	782.9	1922	3094	3925	3925	3325	3402	3455	3455	3455	4313	4322	5101
AUC _{0-24h} [h·µg/L]	n	0	3	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	N.C.	415.5	677.9	1486	2320	2505	2439	2533	2927	2943	2938	3149	3797	4353
	SD	N.C.	22.10	50.31	220.6	412.1	532.6	493.4	485.0	327.8	386.2	362.1	591.1	449.2	437.2
	CV [%]	N.C.	5.319	7.422	14.85	17.76	21.26	20.23	19.14	11.20	13.12	12.33	18.77	11.83	10.04
	Geo. mean	N.C.	415.1	676.3	1472	2287	2458	2396	2486	2910	2916	2914	3100	3772	4334
	Geo. SD	N.C.	1.055	1.075	1.152	1.196	1.217	1.209	1.229	1.121	1.156	1.143	1.196	1.132	1.106
	Minimum	N.C.	394.2	614.1	1251	1692	1870	1692	1580	2366	1855	1855	2351	3077	3629
Median	N.C.	413.9	666.1	1411	2259	2344	2290	2556	2921	3000	2974	2940	3854	4288	
Maximum	N.C.	438.3	783.5	1926	3098	3927	3927	3326	3408	3459	3459	3459	4318	4324	5105
C _{max} [µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	565.0	918.9	1520	3297	5407	5515	5476	5571	6464	6414	6431	6929	8282	9562
	SD	138.3	136.8	109.0	479.2	1780	1207	1406	1131	842.0	964.8	911.3	1305	970.8	1007
	CV [%]	24.48	14.89	7.175	14.53	32.92	21.89	25.67	20.31	13.03	15.04	14.17	18.84	11.72	10.53
	Geo. mean	551.2	911.0	1516	3267	5207	5407	5335	5451	6414	6338	6363	6820	8229	9515
	Geo. SD	1.264	1.146	1.075	1.149	1.313	1.220	1.250	1.247	1.141	1.177	1.163	1.198	1.129	1.112
	Minimum	416.7	789.6	1379	2725	3824	4212	3824	3307	5109	4060	4060	5000	6571	7901
Median	557.1	890.3	1557	3101	4978	5142	5076	5666	6417	6366	6366	6567	8434	9475	
Maximum	832.4	1232	1673	4273	10115	8577	10115	7318	7607	7663	7663	9858	9650	10985	

Source data: Study PNET-12-23 CSR, In-text Table 11.1-4

Table 14. Additional PK parameters (CL, t_{1/2}, T_{max}, V_d) of fosnetupitant following single IV doses

Parameter	Statistics	19.5 mg N=8	32.5 mg N=8	65 mg N=8	130 mg N=10	S-195 mg N=10	P-195 mg N=18	S+P-195 mg N=28	F-234 mg N=19	S-260 mg N=10	P-260 mg N=20	S+P-260 mg N=30	F-286 mg N=18	325 mg N=9	390 mg N=9
CL [L/h]	n	0	3	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	N.C.	78.37	96.33	89.11	86.50	80.71	82.78	96.15	89.87	90.13	90.05	93.62	86.75	90.39
	SD	N.C.	4.151	6.726	12.04	15.67	14.69	15.02	21.57	10.42	14.74	13.27	15.96	11.17	9.086
	CV [%]	N.C.	5.297	6.982	13.52	18.12	18.20	18.15	22.43	11.59	16.35	14.73	17.05	12.88	10.05
	Geo. mean	N.C.	78.30	96.11	88.33	85.25	79.33	81.40	94.14	89.35	89.16	89.22	92.26	86.15	89.99
	Geo. SD	N.C.	1.055	1.075	1.152	1.196	1.217	1.209	1.229	1.121	1.156	1.143	1.196	1.132	1.106
	Minimum	N.C.	74.15	82.96	67.50	62.95	49.66	49.66	70.36	76.30	75.17	75.17	66.23	75.16	76.39
	Maximum	N.C.	82.45	105.8	103.9	115.2	104.3	115.2	148.1	109.9	140.1	140.1	121.6	105.6	107.5
t _{1/2} [h]	n	0	3	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	N.C.	0.0458	0.416	0.703	0.676	0.857	0.792	0.781	1.222	0.823	0.956	0.757	0.873	1.235
	SD	N.C.	0.0094	0.379	0.354	0.225	0.430	0.376	0.426	0.777	0.353	0.553	0.325	0.213	0.312
	CV [%]	N.C.	20.51	91.03	50.40	33.35	50.19	47.42	54.52	63.57	42.87	57.80	42.92	24.43	25.23
	Geo. mean	N.C.	0.0452	0.267	0.584	0.631	0.734	0.695	0.675	1.072	0.754	0.848	0.691	0.848	1.200
	Geo. SD	N.C.	1.217	2.940	2.060	1.532	1.885	1.759	1.783	1.655	1.564	1.629	1.577	1.300	1.295
	Minimum	N.C.	0.0392	0.0539	0.164	0.231	0.140	0.140	0.163	0.603	0.212	0.212	0.231	0.546	0.856
	Maximum	N.C.	0.0417	0.259	0.806	0.702	0.766	0.738	0.685	1.011	0.787	0.887	0.655	0.899	1.243
t _{max} [h]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	0.406	0.409	0.469	0.375	0.330	0.403	0.377	0.374	0.427	0.414	0.418	0.393	0.422	0.417
	SD	0.186	0.126	0.0884	0.132	0.125	0.125	0.128	0.124	0.122	0.123	0.121	0.124	0.118	0.125
	CV [%]	45.79	30.85	18.86	35.14	37.77	31.14	33.93	33.30	28.64	29.79	28.93	31.66	27.84	30
	Geo. mean	N.C.	0.389	0.459	0.354	0.312	0.382	0.355	0.354	0.408	0.393	0.398	0.373	0.405	0.397
	Geo. SD	N.C.	1.414	1.278	1.441	1.405	1.416	1.423	1.409	1.402	1.406	1.397	1.410	1.378	1.414
	Minimum	0	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250	0.250
	Maximum	0.500	0.500	0.500	0.375	0.250	0.500	0.385	0.330	0.500	0.500	0.500	0.500	0.500	0.500
V _d [L]	n	0	3	8	10	10	18	28	19	10	20	30	18	9	9
	Mean	N.C.	5.143	58.27	86.91	81.84	99.47	93.17	107.8	159.9	106.4	124.2	98.62	110.5	163.1
	SD	N.C.	0.785	54.36	40.68	25.72	54.13	46.25	61.15	109.5	45.45	75.70	34.95	33.52	53.98
	CV [%]	N.C.	15.27	93.29	46.81	31.43	54.42	49.65	56.72	68.49	42.71	60.94	35.44	30.33	33.09
	Geo. mean	N.C.	5.105	37.07	74.48	77.66	83.96	81.66	91.65	138.2	97.04	109.2	91.98	105.4	155.8
	Geo. SD	N.C.	1.158	2.949	1.925	1.432	1.906	1.739	1.874	1.694	1.599	1.664	1.500	1.403	1.378
	Minimum	N.C.	4.658	7.448	24.48	35.65	19.13	19.13	16.59	69.46	23.88	23.88	34.68	60.72	99.97
	Maximum	N.C.	4.722	36.45	102.0	78.54	89.51	80.18	105.0	128.2	101.7	107.8	92.23	121.6	170.4
Maximum	N.C.	6.049	160.5	128.8	122.6	200.6	200.6	288.6	449.0	245.3	449.0	155.4	156.0	272.8	

CV: coefficient of variation, N.C. = No Computations, N= number of subjects in PK-R set, n = Number of subjects with computable value, SD: standard deviation.
F: final crossover (F-CO) part, P: pilot crossover (P-CO) part, S: single ascending dose crossover (SAD-CO) part, S+P: SAD-CO + P-CO part, IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and placebo capsule

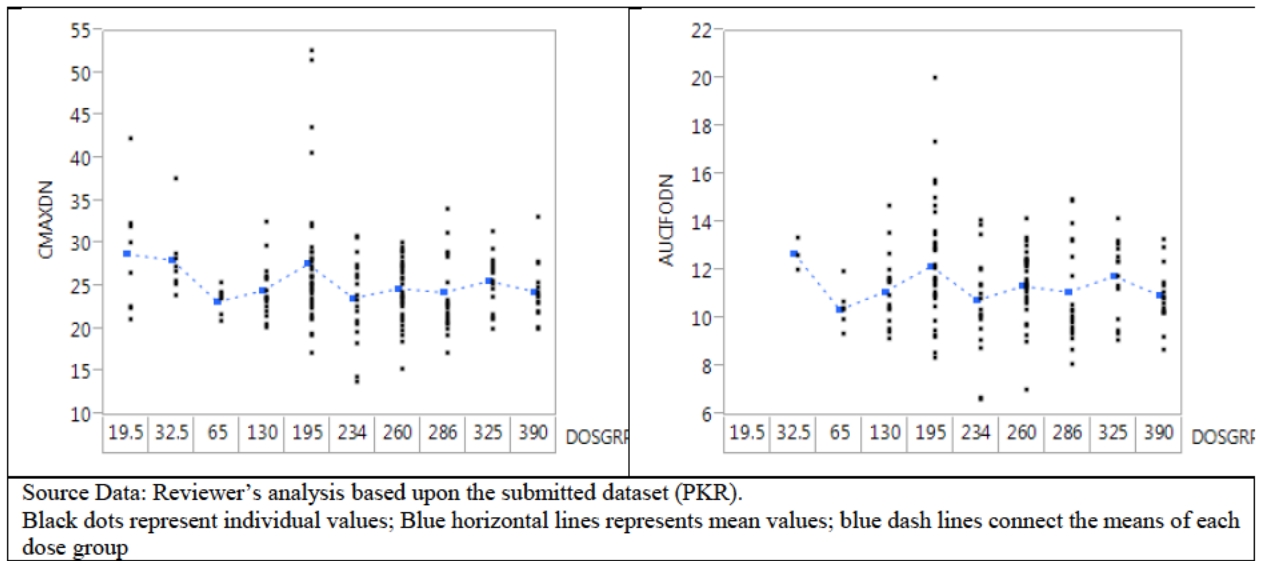
Source: Table 14.2.1.3

Source data: Study PNET-12-23 CSR, In-text Table 11.1-4

Dose proportionality assessment

The dose-normalized C_{max} (C_{MAXDN}) and AUC_{inf} (AUC_{IFODN}) of fosnetupitant vs fosnetupitant dose (DOSGRP) was shown in the figure below.

Figure 5. Dose-normalized Cmax and AUC of fosnetupitant vs Dose

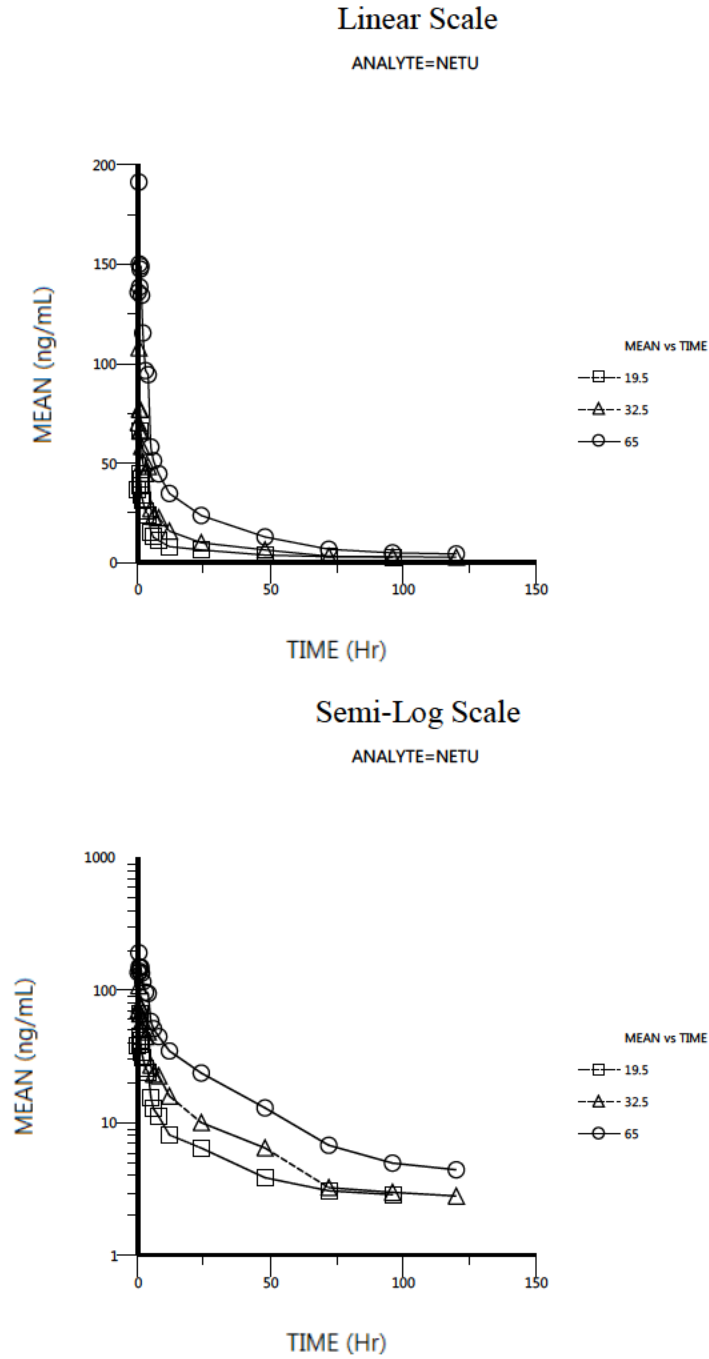


Reviewer's comment: Overall, systemic exposures (Cmax and AUCinf) to fosnetupitant increased in a dose-proportional fashion with the increase of fosnetupitant dose.

Summary of PK Parameters - Netupitant

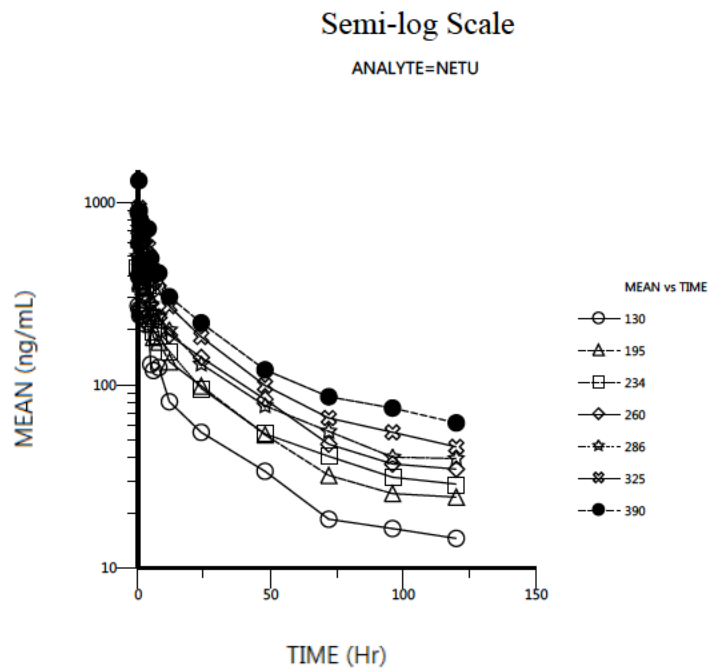
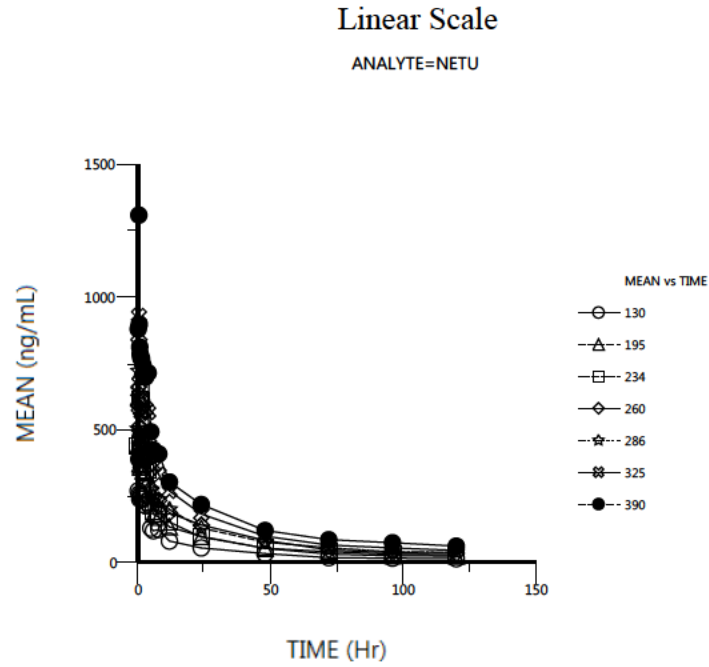
The mean concentration-time profiles of the netupitant is shown below.

Figure 6. Mean Netupitant Plasma Concentration-Time Profile: 19.5, 32.5, and 65 mg



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28

Figure 7. Mean Netupitant Plasma Concentration-Time Profile: 130, 195, 234, 260, 286, 325, 390 mg IV Single Dose Group



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28
For 195 mg and 260 mg dose groups, data were pooled from both SAD period and P-CO period

Descriptive summary of netupitant PK parameters following IV fosnetupitant or oral Akynzeo is shown below.

Table 15. Systemic exposures (AUC and Cmax) of netupitant following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg	32.5 mg	65 mg	130 mg	S-195 mg	P-195 mg	S+P-195 mg	F-234 mg	S-260 mg	P-260 mg	S+P-260 mg	F-286 mg	325 mg	390 mg	300 mg	Oral
		N=8	N=8	N=8	N=10	N=10	N=18	N=28	N=19	N=10	N=20	N=30	N=18	N=9	N=9	N=129	
AUC _{0-12h} [h·µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129	
	Mean	555.6	1001	2139	5205	7972	8643	8403	9095	12320	11861	12014	11836	15885	19647	11317	
	SD	198.7	142.1	421.4	1603	1691	1846	1791	1906	2534	2290	2340	3099	2867	4306	4278	
	CV [%]	35.77	14.20	19.70	30.81	21.22	21.36	21.31	20.96	20.57	19.31	19.48	26.18	18.05	21.92	37.81	
	Geo. mean	529.2	992.3	2102	5007	7789	8461	8215	8922	12078	11643	11786	11517	15662	19226	10502	
	Geo. SD	1.382	1.152	1.226	1.332	1.266	1.237	1.247	1.220	1.237	1.222	1.224	1.261	1.195	1.248	1.492	
	Minimum	368.0	820.1	1517	3549	4508	5581	4508	6593	8082	7443	7443	7443	8555	11427	13131	3195
Median	514.7	989.5	2140	4634	7888	8591	8460	8660	11687	11676	11687	10568	15410	20024	10489		
Maximum	971.7	1223	2720	8270	10672	13499	13499	13935	16537	16185	16537	20675	21809	26310	26564		
AUC _{0-inf} [h·µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129	
	Mean	716.1	1203	2398	6054	9397	10229	9932	11169	14175	13693	13854	14397	19868	23923	13899	
	SD	339.5	197.3	484.3	2060	2330	2778	2614	2049	3286	2854	2957	4355	5632	5878	5549	
	CV [%]	47.41	16.40	20.20	34.03	24.80	27.16	26.32	18.34	23.18	20.84	21.34	30.25	28.35	24.57	39.92	
	Geo. mean	665.4	1189	2354	5777	9119	9896	9611	10993	13824	13398	13538	13870	19266	23239	12798	
	Geo. SD	1.466	1.182	1.228	1.369	1.305	1.301	1.300	1.202	1.270	1.244	1.248	1.313	1.289	1.298	1.522	
	Minimum	452.3	902.9	1799	4048	5196	6192	5196	7736	8955	7947	7947	9347	13872	14527	3872	
Median	641.2	1224	2478	5211	8962	9431	9431	10821	13796	13838	13807	13226	18183	25521	13327		
Maximum	1506	1499	3173	9683	13351	16381	16381	15728	20003	19766	20003	26780	32601	32275	31789		
C _{max} [µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129	
	Mean	65.77	108.0	193.5	389.7	590.4	642.1	623.6	640.2	811.5	855.4	840.8	729.8	936.7	1310	477.3	
	SD	15.75	24.40	51.48	109.5	139.4	197.8	178.2	221.1	110.9	197.4	172.6	193.9	147.9	254.6	231.6	
	CV [%]	23.94	22.59	26.61	28.09	23.60	30.81	28.57	34.53	13.67	23.07	20.53	26.57	15.79	19.44	48.52	
	Geo. mean	64.27	105.9	188.0	376.6	574.6	614.2	599.8	610.0	804.6	831.8	822.6	707.4	925.2	1287	420.9	
	Geo. SD	1.253	1.228	1.285	1.314	1.284	1.360	1.330	1.365	1.148	1.285	1.243	1.289	1.188	1.220	1.695	
	Minimum	46.14	83.18	127.9	265.9	352.4	353.9	352.4	336.2	626.1	478.6	478.6	476.1	633.7	932.5	84.78	
Median	63.81	99.64	184.9	355.2	591.8	670.2	637.5	614.9	819.7	854.8	830.5	690.4	986.5	1328	449.5		
Maximum	98.20	160.0	301.9	563.6	799.0	1083	1083	1336	1015	1189	1189	1181	1153	1674	1298		

Source data: Study PNET-12-23 CSR, In-text Table 11.1-5

Table 16. Additional PK parameters (t1/2 and Tmax) of netupitant following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg	32.5 mg	65 mg	130 mg	S-195 mg	P-195 mg	S+P-195 mg	F-234 mg	S-260 mg	P-260 mg	S+P-260 mg	F-286 mg	325 mg	390 mg	300 mg
		N=8	N=8	N=8	N=10	N=10	N=18	N=28	N=19	N=10	N=20	N=30	N=18	N=9	N=9	Oral N=129
t _{1/2} [h]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	34.94	55.41	40.75	39.68	39.41	43.69	42.16	51.03	40.02	34.07	36.05	45.18	55.40	47.23	51.59
	SD	14.14	51.83	16.48	11.02	8.220	30.63	24.85	22.06	6.826	6.027	6.812	22.57	25.72	14.60	30.90
	CV [%]	40.48	93.54	40.44	27.78	20.86	70.12	58.95	43.22	17.06	17.69	18.90	49.96	46.43	30.91	59.90
	Geo. mean	33.05	44.23	38.04	38.39	38.73	38.31	38.46	47.21	39.44	33.62	35.46	41.50	50.30	45.39	46.02
	Geo. SD	1.398	1.876	1.485	1.306	1.211	1.577	1.459	1.485	1.203	1.174	1.201	1.481	1.594	1.343	1.549
	Minimum	23.63	22.18	21.43	29.29	31.50	26.32	26.32	25.37	26.82	27.50	26.82	26.46	29.00	31.21	21.86
	Median	31.68	39.58	37.23	33.06	37.67	32.70	33.98	44.71	43.26	31.89	34.85	36.59	49.02	48.97	39.39
	Maximum	67.52	181.6	71.23	56.64	58.42	137.1	137.1	107.1	49.05	52.40	52.40	111.3	96.38	77.25	201.1
t _{max} [h]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	0.500	0.500	0.594	0.500	0.505	0.500	0.502	0.564	0.852	0.501	0.618	0.779	0.786	0.502	4.343
	SD	0	0	0.265	0	0.0108	0	0.0067	0.230	1.106	0.0045	0.639	0.812	0.831	0.0067	1.433
	CV [%]	0	0	44.66	0	2.139	0	1.335	40.81	129.8	0.893	103.4	104.2	105.8	1.327	32.99
	Geo. mean	0.500	0.500	0.561	0.500	0.505	0.500	0.502	0.540	0.618	0.501	0.537	0.610	0.619	0.502	4.197
	Geo. SD	1	1	1.383	1	1.021	1	1.013	1.292	1.928	1.009	1.461	1.787	1.810	1.013	1.271
	Minimum	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	2
	Median	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500	4
	Maximum	0.500	0.500	1.250	0.500	0.530	0.500	0.530	1.500	4	0.520	4	3.020	3	0.520	12

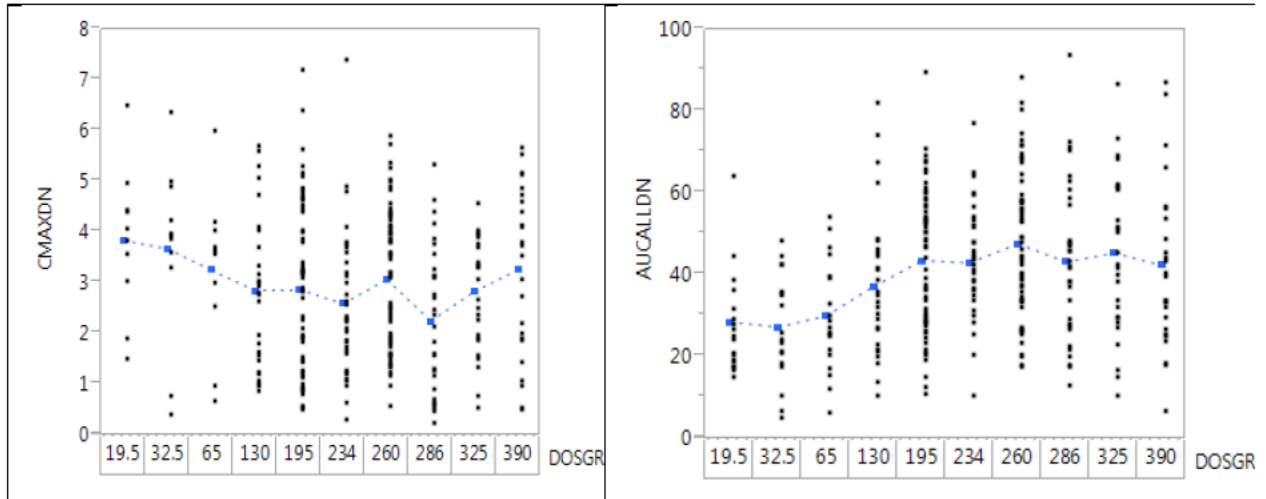
Source data: Study PNET-12-23 CSR, In-text Table 11.1-5

CV: coefficient of variation, N.C. = No Computations, N= number of subjects in PK-R set, n = Number of subjects with computable value
 F: final crossover (F-CO) part, P: pilot crossover (P-CO) part, S: single ascending dose crossover (SAD-CO) part, S+P: SAD-CO + P-CO part
 SD: standard deviation
 IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and placebo capsule, Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) and placebo infusion

Source: [Table 14.2.2.3.1](#), [Table 14.2.2.3.2](#)

Dose proportionality assessment

The dose-normalized Cmax (CMAXDN) and AUClast (AUCALLDN) of netupitant vs fosnetupitant dose (DOSGRP) was shown in the figure below.



Source Data: Reviewer's analysis based upon the submitted dataset (PKR).

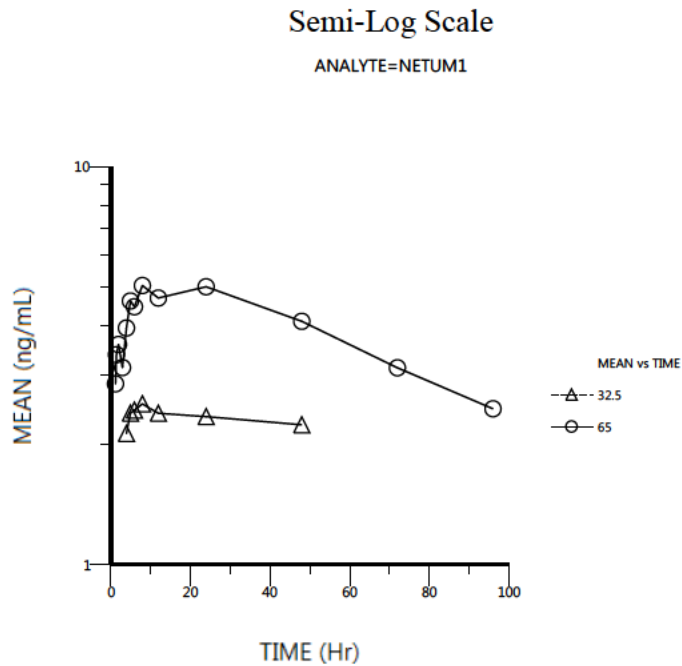
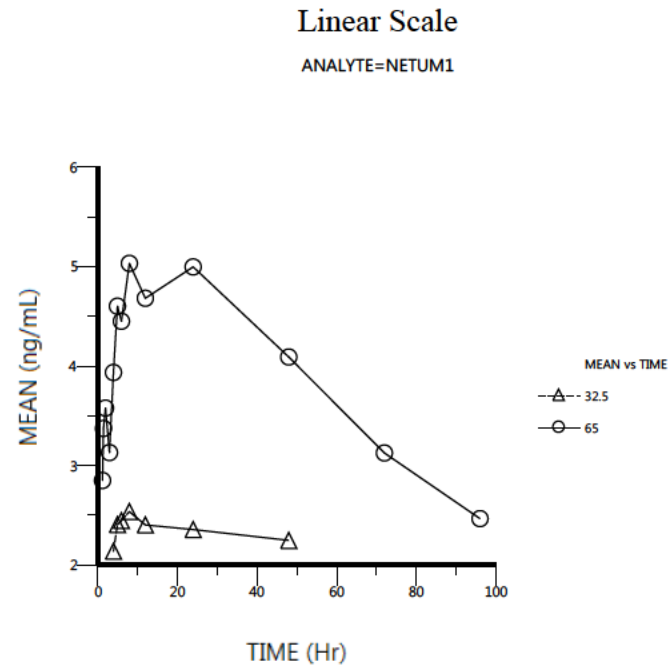
Black dots represent individual values; Blue horizontal lines represents mean values; blue dash lines connect the means of each dose group

Reviewer's comment: AUClast (i.e. AUC_{0-120h}) of netupitant increased in a supra-proportional fashion with the increase of fosnetupitant dose from 19.5 mg to 195 mg. The AUC increased in a dose-proportional fashion with the increase of fosnetupitant dose from 195 mg to 390 mg.

Summary of PK Parameters – Metabolite M1

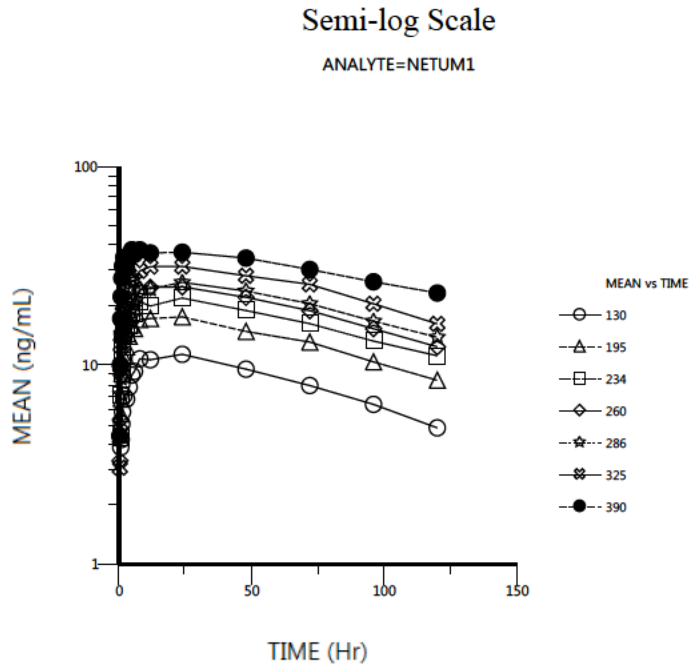
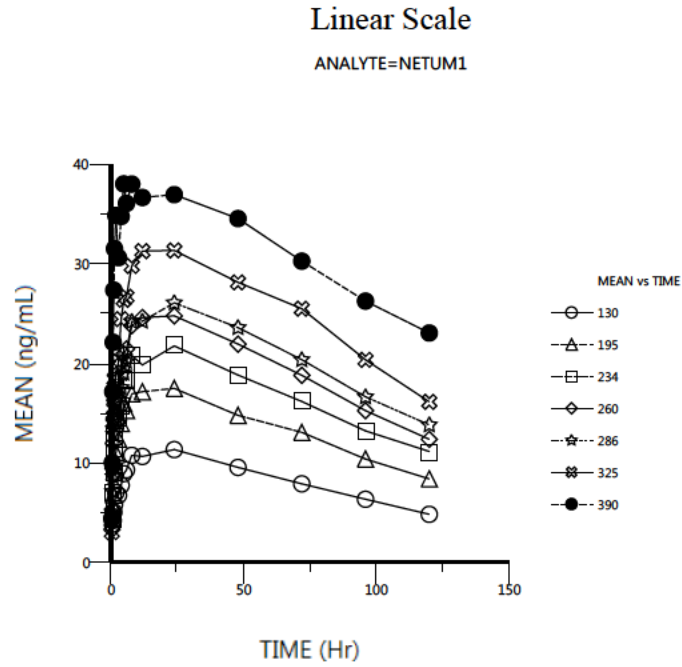
The mean concentration-time profiles of metabolite M1 is shown below.

Figure 8. Mean Metabolite M1 (NETUM1) Plasma Concentration-Time Profile: 19.5, 32.5, 65 mg



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28

Figure 9. Mean Metabolite M1 (NETUM1) Plasma Concentration-Time Profile: 130, 195, 234, 260, 286, 325, 390 mg IV Single Dose Group



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28
For 195 mg and 260 mg dose groups, data were pooled from both SAD period and P-CO period

Descriptive summary of M1 PK parameters following IV fosnetupitant or oral Akynzeo is shown below.

Table 18. Additional PK parameters (t1/2 and Tmax) of M1 following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg	32.5 mg	65 mg	130 mg	S-195 mg	P-195 mg	S-P-195 mg	F-234 mg	S-260 mg	P-260 mg	S+P-260 mg	F-286 mg	325 mg	390 mg	300 mg Oral
		N=8	N=8	N=8	N=10	N=10	N=18	N=28	N=19	N=10	N=20	N=30	N=18	N=9	N=9	N=129
t _{1/2} [h]	n	0	2	7	10	10	15	25	19	10	20	30	16	9	9	128
	Mean	N.C.	193.7	57.57	74.82	80.72	79.38	79.92	98.82	102.6	82.69	89.34	91.16	77.99	133.4	76.88
	SD	N.C.	79.74	16.90	23.24	6.860	28.72	22.35	38.09	72.84	27.87	47.41	26.78	23.04	55.13	27.62
	CV [%]	N.C.	41.17	29.35	31.06	8.498	36.18	27.96	38.55	70.97	33.71	53.06	29.37	29.54	41.33	35.93
	Geo. mean	N.C.	185.3	55.58	71.50	80.46	74.45	76.80	92.67	89.25	78.71	82.08	87.51	75.59	124.4	73.10
	Geo. SD	N.C.	1.528	1.329	1.380	1.088	1.456	1.342	1.437	1.650	1.376	1.470	1.346	1.287	1.474	1.339
	Minimum	N.C.	137.3	37.89	45.60	70.63	41.65	41.65	57.26	44.87	42.65	42.65	42.65	49.93	57.55	73.57
Median	N.C.	193.7	59.69	69.38	81.11	78.68	81.01	92.53	86.99	78.87	78.87	81.88	81.68	68.85	125.3	69.75
Maximum	N.C.	250.0	89.29	106.9	93.00	129.6	129.6	200.6	200.6	302.7	163.2	302.7	141.7	132.7	239.0	238.0
t _{max} [h]	n	1	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	8	18.03	10.50	16.70	16.80	19.96	18.83	17.47	14.81	15.05	14.97	27.42	16.11	12.79	12.64
	SD	N.C.	31.65	8.452	13.69	7.955	24.43	19.98	11.15	6.539	11.08	9.680	18.67	7.820	15.02	9.978
	CV [%]	N.C.	175.5	80.49	81.99	47.35	122.4	106.1	63.79	44.15	73.59	64.64	68.11	48.53	117.4	78.96
	Geo. mean	8,000	8.285	8.281	11.99	14.60	12.03	12.89	14.17	13.64	11.39	12.10	22.51	14.16	7.226	10.44
	Geo. SD	N.C.	3.320	2.010	2.517	1.847	2.386	2.313	1.993	1.526	2.272	2.034	1.940	1.770	3.165	1.761
	Minimum	8	1.250	4	2	4	3	3	5	8	2	2	2	5	5	2
Median	8	8	7	12	18	12	12	24	12.02	12	12	12	24	12	8	8
Maximum	8	96	24	48	24	72.20	72.20	48	48	24	48.02	48.02	72.52	24.02	48.07	72

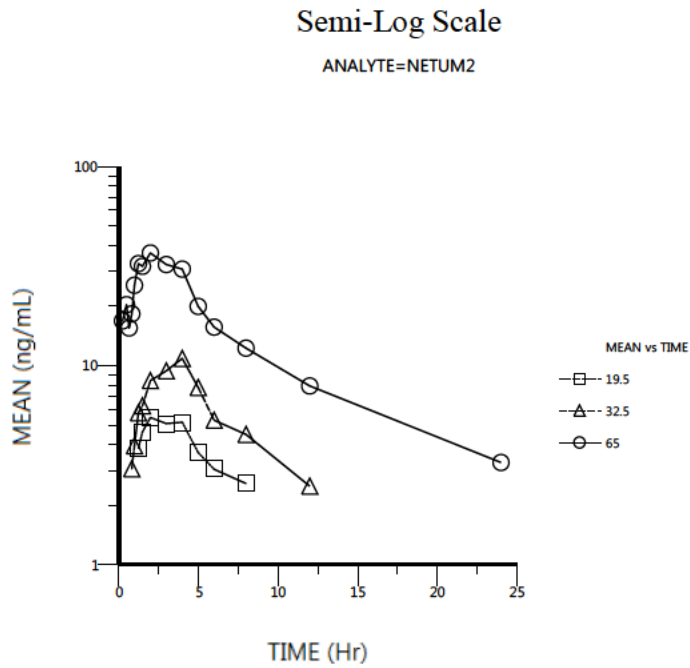
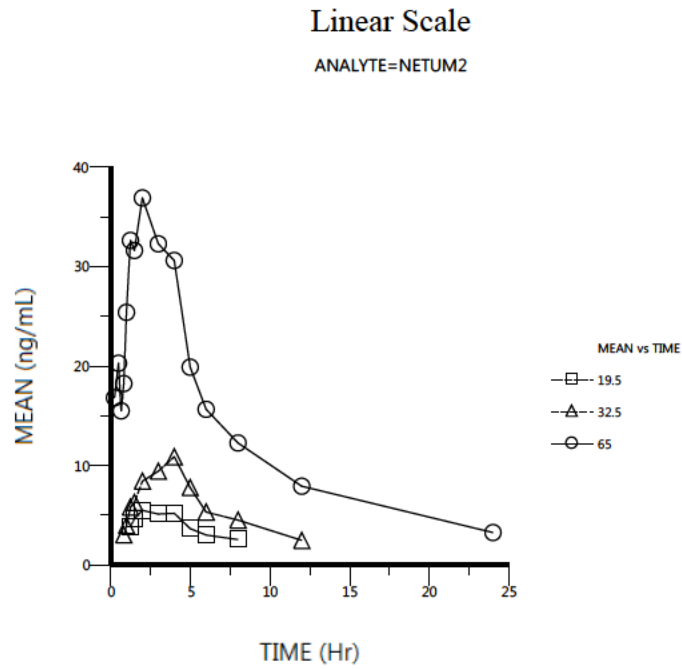
N.C. = No Computations, N= number of subjects in PK-R set, n = Number of subjects with computable value, CV: coefficient of variation
F: final crossover (F-CO) part, S: single ascending dose crossover (SAD-CO) part, P: pilot crossover (P-CO) part, S+P: SAD-CO + P-CO part
SD: standard deviation
IV: intravenous infusion of 19.5 to 390 mg pro-aetupitant and placebo capsule, Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) and placebo infusion
Source: [Table 14.2.3.3.1](#), [Table 14.2.3.3.2](#)

Source data: Study PNET-12-23 CSR, In-text Table 11.1-6

Summary of PK Parameters – Metabolite M2

The mean concentration-time profiles of metabolite M2 is shown below.

Figure 10. Mean Metabolite M2 (NETUM2) Plasma Concentration-Time Profile: 19.5, 32.5, 65 mg

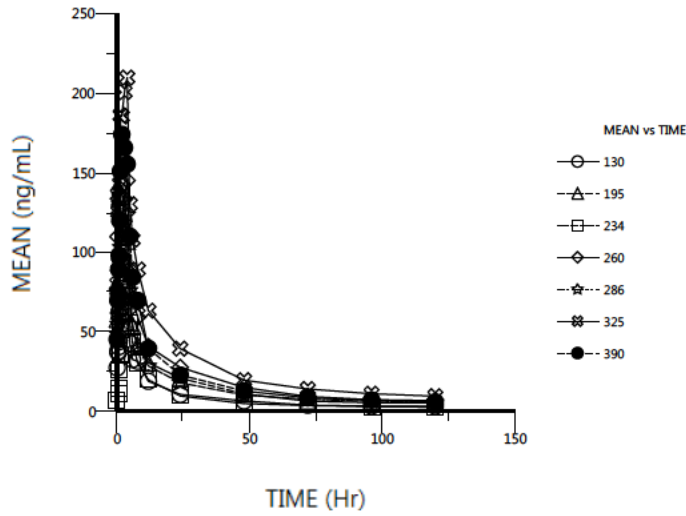


Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28

Figure 11. Mean Metabolite M2 (NETUM2) Plasma Concentration-Time Profile: 130, 195, 234, 260, 286, 325, 390 mg IV Single Dose Group

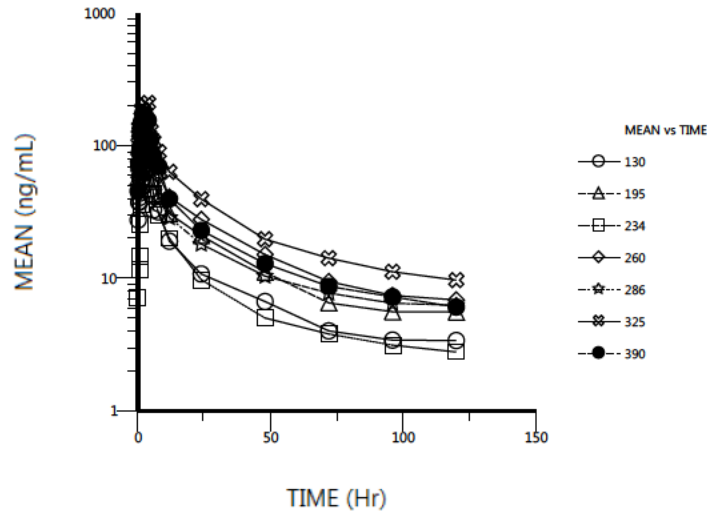
Linear Scale

ANALYTE=NETUM2



Semi-log Scale

ANALYTE=NETUM2



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28
For 195 mg and 260 mg dose groups, data were pooled from both SAD period and P-CO period

Descriptive summary of M2 PK parameters following IV fosnetupitant or oral Akynzeo is shown below.

Table 19. Systemic exposures (AUC and Cmax) of M2 following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg N=8	32.5 mg N=8	65 mg N=8	130 mg N=10	S-195 mg N=10	P-195 mg N=18	S+P-195 mg N=28	F-234 mg N=19	S-260 mg N=10	P-260 mg N=20	S+P-260 mg N=30	F-286 mg N=18	325 mg N=9	390 mg N=9	300 mg Oral N=129
AUC _{0-24h} [h·µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	25.24	65.46	280.9	1115	1652	2050	1908	1086	2513	2618	2583	1908	3761	2554	2640
	SD	10.90	23.25	148.6	462.0	479.4	792.7	714.1	406.7	1052	1368	1254	968.3	1449	962.3	1541
	CV [%]	43.19	35.52	52.91	41.42	29.01	38.66	37.42	37.44	41.88	52.24	48.34	50.75	38.52	37.67	38.38
	Geo. mean	22.61	61.72	244.3	1032	1583	1894	1776	1017	2320	2297	2304	1715	3534	2398	2242
	Geo. SD	1.738	1.451	1.802	1.521	1.380	1.532	1.486	1.464	1.529	1.700	1.633	1.599	1.450	1.465	1.804
	Minimum	7.144	37.53	88.37	567.3	819.3	799.4	799.4	471.4	1196	956.0	956.0	783.1	1961	1306	362.5
Median	26.20	64.16	220.3	1009	1683	2049	1892	1100	2227	2178	2227	1689	3271	2671	2262	
Maximum	43.29	95.19	463.6	1873	2336	3275	3275	2221	4325	5836	5836	4824	6562	4533	9228	
AUC _{0-inf} [h·µg/L]	n	7	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	53.83	88.50	319.9	1311	1937	2294	2167	1231	2834	2986	2935	2240	4339	2969	2993
	SD	21.11	24.45	151.8	522.3	676.2	886.5	823.1	468.3	1212	1591	1456	1275	1720	1196	1766
	CV [%]	39.21	27.63	47.44	39.84	34.90	38.65	37.99	38.06	42.78	53.28	49.60	56.91	39.64	40.29	58.99
	Geo. mean	51.03	85.43	285.4	1220	1831	2124	2014	1148	2617	2603	2608	1983	4048	2765	2530
	Geo. SD	1.399	1.341	1.709	1.497	1.436	1.516	1.488	1.475	1.520	1.727	1.649	1.634	1.487	1.496	1.815
	Minimum	36.68	56.39	105.3	621.6	896.5	976.1	896.5	527.9	1389	1015	1015	926.7	2150	1486	436.0
Median	44.87	87.14	255.2	1133	1836	2222	2154	1176	2447	2866	2662	1974	3676	2853	2501	
Maximum	97.69	122.9	510.2	2107	3303	3744	3744	2409	5174	6940	6940	6315	7468	5483	10281	
C _{max} [µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	5.755	12.37	42.05	83.91	137.5	126.3	130.3	90.45	162.3	176.9	172.0	146.9	240.8	188.3	213.9
	SD	2.042	3.073	25.36	37.44	51.02	57.97	54.90	44.79	68.94	84.47	78.73	67.96	92.55	68.28	108.1
	CV [%]	35.49	24.84	60.30	44.62	37.09	45.90	42.13	49.52	42.48	47.74	45.76	46.27	38.44	36.26	50.55
	Geo. mean	5.466	12.02	35.66	76.77	129.4	113.1	118.7	80.94	148.7	160.2	156.2	132.4	225.0	176.2	188.0
	Geo. SD	1.405	1.302	1.860	1.560	1.445	1.646	1.574	1.633	1.575	1.575	1.564	1.616	1.483	1.491	1.704
	Minimum	3.503	7.347	14.36	42.52	66.67	44.52	44.52	30.86	68.75	69.46	68.75	51.65	132.0	96.95	26.66
Median	5.358	11.63	31.76	70.44	124.3	127.1	124.7	85.76	153.0	157.1	155.1	137.1	245.7	215.0	195.9	
Maximum	9.807	16.72	82.14	141.4	222.4	228.2	228.2	215.7	297.3	405.2	405.2	405.2	392.9	286.9	679.6	

Source data: Study PNET-12-23 CSR, In-text Table 11.1-7

Table 20. Additional PK parameters (t1/2 and Tmax) of M2 following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg	32.5 mg	65 mg	130 mg	S-195 mg	P-195 mg	S+P-195 mg	F-234 mg	S-360 mg	P-260 mg	S+P-260 mg	F-286 mg	325 mg	390 mg	300 mg
		N=8	N=8	N=8	N=10	N=10	N=18	N=28	N=19	N=10	N=20	N=30	N=18	N=9	N=9	Oral N=129
t _{1/2} [h]	n	7	7	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	6.726	5.639	7.897	41.32	34.94	32.63	33.46	36.14	37.46	35.41	36.09	38.89	39.63	45.08	43.16
	SD	4.570	2.271	4.649	32.14	8.556	6.570	7.269	31.08	9.923	29.80	24.77	16.87	24.34	20.07	49.92
	CV [%]	67.94	40.28	58.88	77.78	24.49	20.13	21.73	86.00	26.49	84.17	68.62	43.37	61.42	44.33	115.7
	Geo. mean	5.777	5.286	6.998	34.96	34.06	31.93	32.67	29.80	36.26	30.74	32.48	36.47	35.85	41.62	35.05
	Geo. SD	1.751	1.467	1.654	1.728	1.264	1.252	1.253	1.758	1.312	1.563	1.491	1.408	1.515	1.519	1.696
	Minimum	3.297	3.126	3.592	16.58	25.18	18.22	18.22	14.55	24.18	19.79	19.79	25.11	25.72	23.73	14.34
Median	4.823	4.703	6.560	31.31	33.66	31.88	32.35	27.31	37.91	27.45	29.25	34.70	32.08	44.72	31.73	
Maximum	16.29	9.589	18.35	128.6	52.10	43.63	52.10	151.1	54.07	158.8	158.8	86.80	103.8	89.26	452.7	
t _{max} [h]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	3.375	3.313	2.656	3.100	2.952	2.222	2.483	3.519	2.552	2.376	2.435	2.448	2.444	2.836	4.133
	SD	0.744	1.438	1.232	0.876	1.161	1.153	1.189	0.766	1.554	1.395	1.425	1.349	1.402	1.116	0.630
	CV [%]	22.05	43.40	46.36	28.25	39.32	51.90	47.88	21.77	60.91	58.70	58.54	55.10	57.35	39.36	15.25
	Geo. mean	3.293	2.806	2.394	2.980	2.605	1.859	2.097	3.430	1.889	1.835	1.853	1.935	1.937	2.639	4.085
	Geo. SD	1.280	2.116	1.645	1.553	1.871	1.987	1.963	1.274	2.566	2.299	2.350	2.240	2.281	1.500	1.168
	Minimum	2	0.500	1.250	2	0.520	0.500	0.500	2	0.500	0.500	0.500	0.500	0.500	1.500	2
Median	3.500	4	2.500	3	3	2	2.500	4	3.010	2.500	3	3	3	2	2.020	4
Maximum	4	5	4	4	4	4	4	5	4	4	4	4	4	4	4	6.020

N.C. = No Computations, N= number of subjects in PK-R set, n = Number of subjects with computable value
 F: final crossover (F-CO) part, S: single ascending dose crossover (SAD-CO) part, P: pilot crossover (P-CO) part, S+P: SAD-CO + P-CO part,
 SD: standard

IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and placebo capsule, Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) and placebo infusion

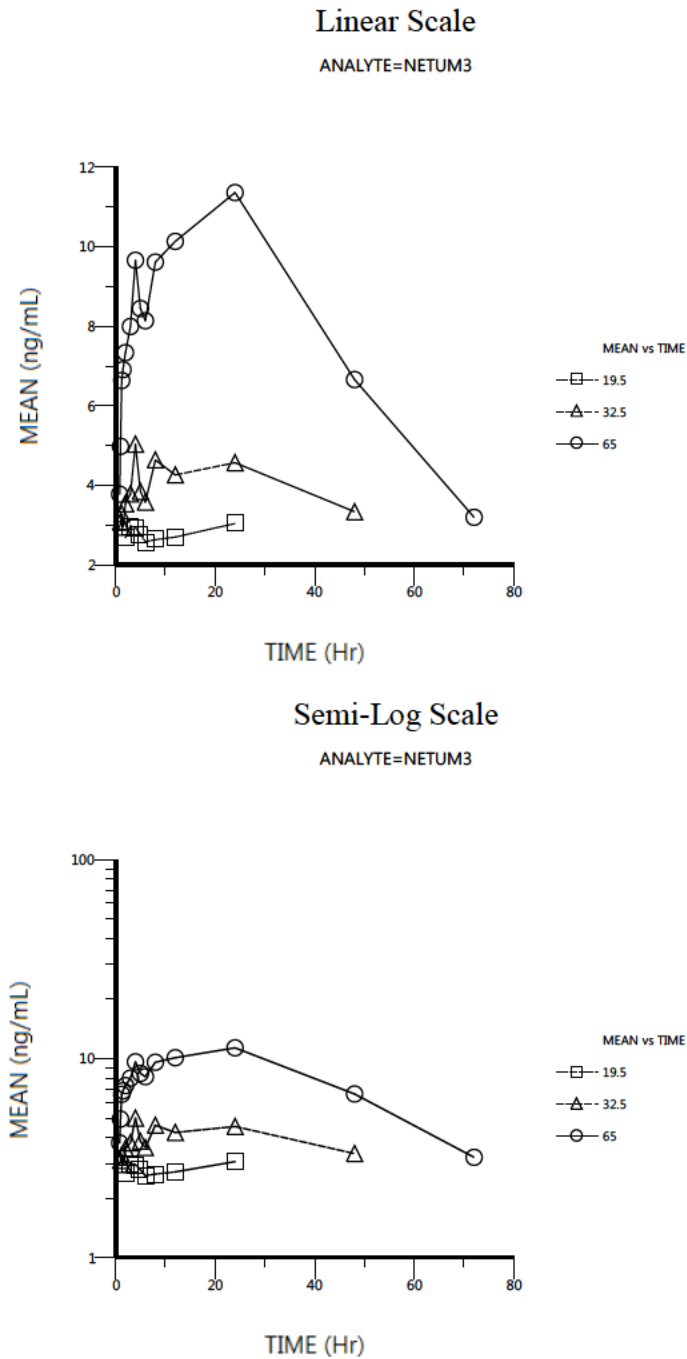
Source: Table 14.2.4.3.1, Table 14.2.4.3.2

Source data: Study PNET-12-23 CSR, In-text Table 11.1-7

Summary of PK Parameters – Metabolite M3

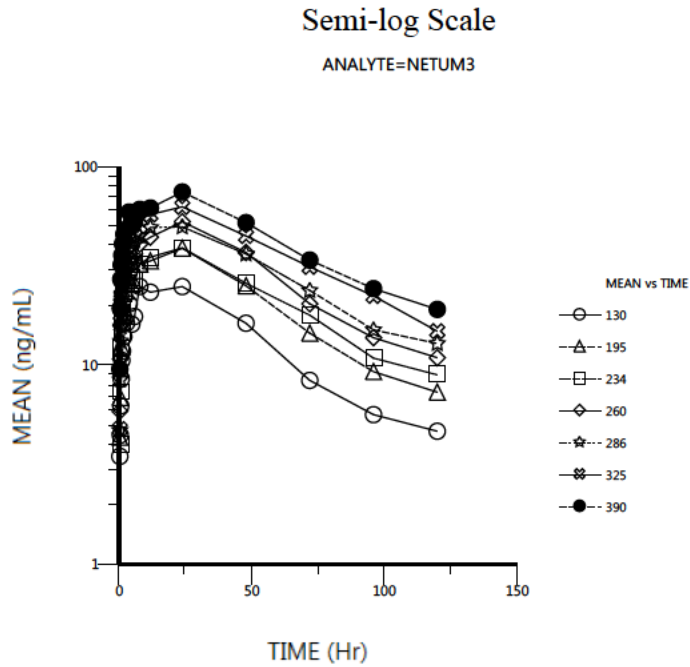
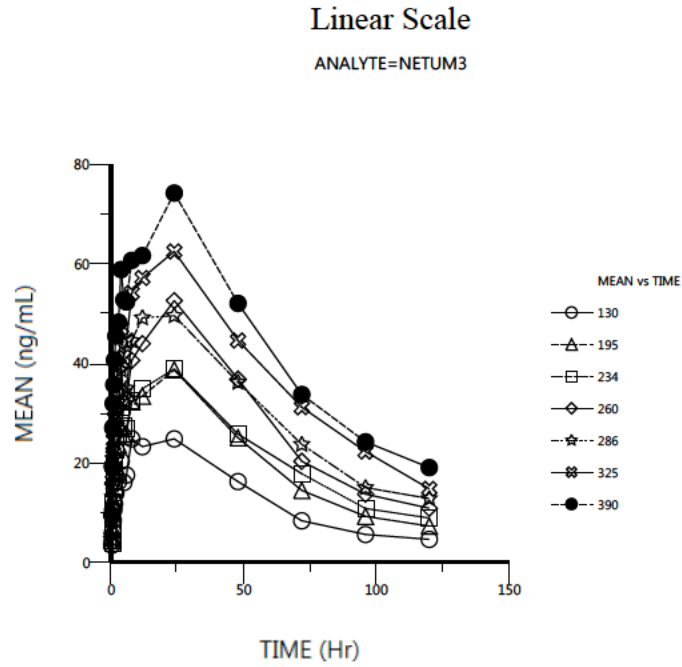
The mean concentration-time profiles of metabolite M3 is shown below.

Figure 12. Mean Metabolite M3 (NETUM3) Plasma Concentration-Time Profile: 19.5, 32.5, 65 mg



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28

Figure 13. Mean Metabolite M3 (NETUM3) Plasma Concentration-Time Profile: 130, 195, 234, 260, 286, 325, 390 mg IV Single Dose Group



Source data: Reviewer's summary plot based upon sponsor's dataset in SDN28
For 195 mg and 260 mg dose groups, data were pooled from both SAD period and P-CO period

Descriptive summary of M3 PK parameters following IV fosnetupitant or oral Akynzeo is shown below.

Table 21. Systemic exposures (AUC and Cmax) of M3 following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg	32.5 mg	65 mg	130 mg	S-195 mg	P-195 mg	S+P-195 mg	F-234 mg	S-260 mg	P-260 mg	S+P-260 mg	F-286 mg	325 mg	390 mg	300 mg
AUC _{0-last} [h·µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	71.69	202.0	606.7	1593	2575	2410	2469	2654	3386	3488	3454	3576	4527	5198	3783
	SD	30.75	97.41	197.0	583.1	461.5	705.8	625.4	649.8	625.4	804.2	739.9	993.1	1394	1673	1303
	CV [%]	42.89	48.22	32.47	36.61	17.92	29.28	25.33	24.48	18.47	23.05	21.42	27.77	30.80	32.18	34.44
	Geo. mean	66.37	173.8	581.5	1507	2538	2312	2390	2579	3332	3399	3376	3468	4372	4978	3556
	Geo. SD	1.515	1.913	1.357	1.412	1.195	1.350	1.301	1.280	1.213	1.267	1.246	1.276	1.307	1.360	1.437
	Minimum	41.97	57.35	422.7	974.7	2023	1305	1305	1830	2312	2017	2017	2551	3388	3383	1215
Median	64.68	212.7	522.6	1468	2568	2342	2402	2770	3414	3496	3496	3197	4201	5008	3578	
Maximum	126.1	316.2	936.5	2752	3355	3792	3792	3727	4356	5147	5147	6203	7829	8172	7701	
AUC _{0-inf} [h·µg/L]	n	0	5	5	10	10	18	28	19	10	20	30	18	9	9	128
	Mean	N.C.	509.5	781.2	1910	3105	2901	2974	3268	4025	4457	4313	4904	5501	6742	4620
	SD	N.C.	138.3	225.5	712.4	613.8	970.3	853.4	837.3	1022	1256	1183	2642	1785	2409	1845
	CV [%]	N.C.	27.15	28.86	37.29	19.77	33.44	28.69	25.62	25.40	28.18	27.44	53.86	32.44	35.73	39.93
	Geo. mean	N.C.	494.2	754.0	1811	3047	2766	2863	3172	3908	4281	4153	4480	5296	6403	4279
	Geo. SD	N.C.	1.323	1.352	1.393	1.232	1.366	1.322	1.283	1.293	1.347	1.328	1.492	1.320	1.395	1.488
	Minimum	N.C.	334.5	538.3	1256	2147	1785	1785	1981	2530	2141	2141	2776	3949	4486	1467
Median	N.C.	482.2	809.1	1606	3160	2609	2960	3139	3790	4554	4294	4080	4770	6366	4343	
Maximum	N.C.	690.9	1010	3517	3876	5455	5455	5194	5619	7029	7029	13862	9763	10928	11908	
C _{max} [µg/L]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	3.260	5.784	12.42	27.66	42.98	40.12	41.14	40.92	55.26	53.44	54.05	53.89	65.26	75.97	65.96
	SD	0.656	1.781	3.348	11.48	10.79	13.55	12.51	10.59	10.83	12.85	12.06	11.22	17.98	22.97	22.15
	CV [%]	20.12	30.80	26.95	41.50	25.11	33.79	30.40	25.87	19.60	24.05	22.31	20.82	27.55	30.23	33.58
	Geo. mean	3.201	5.537	12.08	25.72	41.69	38.09	39.34	39.61	54.25	52.02	52.75	52.88	63.41	73.06	62.09
	Geo. SD	1.227	1.379	1.282	1.488	1.304	1.391	1.359	1.304	1.228	1.269	1.253	1.217	1.279	1.343	1.436
	Minimum	2.416	3.076	8.669	14.82	25.65	19.99	19.99	23.83	37.27	35.36	35.36	39.02	45.57	46.77	17.79
Median	3.180	5.312	12.15	25.06	42.39	35.64	37.00	38.43	55.45	52.37	52.90	51.84	61.31	75.02	64.00	
Maximum	4.076	8.395	19.55	49.32	56.67	65.78	65.78	61.32	70.61	78.69	78.69	83.94	106.6	122.1	139.1	

Source data: Study PNET-12-23 CSR, In-text Table 11.1-8

Table 22. Additional PK parameters (t1/2 and Tmax) of M3 following single IV doses of fosnetupitant or oral Akynzeo

Parameter	Statistics	19.5 mg	32.5 mg	65 mg	130 mg	S-195 mg	P-195 mg	S+P-195 mg	F-234 mg	S-260 mg	P-260 mg	S+P-260 mg	F-286 mg	325 mg	390 mg	300 mg
t _{1/2} [h]	n	N=8	N=8	N=8	N=10	N=10	N=18	N=28	N=19	N=10	N=20	N=30	N=18	N=9	N=9	N=129
	Mean	N.C.	68.72	31.93	47.30	43.24	43.10	43.15	46.20	43.06	49.45	47.32	55.08	44.84	53.79	46.35
	SD	N.C.	14.73	5.382	15.22	15.97	17.87	16.92	10.80	13.85	26.15	22.73	38.98	10.98	9.477	16.29
	CV [%]	N.C.	21.44	16.85	32.19	36.93	41.47	39.20	23.37	32.17	52.88	48.04	70.77	24.49	17.62	35.16
	Geo. mean	N.C.	67.44	31.56	44.95	40.85	40.38	40.55	45.04	41.37	44.15	43.21	47.84	43.68	52.98	43.86
	Geo. SD	N.C.	1.244	1.190	1.413	1.424	1.430	1.419	1.239	1.334	1.608	1.519	1.632	1.275	1.209	1.390
	Minimum	N.C.	52.78	25.42	24.75	22.04	21.52	21.52	28.54	28.74	20.51	20.51	20.51	25.91	28.23	35.81
Median	N.C.	74.11	33.99	48.56	40.33	39.51	39.88	43.42	40.74	42.34	42.34	40.93	45.02	41.91	52.37	43.65
Maximum	N.C.	87.53	37.57	72.50	79.03	101.1	101.1	65.79	75.16	119.8	119.8	119.8	190.7	65.13	65.59	106.0
t _{max} [h]	n	8	8	8	10	10	18	28	19	10	20	30	18	9	9	129
	Mean	16.88	6.753	19.02	18.00	21.60	16.45	18.29	17.90	19.20	21.60	20.80	16.67	19.57	19.12	15.65
	SD	9.939	3.535	7.000	7.829	5.060	7.983	7.414	8.577	7.955	9.025	8.621	7.028	6.742	7.429	9.085
	CV [%]	58.88	52.35	36.80	43.49	23.42	48.53	40.54	47.93	41.43	41.77	41.44	42.16	34.45	38.86	58.06
	Geo. mean	12.90	6.042	17.62	16.11	20.89	14.27	16.35	14.75	16.77	19.39	18.47	15.02	18.24	17.41	12.77
	Geo. SD	2.457	1.637	1.562	1.695	1.339	1.794	1.694	2.090	1.884	1.706	1.755	1.654	1.532	1.642	1.982
	Minimum	3	4	8	8	12	4	4	4	4	4	4	4	4	8	4
Median	24	5.010	24	24	24	18	24	24	24	24	24	24	12.02	24	24	12
Maximum	24.02	12	24.07	24	24	24.02	24.02	24.02	24.02	24	48	48	24	24.02	24.07	48.02

CV: coefficient of variation, N.C. = No Computations, N= number of subjects in PK-R set, n = Number of subjects with computable value
F: final crossover (F-CO) part, S: single ascending dose crossover (SAD-CO) part, P: pilot crossover (P-CO) part, S+P: SAD-CO + P-CO part,
SD: standard deviation
IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and placebo capsule, Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) and placebo infusion
Source: [Table 14.2.5.3.1](#), [Table 14.2.5.3.2](#)

Source data: Study PNET-12-23 CSR, In-text Table 11.1-8

Sex effect

Reviewer's comment: The study is not powered to evaluate effect of sex on PK of fosnetupitant. The data are exploratory in nature.

The descriptive statistics of key PK parameters in males and females following single dose 260 mg IV of fosnetupitant are the followings:

Fosnetupitant

C_{max} and AUC_{0-inf} of pro-netupitant averaged (mean ± SD) 6456±862.5 µg/L and 2955±299.2 h*µg/L in females, 6416±961.3 µg/L and 2928 ±401.5 h*µg/L in males, respectively.

The elimination efficiency and the volume of distribution, expressed by CL and V_d, were 88.85±9.459 L/h and 155.8±111.8 L in females, 90.74±15.25 L/h and 106.0±36.38 L in males, respectively. The terminal half-life was 1.198±0.801 h in females and 0.816±0.281 h in males.

Reviewer's comment: PK parameters are comparable between males and females.

Netupitant

C_{max} and AUC_{0-inf} were 922.4±167.6 µg/L and 14216±2831 h*µg/L in females, 793.5±161.1 µg/L and 13643±3083 h*µg/L in males, respectively.

The terminal half-life was 34.86±6.652 h in females, and 36.74±6.987 h in males.

Reviewer's comment: C_{max} in males was ~14% lower than females while the AUC was comparable.

Netupitant metabolites

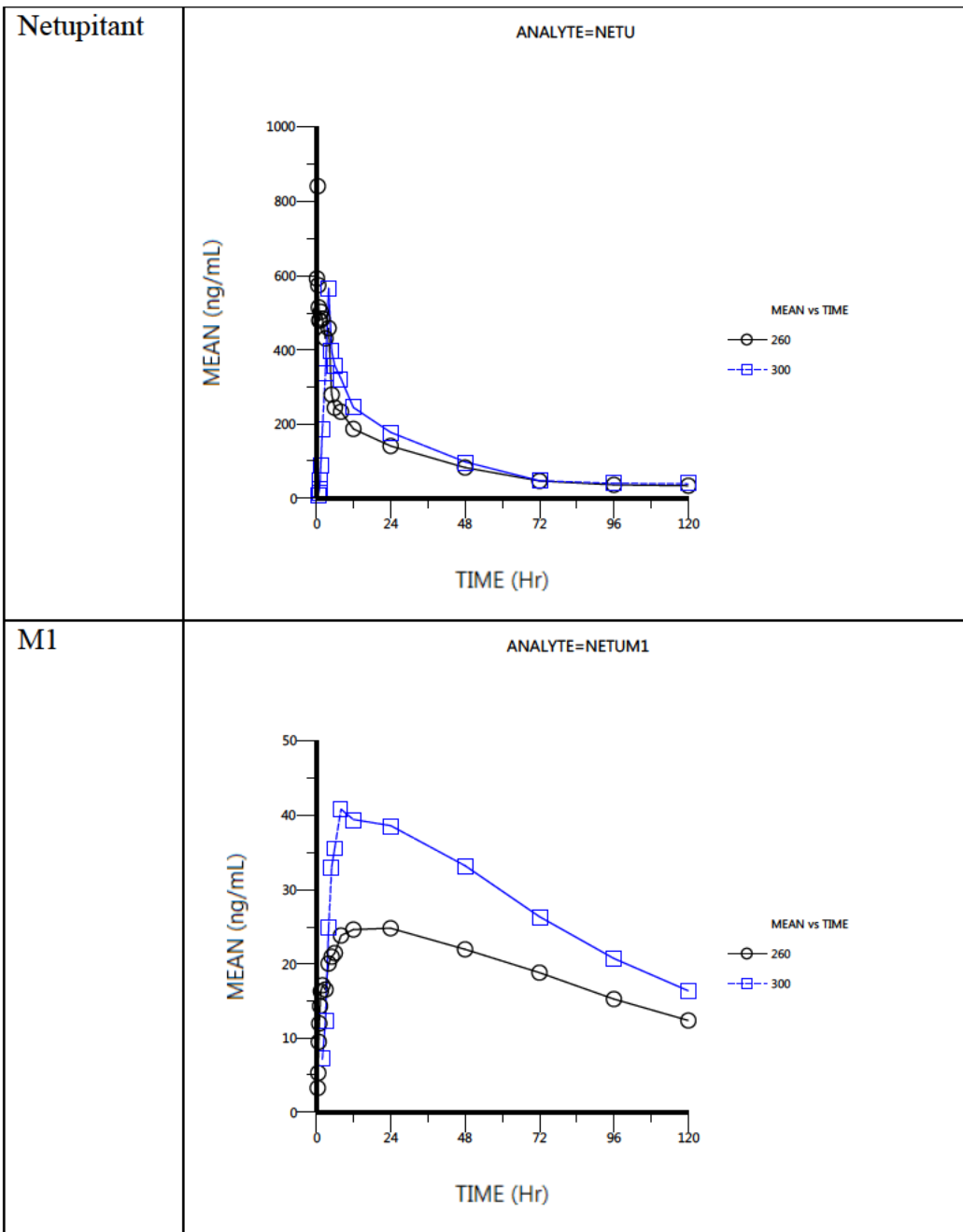
C_{max} of M1, M2, and M3 averaged 28.91±4.337 µg/L, 186.3±56.12 µg/L and 60.48±12.64 µg/L in females, 24.51±4.048 µg/L, 163.8±89.67 µg/L and 50.33±10.27 µg/L in males, respectively.

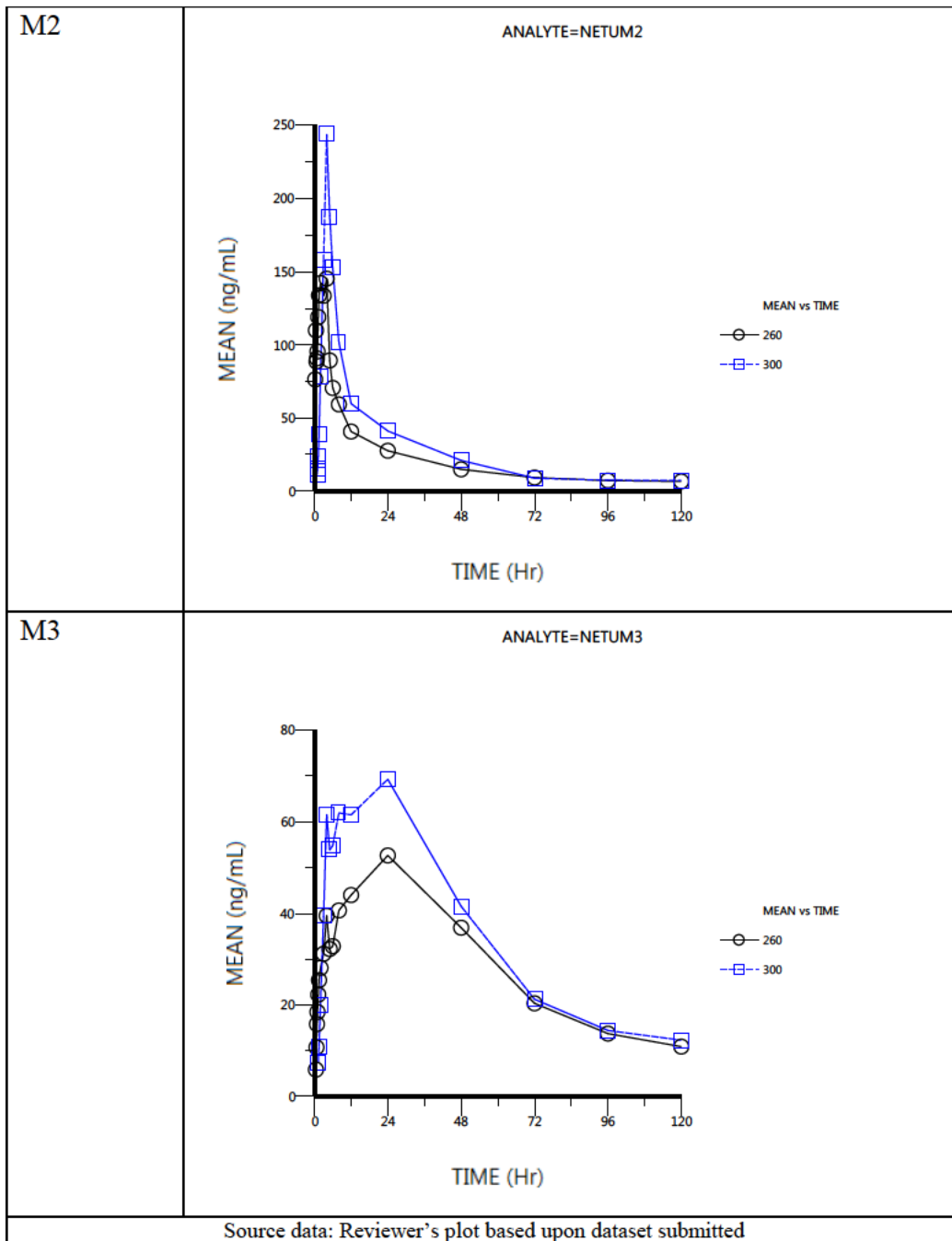
AUC_{0-inf} of M1, M2, and M3 averaged 3802±643.3 h*µg/L, 2920±1183 h*µg/L and 4878±1064 h*µg/L in females, 4226±2043 h*µg/L, 2944±1624 h*µg/L and 3986±1149 h*µg/L in males, respectively.

Terminal half-lives of M1, M2 and M3 were 77.78±21.56 h, 31.75±9.975 h and 58.89±31.65 h in females, 96.03±56.86 h, 38.61±30.25 h and 40.62±12.12 h in males.

Bioequivalence analysis for netupitant, M1, M2, and M3

The mean concentration-time profiles of netupitant, M1, M2, and M3 following 260 mg fosnetupitant IV or 300 mg oral Akynzeo were shown in the figure below.





Bioequivalence analysis for the systemic exposure to netupitant is shown below.

Table 23. Bioequivalence assessment of 260 mg IV fosnetupitant (Test) vs. 300mg oral netupitant (Reference) based on netupitant PK parameters

NETUPITANT				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	11876 (n=30)	0.94	0.88 - 1.01
	Oral netupitant (Ref)	12621 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	11876 (n=30)	0.94	0.88 - 1.01
	Oral netupitant (Ref)	12621 (n=30)		
AUC _{0-inf} (ng*h/mL)	IV fosnetupitant (Test)	13290 (n=26)	0.88	0.82 - 0.94
	Oral netupitant (Ref)	15073 (n=21)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	825.2 (n=30)	1.51	1.33 - 1.73
	Oral netupitant (Ref)	544.8 (n=30)		

n = number of subjects

Source data: Response to IR (SDN13, 22) Table 1

Bioequivalence analysis for the systemic exposure to the metabolite M1 is shown below.

Table 24. Comparative exposure to netupitant metabolite M1 following administration of 260mg IV fosnetupitant (Test) vs. 300mg oral netupitant (Reference)

Metabolite M1				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	2325 (n=30)	0.71	0.67 - 0.75
	Oral netupitant (Ref)	3293 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	2325 (n=30)	0.71	0.67 - 0.75
	Oral netupitant (Ref)	3293 (n=30)		
AUC _{0-inf} (ng*h/mL)	IV fosnetupitant (Test)	2931 (n=2)	NE	NE
	Oral netupitant (Ref)	3267 (n=1)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	26.1 (n=30)	0.61	0.58 - 0.65
	Oral netupitant (Ref)	42.4 (n=30)		

n = number of subjects; NE = not-evaluated

Source data: Response to IR (SDN13, 22) Table 2

Table 25. Comparative exposure to netupitant metabolite M2 following administration of 260mg IV fosnetupitant (Test) vs. 300mg oral netupitant (Reference)

Metabolite M2				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	2295 (n=30)	0.76	0.70 - 0.82
	Oral netupitant (Ref)	3034 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	2402 (n=28)	0.75	0.69 - 0.81
	Oral netupitant (Ref)	3219 (n=27)		
AUC _{0-∞} (ng*h/mL)	IV fosnetupitant (Test)	2567 (n=28)	0.77	0.71 - 0.84
	Oral netupitant (Ref)	3330 (n=28)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	155.3 (n=30)	0.66	0.57 - 0.76
	Oral netupitant (Ref)	235.5 (n=30)		

n = number of subjects

Source data: Response to IR (SDN13, 22) Table 3

Table 26. Comparative exposure to netupitant metabolite M3 following administration of 260mg IV fosnetupitant (Test) vs. 300mg oral netupitant (Reference)

Metabolite M3				
Parameter	Treatment	LSM, antilog	T/R Ratio	90% CI (lower - upper limits)
AUC _{0-tlast} (ng*h/mL)	IV fosnetupitant (Test)	3389 (n=30)	0.84	0.80 - 0.89
	Oral netupitant (Ref)	4028 (n=30)		
AUC _{0-120h} (ng*h/mL)	IV fosnetupitant (Test)	3389 (n=30)	0.84	0.80 - 0.89
	Oral netupitant (Ref)	4028 (n=30)		
AUC _{0-∞} (ng*h/mL)	IV fosnetupitant (Test)	3790 (n=22)	0.86	0.78 - 0.95
	Oral netupitant (Ref)	4417 (n=15)		
C _{max} (ng/mL)	IV fosnetupitant (Test)	53.0 (n=30)	0.75	0.70 - 0.80
	Oral netupitant (Ref)	70.8 (n=30)		

n = number of subjects

Source data: Response to IR (SDN13, 22) Table 4

4.2.2. PK of IV Akynzeo in cancer patients: NEPA-15-19

Title: A Phase 1, open label study to evaluate the pharmacokinetic profile and safety of IV pronetupitant*/palonosetron (260 mg/0.25 mg) fixed-dose combination administered for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving a single cycle of highly emetogenic chemotherapy (* “Pronetupitant” is the new INN “fosnetupitant”)

Study Design: Open label, multicenter study for evaluation of PK profile of a single IV administration of fosnetupitant/ palonosetron (260 mg/0.25 mg) fixed-dose combination (IV NEPA FDC) infused in 30 minutes, in association with oral dexamethasone administered prior to HEC.

Treatment product: IV fosnetupitant 260 mg/palonosetron 0.25 mg fixed-dose combination for infusion. Batch number 238021-01.

PK sampling: Blood samples for the determination of fosnetupitant, netupitant and its metabolites (M1, M2 and M3), and palonosetron concentrations were collected at predose, 30 min (tend), 45 min, 1h, 2h, 3h, 4h, 5h, 6h, 12h, 24h, 48h, 72h, 96h, 144h and 192h after the start of the IV NEPA FDC infusion.

Results:

Demography

For all patients were administered cisplatin, a HEC agent.

Parameter	Statistic	Safety population (N = 36)	PK population (N=24)
Age (years)			
Overall	n	36	24
	Nmiss	0	0
	Arithmetic mean	59.97	61.96
	Std Dev	10.76	9.15
	Minimum	26	42
	Median	61	61
	Maximum	76	76
Gender			
Total	n(%)	36 (100%)	24 (100%)
Female	n(%)	19 (52.78%)	13 (54.17%)
Male	n(%)	17 (47.22%)	11 (45.83%)
Race			
Total	n(%)	36 (100%)	24 (100%)
American Indian Or Alaska Native	n(%)	0 (0%)	0 (0%)
Asian	n(%)	0 (0%)	0 (0%)

Parameter	Statistic	Safety population (N = 36)	PK population (N=24)
Black Or African American	n(%)	0 (0%)	0 (0%)
Native Hawaiian Or Other Pacific Islander	n(%)	0 (0%)	0 (0%)
Other	n(%)	0 (0%)	0 (0%)
White	n(%)	36 (100%)	24 (100%)
Height (cm)			
Overall	n	36	24
	Nmiss	0	0
	Arithmetic mean	166.56	164.71
	Std Dev	10.06	8.98
	Minimum	149.00	149.00
	Median	167.50	164.50
	Maximum	186.00	183.00
Female	n	19	13
	Nmiss	0	0
	Arithmetic mean	159.68	158.92
	Std Dev	6.31	6.32
	Minimum	149.00	149.00
	Median	159.00	158.00
	Maximum	170.00	170.00
Male	n	17	11
	Nmiss	0	0
	Arithmetic mean	174.24	171.55
	Std Dev	7.61	6.53
	Minimum	160.00	160.00
	Median	173.00	173.00
	Maximum	186.00	183.00
Weight (kg)			
Overall	n	36	24
	Nmiss	0	0
	Arithmetic mean	74.94	75.88
	Std Dev	14.20	14.59
	Minimum	48.00	48.00
	Median	73.50	71.50
	Maximum	118.00	118.00
Female	n	19	13
	Nmiss	0	0
	Arithmetic mean	71.47	73.54

Parameter	Statistic	Safety population (N = 36)	PK population (N=24)
	Std Dev	13.64	12.39
	Minimum	48.00	48.00
	Median	73.00	80.00
	Maximum	91.00	90.00
Male	n	17	11
	Nmiss	0	0
	Arithmetic mean	78.82	78.64
	Std Dev	14.20	17.02
	Minimum	62.00	62.00
	Median	74.00	71.00
	Maximum	118.00	118.00
BMI (kg/m²)			
Overall	n	36	24
	Nmiss	0	0
	Arithmetic mean	27.02	27.96
	Std Dev	4.71	4.86
	Minimum	19.66	20.50
	Median	26.96	27.19
	Maximum	38.97	38.97
BSA (m²)			
Overall	n	36	24
	Nmiss	0	0
	Arithmetic mean	1.86	1.86
	Std Dev	0.21	0.20
	Minimum	1.42	1.43
	Median	1.86	1.83
	Maximum	2.39	2.39
Childbearing Potential			
Total	n(%)	19 (100%)	13 (100%)
No	n(%)	18 (94.74%)	12 (92.31%)
Yes	n(%)	1 (5.26%)	1 (7.69%)

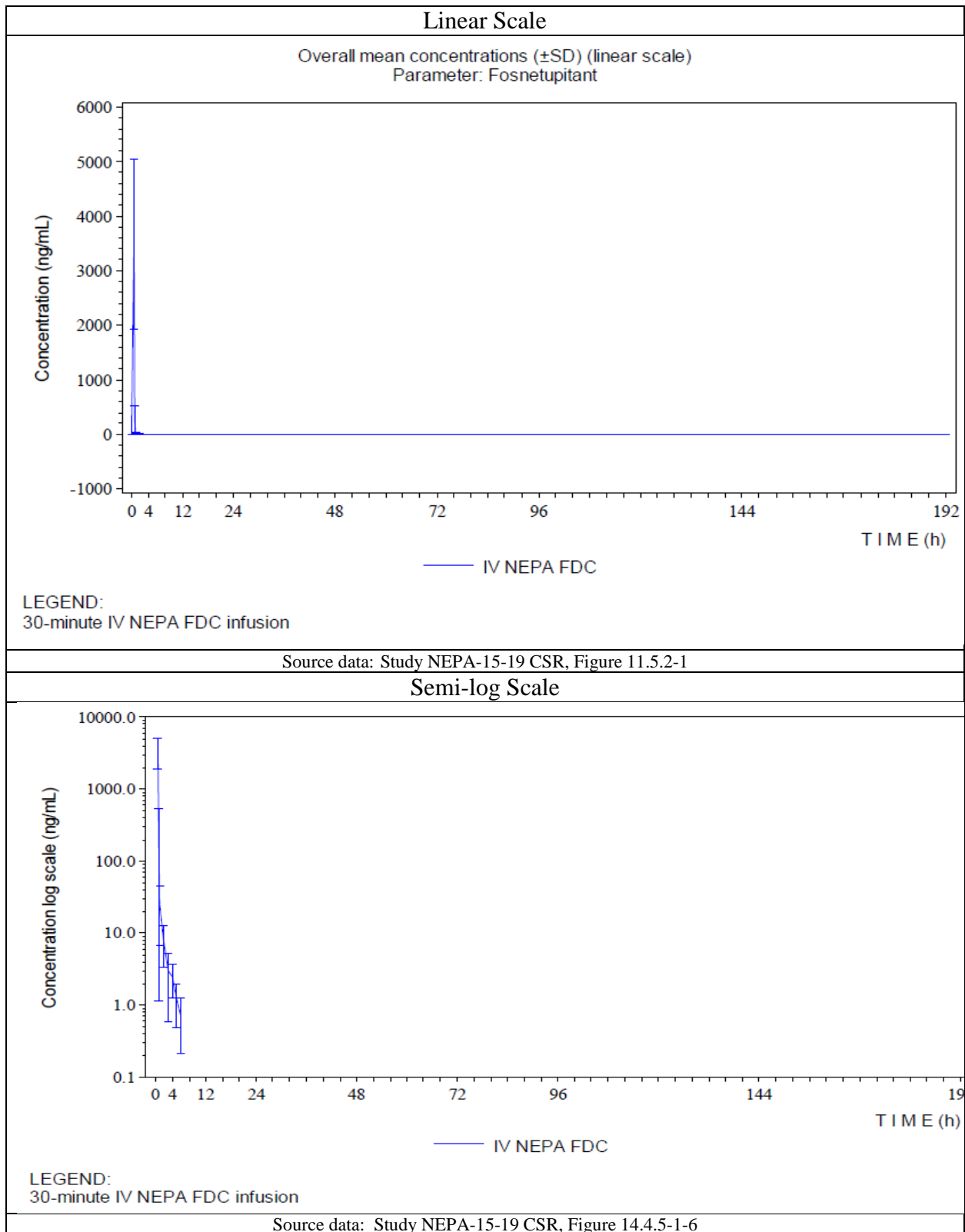
Source: Table 14.1.4-1; Table 14.1.4-2

N – Number of patients; Nmiss – Number of patients with missing observations;
Std Dev – Standard Deviation; n – Number of patients in the category

Summary of PK Parameters - Fosnetupitant

The mean concentration-time profile of fosnetupitant is shown below.

Figure 14. Mean (SD) of fosnetupitant plasma concentration - time profiles



Descriptive summary of fosnetupitant PK parameters following IV Akynzeo is shown below.

Table 27. Summary of plasma fosnetupitant pharmacokinetic parameters

Summary Statistics (N = 24)	n	AUC ₀₋₂₄ (ng.h/mL)	AUC _∞ (ng.h/mL)	%AUC _{extrap}	C _{max} (ng/mL)	t _{max} (h)	λ _z (1/h)	t _{1/2} (h)	MRT (h)	CL (L/h)	V _d (L)	V _{ss} (L)	C _{end} (ng/mL)	C _{last} (ng/mL)	t _{last} (h)
Arithmetic Mean	24	1398.39	1400.98	0.54	3478.33	0.55	1.255195	0.75	0.6	249.08	295.79	169.98	3478.33	3.48	3.13
Std Dev		634.91	649.04	1.31	1558.23	0.03	0.725563	0.4	0.09	269.74	534.58	271.7	1558.23	1.18	1.12
Minimum		156.41	167.26	0.05	340	0.52	0.39194	0.25	0.54	91.04	55	57.74	340	2.09	2
Median		1395.65	1385.82	0.21	3480	0.53	0.95249	0.73	0.57	169.57	178.43	97.84	3480	3.33	3
Maximum		2578.13	2581.19	6.48	6400	0.62	2.7979	1.77	0.99	1405.04	2706.65	1390.33	6400	6.2	6
Geometric Mean		1215.53	1213.75	0.25	3017.71	0.55	1.073247	0.65	0.6	193.61	180.4	115.82	3017.71	3.31	2.95
CV (%)		45.4	46.33	243.41	44.8	4.67	57.80	53.5	15.34	108.3	180.73	159.84	44.8	33.98	35.7

Source Table 14.2.1.7: Analysis dataset: ADPP.SAS7BDAT
 Std Dev - Standard Deviation; CV - Coefficient of Variation; N - Number of patients; n - Number of patients in the category

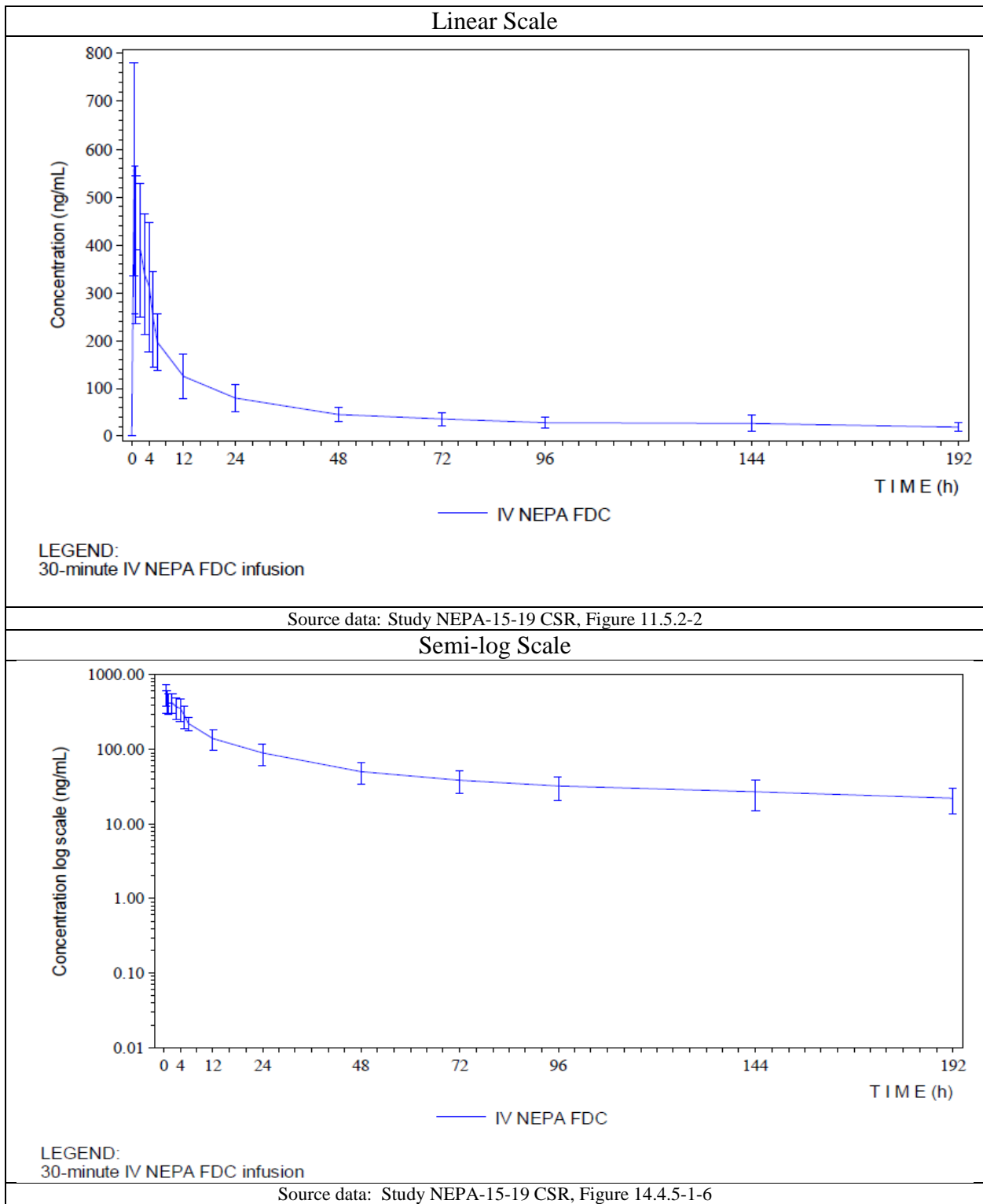
Source data: Study NEPA-15-19 CSR, In-text Table 11.5.2-1

Summary of PK Parameters - Netupitant

The mean concentration-time profile of netupitant is shown below.

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Figure 15. Mean (SD) of netupitant plasma concentration - time profiles



Descriptive summary of netupitant PK parameters following IV Akynzeo is shown below.

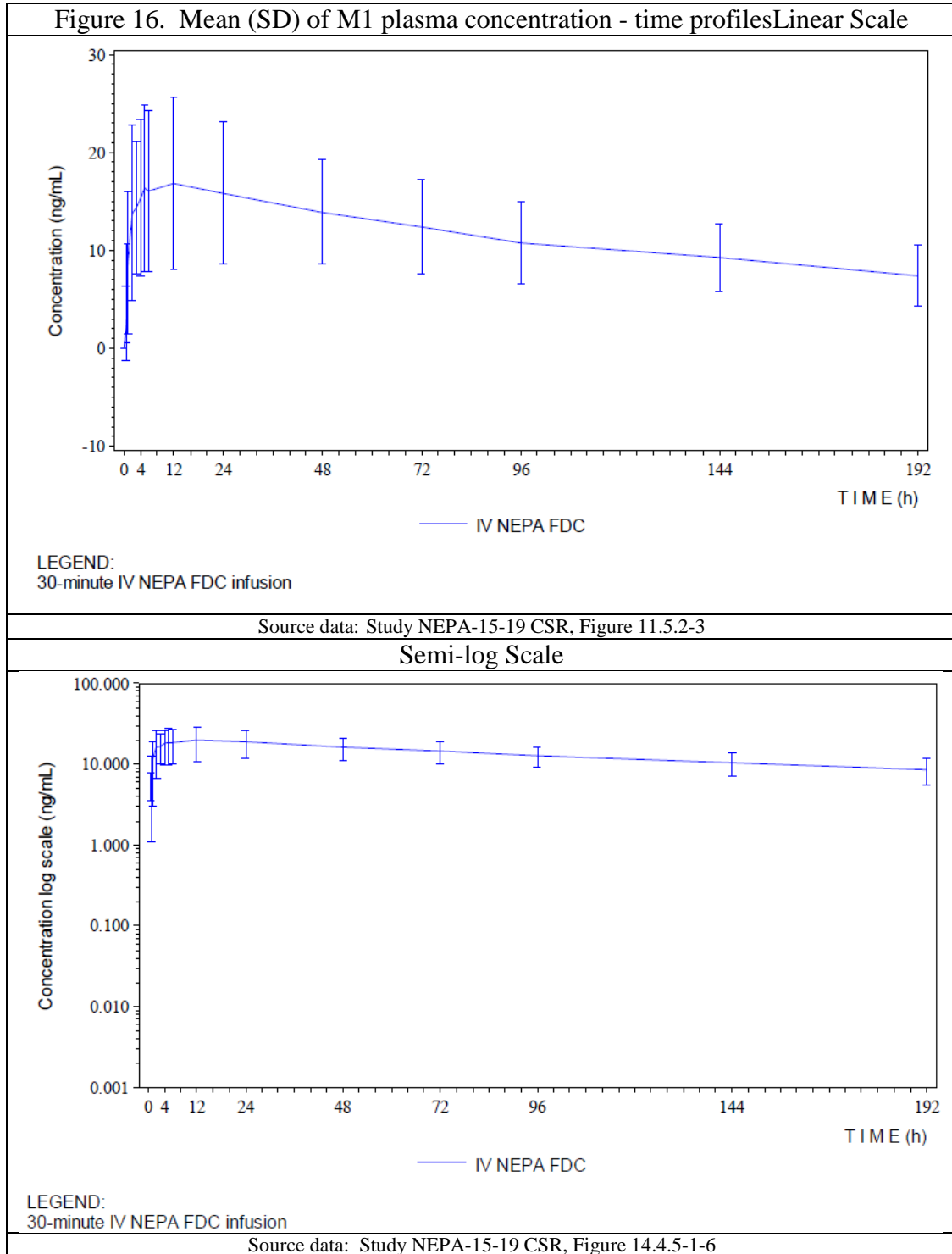
Table 28. Summary of netupitant pharmacokinetic parameters

Summary Statistics (N = 24)	AUC _{last} (ng.h/mL)	AUC _∞ (ng.h/mL)	%AUC _{extrap}	C _{max} (ng/mL)	t _{max} (h)	λ _z (1/h)	t _{1/2} (h)	MRT (h)	RAUC _{net/pnet}	C _{end} (ng/mL)	C _{last} (ng/mL)	t _{last} (h)
n	24	24	24	24	24	24	24	24	23	24	24	24
Arithmetic Mean	10724.07	15588.49	27.93	589.54	1.05	0.005885	143.73	162.59	17.26	562.13	21.15	191.96
Std Dev	2491.42	5022.77	14.55	164.91	1.03	0.002617	72.57	97.75	11.82	181.4	9.12	0.19
Minimum	5934.3	6150.79	3.52	310	0.52	0.0018	57.27	40.81	4.75	274	2.62	191.08
Median	10563.92	15578.92	28.19	556.5	0.56	0.005095	136.05	147.39	14.05	512	19.85	192
Maximum	15494.75	26238.86	63.09	977	4	0.0121	385.55	493.39	47.98	977	38.6	192
Geometric Mean	10428.6	14796.61	23.73	568.41	0.8	0.005348	129.61	140.4	14.37	534.73	18.78	191.96
CV (%)	23.23	32.22	52.07	27.97	97.81	44.47	50.49	60.12	68.51	32.27	43.14	0.1

Source: Table 14.2.1.8; Analysis dataset: ADPP.SAS7BDAT
 Std Dev - Standard Deviation; CV - Coefficient of Variation; N - Number of patients; n - Number of patients in the category

Source data: Study NEPA-15-19 CSR, Table 11.5.2-2

Summary of PK Parameters – Metabolite M1 The mean concentration-time profile of M1 is shown below.



Descriptive summary of M1 PK parameters following IV Akynzeo is shown below.

Table 29. Summary of plasma metabolite M1 pharmacokinetic parameters

Summary Statistics (N = 24)	AUC _{last} (ng.h/mL)	AUC _∞ (ng.h/mL)	%AUC _{extrap}	C _{max} (ng/mL)	t _{max} (h)	λ _z (1/h)	t _{1/2} (h)	MRT (h)	RAUC _{M1/net}	C _{end} (ng/mL)	C _{last} (ng/mL)	t _{last} (h)
n	24	22	22	24	24	22	22	22	22	24	24	24
Arithmetic Mean	2566.78	4730.18	39.62	23.31	28.14	0.00558	159.54	229.58	0.32	3.63	8.39	190
Std Dev	726.9	1900.19	15.81	9.26	46.56	0.003551	72.62	102.4	0.07	4.22	3.25	9.8
Minimum	1249.77	1737.71	6.77	7.53	2	0.00217	37.42	52.4	0.23	0	2.18	144
Median	2475.95	4186.72	41.07	22.6	12	0.004585	152.11	217.93	0.28	2.58	7.59	192
Maximum	4596.11	10283.09	63.72	48.4	192	0.01852	318.76	445.49	0.46	15.7	17.8	192
Geometric Mean	2475.13	4398.06	35.63	21.58	11.97	0.004858	142.66	206.13	0.31	4.42	7.77	189.71
CV (%)	28.32	40.17	39.91	39.74	165.5	63.64	45.52	44.6	22.72	116.13	38.8	5.16

Source: Table 14.2.1.9; Analysis dataset: ADPP.SAS7BDAT

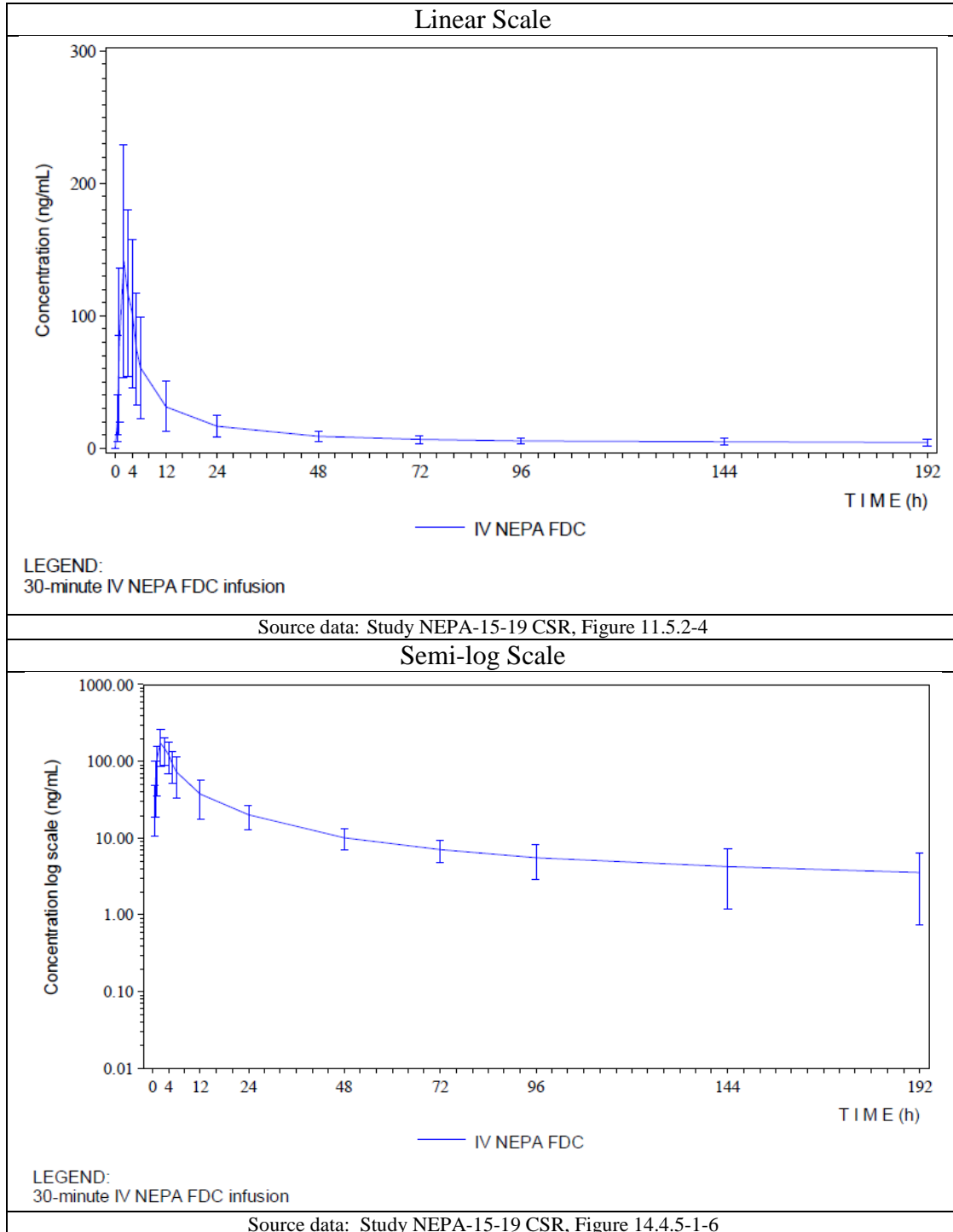
Std Dev - Standard Deviation; CV - Coefficient of Variation; N - Number of patients; n - Number of patients in the category

Source data: Study NEPA-15-19 CSR, Table 11.5.2-3

Summary of PK Parameters – Metabolite M2

The mean concentration-time profile of M2 is shown below.

Figure 17. Mean (SD) of M2 plasma concentration - time profiles



Descriptive summary of M2 PK parameters following IV Akynzeo is shown below.

Table 30. Summary of plasma M2 pharmacokinetic parameters

Summary Statistics (N = 24)	n	AUC _{last} (ng.h/mL)	AUC _∞ (ng.h/mL)	%AUC _{extrap}	C _{max} (ng/mL)	t _{max} (h)	λ _z (1/h)	t _{1/2} (h)	MRT (h)	RAUC M2/net	C _{end} (ng/mL)	C _{last} (ng/mL)	t _{last} (h)
Arithmetic Mean	24	2461.4	3407.5	22.79	178.74	2.38	0.008965	136.4	139.16	0.21	29.19	4.06	173
Std Dev		902.54	1688.69	16.46	84.52	0.58	0.007712	107.06	120.37	0.06	18.62	2.3	39.39
Minimum		1281.55	1539.78	5.44	61	2	0.00175	19.97	20.54	0.09	9.02	2.14	72
Median		2490.68	2974.18	16.73	152.5	2	0.007515	92.26	75.85	0.21	24.4	3.08	192
Maximum		4654.87	7897.86	51.49	379	4	0.03471	397.03	398.93	0.34	79.9	10.5	192
Geometric Mean		2311.33	3069.76	17.58	161.44	2.32	0.006719	103.16	98.61	0.2	24.45	3.63	167
CV (%)		36.67	49.56	72.19	47.28	24.38	86.02	78.49	86.5	29.58	63.79	56.61	22.77

Source: Table 14.2.1.10; Analysis dataset: ADPP.SAS7BDAT

Std Dev - Standard Deviation; CV - Coefficient of Variation; N - Number of patients; n - Number of patients in the category

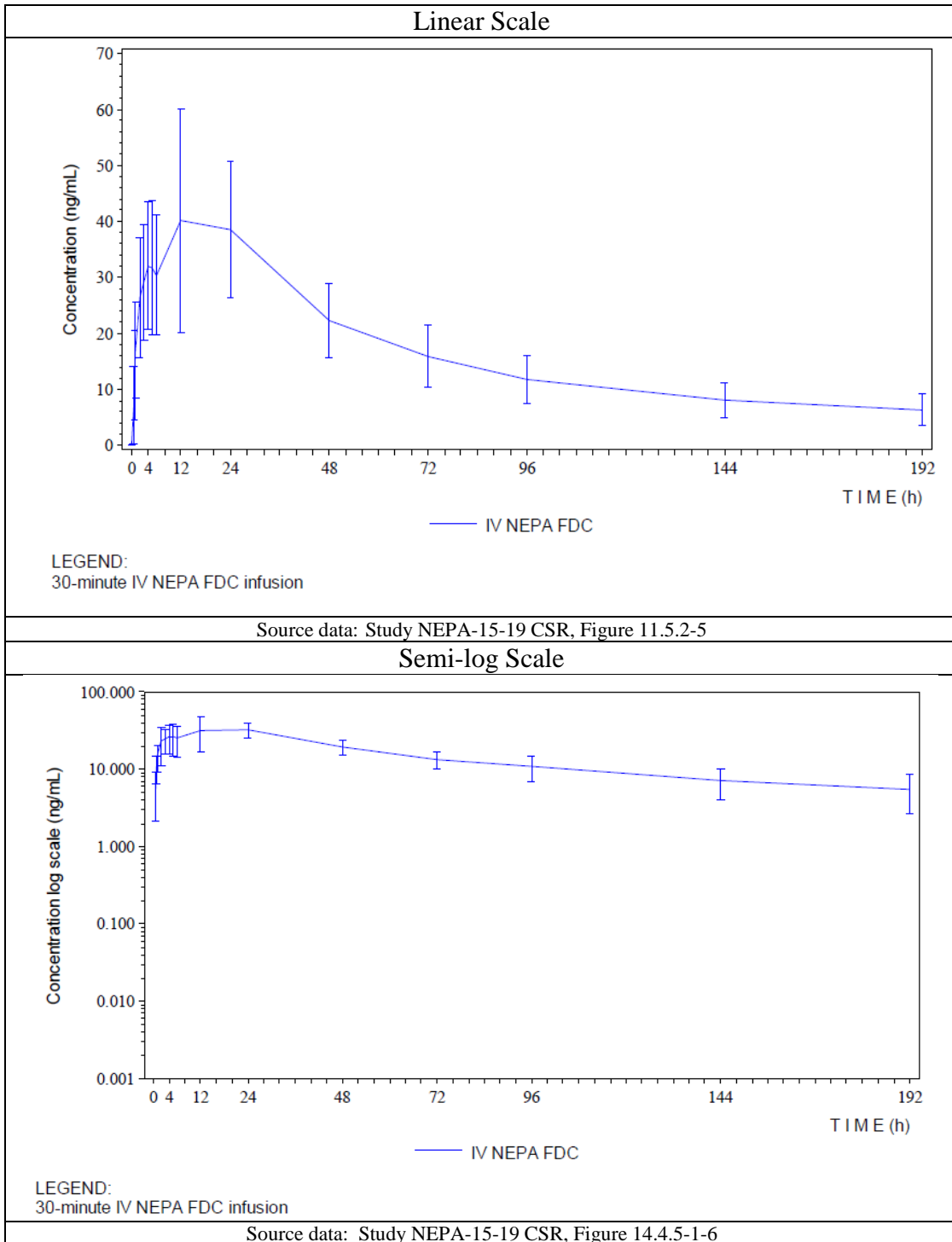
Source data: Study NEPA-15-19 CSR, Table 11.5.2-4

Summary of PK Parameters – Metabolite M3

The mean concentration-time profile of M3 is shown below.

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Figure 18. Mean (SD) of M3 plasma concentration - time profiles



Descriptive summary of M3 PK parameters following IV Akynzeo is shown below.

Table 31. Summary of plasma M3 pharmacokinetic parameters

Summary Statistics (N = 24)	AUC _{last} (ng.h/mL)	AUC _∞ (ng.h/mL)	%AUC _{extrap}	C _{max} (ng/mL)	t _{max} (h)	λ _z (1/h)	t _{1/2} (h)	MRT (h)	RAUC _{M3/net}	C _{end} (ng/mL)	C _{last} (ng/mL)	t _{last} (h)
n	24	24	24	24	24	24	24	24	24	24	24	24
Arithmetic Mean	3172.11	4298.02	23.99	46.49	14.67	0.007659	111.4	141.8	0.28	7.14	6.23	190
Std Dev	782.11	1174.28	15.08	16.86	8.66	0.003458	54.13	79.79	0.08	6.9	2.76	9.8
Minimum	1582.28	2569.59	6.35	14.7	2	0.00265	48.12	64.88	0.17	0	2.3	144
Median	3179.02	4211.14	20.92	43.05	12	0.00709	97.87	121.35	0.27	6.05	5.71	192
Maximum	5056.55	6453.79	63.58	94.8	24.1	0.01441	261.59	393.03	0.49	32.6	12.2	192
Geometric Mean	3079.13	4144.75	19.71	43.56	11.48	0.006919	100.17	125.07	0.27	6.57	5.65	189.71
CV (%)	24.66	27.32	62.83	36.27	59.01	45.15	48.59	56.27	27.96	96.73	44.36	5.16

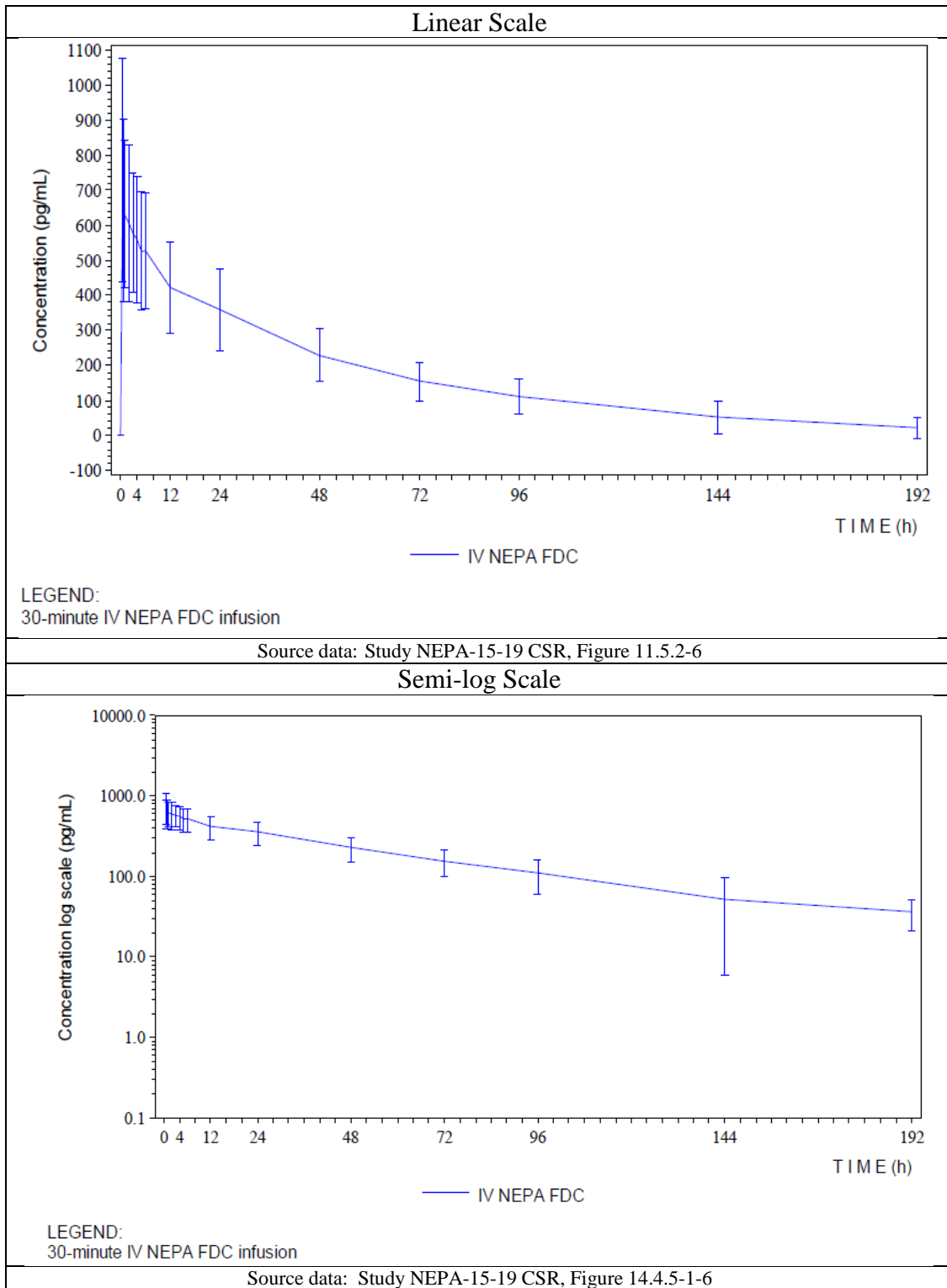
Source Table 14.2.1.11; Analysis dataset: ADPP.SAS7BDAT
 Std Dev - Standard Deviation; CV - Coefficient of Variation; N - Number of Variation; n - Number of patients in the category

Source data: Study NEPA-15-19 CSR, Table 11.5.2-5

Summary of PK Parameters – Palonosetron

The mean concentration-time profile of M3 is shown below.

Figure 19. Mean (SD) of palonosetron plasma concentration - time profiles



Descriptive summary of palonosetron PK parameters following IV Akynzeo is shown below.

Table 32. Summary of plasma palonosetron pharmacokinetic parameters

Summary Statistics (N = 24)	AUC _{last} (pg.h/mL)	AUC _∞ (pg.h/mL)	%AUC _{extrap}	C _{max} (pg/mL)	t _{max} (h)	λ _z (1/h)	t _{1/2} (h)	MRT (h)	CL (L/h)	V _d (L)	V _{ss} (L)	C _{end} (pg/mL)	C _{last} (pg/mL)	t _{last} (h)
n	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Arithmetic Mean	30177.39	36066.22	16.58	823	1.31	0.014347	58.42	77.2	7.61	593.89	545.94	756.42	70.99	140
Std Dev	9798.27	10726.79	6.72	288.69	1.39	0.006215	27.2	34.1	2.59	238.81	206.35	318.86	16.97	44.01
Minimum	14546.07	16416.18	7.12	471	0.52	0.00509	24.05	32.92	4.38	238.45	233.4	288	50.3	72
Median	29119.59	33957.79	15.59	748	0.58	0.01293	53.61	71.09	7.36	552.61	534.43	712	66.75	144
Maximum	53068.4	57133.62	33.18	1600	6	0.02882	136.08	175.3	15.23	1427.62	1274.78	1600	101	192
Geometric Mean	28670.72	34480.98	15.34	780.29	0.92	0.013075	53.01	70.81	7.25	554.51	513.39	696.03	69.15	132.91
CV (%)	32.47	29.74	40.51	35.08	106.34	43.32	46.56	44.17	33.96	40.21	37.8	42.15	23.9	31.43

Source: Table 14.2.1.12; Analysis dataset: ADPP.SAS7BDAT
 Std Dev - Standard Deviation; CV - Coefficient of Variation; N - Number of patients; n - Number of patients in the category

Source data: Study NEPA-15-19 CSR, Table 11.5.2-6

Sex effect

Reviewer's comment: The study is not powered to evaluate effect of sex on PK of fosnetupitant. The data are exploratory in nature.

Mean (SD) C_{max} values were 3154.55 (1402.46) ng/mL in males and 3752.31 (1684.43) ng/mL in females, whereas mean (SD) AUC_∞ values were 1246.95 (612.00) h*ng/mL in males and 1519.47 (675.57) h*ng/mL in females. The systemic clearance was similar between genders with values of 233.17 (114.3) L/h in males and 261.32 (351.03) L/h in females. The mean (SD) apparent terminal half-life was slightly shorter in males [0.57 (0.29) h] than in females [0.89 (0.43) h] likely due to inter-patient variability, which may also explain differences in the volume of distribution [mean V_{ss} (SD) was 133.51 (64.22) L in males and 198.04 (360.94) L in females].

Netupitant PK after IV fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination administration was similar in males and females. Mean (SD) C_{max} values were 567.09 (174.25) ng/mL in males and 608.54 (161.16) ng/mL in females, whereas mean (SD) AUC_∞ values were 15672.01 (5495.62) h*ng/mL in males and 15517.83 (4813.95) h*ng/mL in females. The apparent terminal half-life was 147.18 (96.64) h in males and 140.80 (47.88) h in females.

4.2.3. In vivo drug interaction study : PNET-13-63

Title: Evaluation of pharmacokinetic interaction between three doses of intravenous pro-netupitant and oral dexamethasone regimen: a randomized three period crossover study in healthy male and female volunteers

Study Design: This was a 3-period, 4-treatment, open-label, crossover study to evaluate the effect of single dose of IV fosnetupitant on the PK of oral dexamethasone given for 4 days. Each treatment period consists of 7 days and separated by a wash-out phase of at 28 days.

	Period 1	Period 2	Period 3
Sequence 1	A	B	C
Sequence 2	B	D	A
Sequence 3	C	A	D

A: oral dexamethasone plus 5% glucose solution infusion
B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)
C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)
D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)

Treatment groups:

Dexamethasone: 20 mg PO x1 on day 1 → 8 mg PO BID on Days 2, 3, and 4.

Fosnetupitant: 130 mg, 195 mg, 260 mg single dose on Day 1.

Treatment	Study drug	Mode of administration	Dose per treatment day	Duration of treatment	Number of tablets per day (Posology*) or Volume for infusion (Duration of infusion)	Total Dose
A	Dexamethasone	Oral	Day 1: 20 mg Days 2, 3, and 4: 16 mg/day (8 mg b.i.d.)	4 days	Day 1: 5 tablets (5-0-0) Days 2, 3, and 4: 4 tablets/day (2-0-2)	68 mg
	Placebo	IV infusion	Placebo on Day 1	1 day	50 mL (30 min)	-
B	Dexamethasone	Oral	Day 1: 20 mg Days 2, 3, and 4: 16 mg/day (8 mg b.i.d.)	4 days	Day 1: 5 tablets (5-0-0) Days 2, 3, and 4: 4 tablets/day (2-0-2)	68 mg
	Pro-netupitant	IV infusion	130 mg on Day 1	1 day	50 mL (30 min)	130 mg
C	Dexamethasone	Oral	Day 1: 20 mg Days 2, 3, and 4: 16 mg/day (8 mg b.i.d.)	4 days	Day 1: 5 tablets (5-0-0) Days 2, 3, and 4: 4 tablets/day (2-0-2)	68 mg
	Pro-netupitant	IV infusion	195 mg on Day 1	1 day	50 mL (30 min)	195 mg
D	Dexamethasone	Oral	Day 1: 20 mg Days 2, 3, and 4: 16 mg/day (8 mg b.i.d.)	4 days	Day 1: 5 tablets (5-0-0) Days 2, 3, and 4: 4 tablets/day (2-0-2)	68 mg
	Pro-netupitant	IV infusion	260 mg on Day 1	1 day	50 mL (30 min)	260 mg

*: morning, noon, and evening doses

b.i.d.: twice a day, IV: intravenous

A: oral dexamethasone plus 5% glucose solution infusion

B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)

C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)

D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)

PK samples:

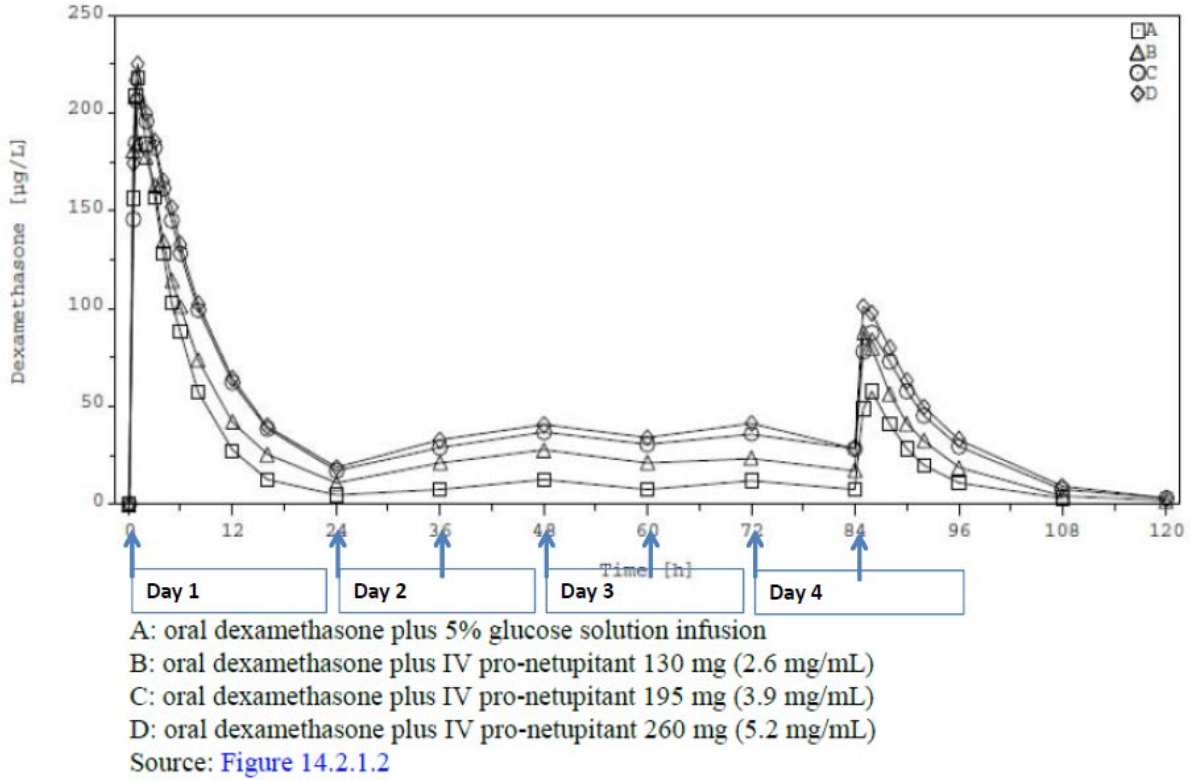
Dexamethasone: blood samples were taken at predose, 30 min, 45 min, then 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84, 85, 86, 88, 90, 92, 96, 108 and 120 hours after first administration (start of infusion) (applicable for all treatments).

fosnetupitant, netupitant and netupitant metabolites: blood samples were taken at pre-dose, 30 min, 45 min, then 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96 and 120 hours after start of infusion (not applicable for Treatment A).

Results

The dexamethasone concentration-time profiles following each dose were shown below.

Figure 20. Mean Dexamethasone Plasma Concentration - Time Profiles



Source data: Study NEPA-13-63 CSR, Table 11.1-1

Table 33. Summary of Plasma Dexamethasone Pharmacokinetic Parameters with co-administration of single dose of IV fosnetupitant – Day 1

Parameter	Statistics	Treatment			
		A Dexamethasone alone N=28	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC ₀₋₂₄ [h*µg/L] (equal to AUC _{0-t})	n	28	18	19	17
	Mean	1319.38	1556.37	1950.27	2037.26
	SD	413.09	422.29	585.68	451.31
	CV [%]	31.31	27.13	30.03	22.15
	Geo. mean	1256.95	1503.15	1870.39	1992.34
C _{max} [µg/L]	n	28	18	19	17
	Mean	250.59	258.71	255.12	256.63
	SD	84.55	59.92	61.53	62.66
	CV [%]	33.74	23.16	24.12	24.42
	Geo. mean	238.57	251.69	248.58	249.17
t _{max} [h]	n	28	18	19	17
	Min	0.50	0.50	0.50	0.50
	Median	1.00	0.75	1.00	1.00
	Max	2.00	3.00	3.00	2.00
C _{min} [µg/L]	n	28	18	19	17
	Mean	4.26	10.62	17.08	18.64
	SD	2.97	7.43	9.40	7.43
	CV [%]	69.60	69.93	55.01	39.85
	Geo. mean	3.47	8.90	14.92	17.36
t _{1/2} [h]	n	28	18	19	17
	Mean	3.68	5.63	6.16	6.37
	SD	0.79	1.18	0.82	0.94
	CV [%]	21.50	20.90	13.26	14.72
	Geo. mean	3.60	5.52	6.11	6.31

Data: number of subjects in the PK population (N); all parameters except t_{max}: number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t_{max}: number of subjects with data (n), minimum (min), median, and maximum (max)

A: oral dexamethasone plus 5% glucose solution infusion
B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)
C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)
D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)

Source: Table 14.2.1.3

Table 34. Summary of Plasma Dexamethasone Pharmacokinetic Parameters with co-administration of single dose of IV fosnetupitant – Day 4

Parameter	Statistics	Treatment			
		A Dexamethasone alone N=28	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC ₈₄₋₁₀₈ [h*µg/L]	n	28	18	18 [#]	17
	Mean	411.36	669.79	898.07	1013.46
	SD	175.63	219.19	367.30	314.67
	CV [%]	42.70	32.72	40.90	31.05
	Geo. mean	377.92	631.80	830.87	959.87
C _{max} [µg/L]	n	28	18	18 [#]	17
	Mean	63.64	93.92	97.73	111.17
	SD	17.42	24.97	38.44	27.48
	CV [%]	27.38	26.58	39.33	24.72
	Geo. mean	61.29	90.81	90.81	107.24
t _{max} [h]	n	28	18	18 [#]	17
	Min	1.00	1.00	1.00	0.97
	Median	2.00	1.00	2.00	1.00
	Max	4.00	6.00	4.00	4.00
C _{min} [µg/L]	n	28	18	18 [#]	17
	Mean	10.52	18.57	29.36	32.98
	SD	5.74	8.22	13.40	14.44
	CV [%]	54.53	44.26	45.62	43.80
	Geo. mean	9.05	16.66	26.46	30.18
t _{1/2} [h]	n	28	18	18	17
	Mean	4.22	4.92	6.14	6.07
	SD	0.97	1.17	0.95	0.97
	CV [%]	22.90	23.77	15.43	15.92
	Geo. mean	4.12	4.80	6.07	6.00
#: For Subject No. (b) (4) PK parameters for Day 4 were not calculated because all concentrations were BLLQ starting from 84 hours. Data: number of subjects in the PK population (N); all parameters except t_{max}: number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t_{max}: number of subjects with data (n), minimum (min), median, and maximum (max) A: oral dexamethasone plus 5% glucose solution infusion B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL) C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL) D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL) Source: Table 14.2.1.3					

Statistical analysis for the systemic exposure to dexamethasone is shown below.

Table 35. Effect of single IV doses of fosnetupitant on dexamethasone pharmacokinetics: Analysis of variance for dexamethasone parameters – Day 1

Dexamethasone Parameter	Ratio	Point estimate*	90% Confidence interval	
			Lower limit	Upper limit
AUC ₀₋₂₄ /D (equal to AUC _{0,t} /D)	B/A	126.55	118.80	134.81
	C/A	149.49	140.52	159.04
	D/A	150.10	140.60	160.25
C _{max} /D	B/A	110.86	100.03	122.87
	C/A	103.46	93.54	114.43
	D/A	96.92	87.15	107.78
C _{min} /D	B/A	275.83	232.62	327.08
	C/A	420.59	355.94	496.98
	D/A	517.75	434.10	617.52

ANOVA model with fixed factors for period and treatment and a random factor for subject.
 *Point estimate is the ratio of adjusted geometric means
 A: oral dexamethasone plus 5% glucose solution infusion
 B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)
 C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)
 D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)
 Source: [Table 14.2.1.5](#)

Source data: Study NEPA-13-63 CSR, Table 11.1-17

Table 36. Effect of single IV doses fosnetupitant on dexamethasone pharmacokinetics: Analysis of variance for dexamethasone parameters – Day 4

Dexamethasone Parameter	Ratio	Point estimate*	90% Confidence interval	
			Lower limit	Upper limit
AUC ₈₄₋₁₀₈ /D	B/A	172.86	151.16	197.68
	C/A	220.92	193.28	252.50
	D/A	241.54	210.25	277.48
AUC _{84-t} /D	B/A	176.98	154.23	203.10
	C/A	230.71	201.15	264.61
	D/A	254.19	220.47	293.06
C _{max} /D	B/A	140.33	122.16	161.20
	C/A	158.15	137.75	181.57
	D/A	170.25	147.53	196.46
C _{min} /D	B/A	199.86	170.51	234.26
	C/A	282.00	240.73	330.34
	D/A	323.00	274.08	380.65

ANOVA model with fixed factors for period and treatment and a random factor for subject.
 *Point estimate is the ratio of adjusted geometric means
 A: oral dexamethasone plus 5% glucose solution infusion
 B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL)
 C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL)
 D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL)
 Source: [Table 14.2.1.5](#)

Source data: Study NEPA-13-63 CSR, Table 11.1-18

Concentration data of fosnetupitant, netupitant, M1, M2, and M3 were also collected and the PK parameters of these four analytes were shown in the tables below.

Table 37. Summary of PK parameters of fosnetupitant following single dose of fosnetupitant IV infusion

Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC _{0-t} [h*µg/L]	n	18	19	17
	Mean	1516.12	2186.29	2851.65
	SD	295.60	418.29	662.30
	CV [%]	19.50	19.13	23.23
	Geo. mean	1488.39	2147.58	2772.72
AUC _{0-t} /D [h/kL]	n	18	19	17
	Mean	11.66	11.21	10.97
	SD	2.27	2.15	2.55
	CV [%]	19.50	19.13	23.23
	Geo. mean	11.45	11.01	10.66
AUC _{0-inf} [h*µg/L]	n	15 [#]	19	17
	Mean	1558.88	2189.70	2855.47
	SD	294.03	418.54	662.62
	CV [%]	18.86	19.11	23.21
	Geo. mean	1532.05	2150.98	2776.58
AUC _{0-inf} /D [h/kL]	n	15 [#]	19	17
	Mean	11.99	11.23	10.98
	SD	2.26	2.15	2.55
	CV [%]	18.86	19.11	23.21
	Geo. mean	11.79	11.03	10.68
C _{max} [µg/L]	n	18	19	17
	Mean	3862.84	5693.43	7366.61
	SD	1106.15	1093.85	1737.41
	CV [%]	28.64	19.21	23.58
	Geo. mean	3548.51	5590.67	7159.58
C _{max} /D [kL ⁻¹]	n	18	19	19
	Mean	29.71	29.20	28.33
	SD	8.51	5.61	6.68
	CV [%]	28.64	19.21	23.58
	Geo. mean	27.30	28.67	27.54
t _{max} [h]	n	18	19	17
	Min	0.50	0.50	0.50
	Median	0.50	0.50	0.50
	Max	0.75	0.50	0.50

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Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
$t_{1/2}$ [h]	n	15 [#]	19	17
	Mean	0.51	0.74	0.92
	SD	0.16	0.34	0.42
	CV [%]	31.47	46.77	45.08
	Geo. mean	0.49	0.66	0.84
CL [L/h]	n	15 [#]	19	17
	Mean	86.42	92.36	96.59
	SD	17.58	18.79	26.10
	CV [%]	20.34	20.34	27.02
	Geo. mean	84.85	90.66	93.64
V_z [L]	n	15 [#]	19	17
	Mean	62.89	96.55	127.32
	SD	19.89	44.66	58.54
	CV [%]	31.63	46.26	45.98
	Geo. mean	60.08	86.73	112.90
#: For 3 subjects, not all PK parameters could be provided because no reliable estimate of λ_z and $t_{1/2}$ could be determined. Data: number of subjects in the PK population (N); all parameters except t_{max}: number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t_{max}: number of subjects with data (n), minimum (min), median, and maximum (max) A: oral dexamethasone plus 5% glucose solution infusion B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL) C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL) D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL) Source: Table 14.2.2.3				

Table 38. Summary of PK parameters of netupitant following single dose of fosnetupitant IV infusion

Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC _{0-t} [h*µg/L]	n	18	19	17
	Mean	4793.61	8177.65	12305.61
	SD	1108.41	2047.93	3817.43
	CV [%]	23.12	25.04	31.02
	Geo. mean	4663.19	7944.08	11796.23
AUC _{0-t} /D [h/kL]	n	18	19	17
	Mean	47.94	54.52	61.53
	SD	11.08	13.65	19.09
	CV [%]	23.12	25.04	31.02
	Geo. mean	46.63	52.96	58.98
AUC _{0-inf} [h*µg/L]	n	18	19	17
	Mean	5295.59	9010.36	13600.41
	SD	1356.09	2324.50	4355.21
	CV [%]	25.61	25.80	32.02
	Geo. mean	5122.96	8732.39	12987.62
AUC _{0-inf} /D [h/kL]	n	18	19	17
	Mean	52.96	60.07	68.00
	SD	13.56	15.50	21.78
	CV [%]	25.61	25.80	32.02
	Geo. mean	51.23	58.22	64.94
C _{max} [µg/L]	n	18	19	17
	Mean	383.82	604.59	812.78
	SD	63.43	135.52	200.89
	CV [%]	16.53	22.42	24.72
	Geo. mean	378.82	589.72	786.65
C _{max} /D [kL ⁻¹]	n	18	19	17
	Mean	3.84	4.03	4.06
	SD	0.63	0.90	1.00
	CV [%]	16.53	22.42	24.72
	Geo. mean	3.79	3.93	3.93
t _{max} [h]	n	18	19	17
	Min	0.50	0.50	0.50
	Median	0.50	0.50	0.50
	Max	4.00	2.00	4.00

Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
$t_{1/2}$ [h]	n	18	19	17
	Mean	40.02	36.21	37.57
	SD	18.54	17.73	12.38
	CV [%]	46.32	48.96	32.94
	Geo. mean	36.44	33.11	35.66
Data: number of subjects in the PK population (N); all parameters except t_{max} : number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t_{max} : number of subjects with data (n), minimum (min), median, and maximum (max) A: oral dexamethasone plus 5% glucose solution infusion B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL) C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL) D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL) Source: Table 14.2.3.3				

Table 39. Summary of PK parameters of M1 following single dose of fosnetupitant IV infusion

Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC _{0-t} [h*µg/L]	n	18	19	17
	Mean	928.22	1538.47	2224.11
	SD	175.16	265.25	571.67
	CV [%]	18.87	17.24	25.70
	Geo. mean	913.00	1516.27	2166.97
AUC _{0-inf} [h*µg/L]	n	18	19	17
	Mean	1391.42	2622.85	3469.82
	SD	521.93	1039.91	1203.54
	CV [%]	37.51	39.65	34.69
	Geo. mean	1320.29	2468.14	3300.94
C _{max} [µg/L]	n	18	19	17
	Mean	13.95	21.75	29.16
	SD	3.13	4.60	8.30
	CV [%]	22.40	21.13	28.47
	Geo. mean	13.64	21.26	28.25
t _{max} [h]	n	18	19	17
	Min	4.00	3.00	2.00
	Median	8.00	8.00	12.00
	Max	35.92	23.92	35.92
t _{1/2} [h]	n	18	19	17
	Mean	69.26	92.08	74.86
	SD	35.33	55.34	37.13
	CV [%]	51.01	60.10	49.59
	Geo. mean	63.77	80.41	68.15
Data: number of subjects in the PK population (N); all parameters except t _{max} : number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t _{max} : number of subjects with data (n), minimum (min), median, and maximum (max) A: oral dexamethasone plus 5% glucose solution infusion B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL) C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL) D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL) Source: Table 14.2.4.3				

Table 40. Summary of PK parameters of M2 following single dose of fosnetupitant IV infusion

Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC _{0-t} [h*µg/L]	n	18	19	17
	Mean	600.84	1089.53	2002.61
	SD	232.94	379.52	909.13
	CV [%]	38.77	34.83	45.40
	Geo. mean	558.43	1027.09	1859.96
AUC _{0-inf} [h*µg/L]	n	18	19	17
	Mean	681.25	1229.60	2154.82
	SD	268.00	465.09	962.88
	CV [%]	39.34	37.82	44.68
	Geo. mean	634.30	1147.63	2007.57
C _{max} [µg/L]	n	18	19	17
	Mean	64.32	106.25	172.16
	SD	27.40	36.27	66.35
	CV [%]	42.60	34.14	38.54
	Geo. mean	58.14	99.63	161.11
t _{max} [h]	n	18	19	17
	Min	2.00	2.00	2.00
	Median	4.00	3.00	4.00
	Max	4.00	4.00	4.00
t _{1/2} [h]	n	18	19	17
	Mean	22.24	36.98	35.49
	SD	22.37	41.80	14.70
	CV [%]	100.56	113.02	41.43
	Geo. mean	16.70	24.69	32.83
Data: number of subjects in the PK population (N); all parameters except t _{max} : number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t _{max} : number of subjects with data (n), minimum (min), median, and maximum (max) B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL) C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL) D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL) Source: Table 14.2.5.3				

Table 41. Summary of PK parameters of M3 following single dose of fosnetupitant IV infusion

Parameter	Statistics	B 130 mg pro- netupitant N=18	C 195 mg pro- netupitant N=19	D 260 mg pro- netupitant N=17
AUC _{0-t} [h*µg/L]	n	18	19	17
	Mean	1421.69	2447.64	3675.40
	SD	496.74	640.59	1396.41
	CV [%]	34.94	26.17	37.99
	Geo. mean	1342.71	2357.58	3476.49
AUC _{0-inf} [h*µg/L]	n	18	19	17
	Mean	1586.39	2828.25	4231.51
	SD	551.39	784.38	1545.97
	CV [%]	34.76	27.73	36.53
	Geo. mean	1501.02	2711.16	4010.55
C _{max} [µg/L]	n	18	19	17
	Mean	32.48	52.16	69.73
	SD	11.88	17.21	20.09
	CV [%]	36.57	33.00	28.80
	Geo. mean	30.18	49.24	67.45
t _{max} [h]	n	18	19	17
	Min	4.00	4.00	4.00
	Median	16.00	16.00	23.92
	Max	23.92	23.92	23.95
t _{1/2} [h]	n	18	19	17
	Mean	33.38	42.27	42.42
	SD	9.16	14.47	25.54
	CV [%]	27.43	34.24	60.20
	Geo. mean	32.25	40.37	38.62
N Data: number of subjects in the PK population (N); all parameters except t _{max} : number of subjects with data (n), mean, standard deviation (SD), coefficient of variation (CV) and geometric mean; t _{max} : number of subjects with data (n), minimum (min), median, and maximum (max) B: oral dexamethasone plus IV pro-netupitant 130 mg (2.6 mg/mL) C: oral dexamethasone plus IV pro-netupitant 195 mg (3.9 mg/mL) D: oral dexamethasone plus IV pro-netupitant 260 mg (5.2 mg/mL) Source: Table 14.2.6.3				

Conclusions:

- On Day 1, the point estimates of treatment comparisons for dose-normalized dexamethasone AUC and Cmin increased remarkably with increasing fosnetupitant doses. At the dose of 260 mg fosnetupitant, dexamethasone AUC_{0-24h} and Cmin increased approximately of 1.5- and 5.2-folds, respectively, as compared to the parameter values observed with dexamethasone given alone. On Day 1, dose normalized dexamethasone Cmax did not change appreciably with fosnetupitant co-administration. The 90% confidence intervals for dexamethasone Cmax fell within the standard bioequivalence interval 80.00%-125.00%.

- On Day 4, the point estimates of treatment comparisons for dose-normalized dexamethasone AUC, C_{max} and C_{min} indicated that dexamethasone PK was still altered by the metabolic interaction with fosnetupitant. At the dose of 260 mg fosnetupitant, dose-normalized dexamethasone AUC_{0-24h}, C_{max} and C_{min} increased approximately of 2.5, 1.7 and 3.2 folds, respectively, as compared to the parameter values observed with dexamethasone given alone.

4.2.4. *In vitro drug-drug interaction studies*

In vitro drug interaction potential via transporters: PNET-15-27

Title: In vitro Interaction Studies of Fosnetupitant with human BSEP, BCRP and MDR1 Efflux (ABC) Transporters, and with human MATE1, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters

Fosnetupitant and probe concentrations for in vitro transporters assessment

Fosnetupitant	VT inhibition	BSEP	TC (2 µM)	0.03, 0.08, 0.25, 0.74, 2.22, 6.67 and 20 µM
		BCRP	E3S (1 µM)	0.07, 0.21, 0.62, 1.85, 5.56, 16.67 and 50 µM
		MDR1	NMQ (2 µM)	
	UPT inhibition	MATE1	Metformin (10 µM)	
		OAT1	Tenofovir (5 µM)	
		OAT3	Methotrexate (1 µM)	
		OATP1B1	E ₂ 17βG (1 µM)	0.41, 1.2, 3.7, 11, 33, 100 and 300 µM
		OATP1B3	CCK-8 (0.1 µM)	
		OCT1	Metformin (10 µM)	
		OCT2	Metformin (10 µM)	
UPT Substrate	OATP1B1	NA	1 and 10 µM	
	OATP1B3	NA	(2 and 20 min)	

UPT: Uptake assay; VT: vesicular transport

TC: taurocholate; E₂17βG: Estradiol-17-β-glucuronide; E3S: Estrone-3-sulfate; CCK-8: Cholecystokinin octapeptide; NMQ: N-methyl quinidine

Vesicular transporter inhibition

Test system for vesicular (VT) transport inhibition: Vesicular transport assays were inside-out membrane vesicles prepared from cells overexpressing human ABC transporters. The transporters have been expressed by SOLVO Biotechnology in insect (*Trichoplusia ni* [Hi5] ovarian cells) and mammalian (K and M) cells. Hi5 cells were infected with recombinant baculovirus as a means of achieving the overexpression of BSEP ABC transporter. The mammalian cells were chemically selected for BCRP or MDR1 ABC transporters.

Transporter	Applying protocol	Protein content/well (μg)	Incubation time (min)	Probe substrate	Reference inhibitor
human BSEP	VT-HTS-BSEP-Hi5-TC	50	5	TC (2 μM)	Cyclosporin A (20 μM)
human BCRP	VT-HTS-BCRP-M-E3S	25	1	E3S (1 μM)	Ko134 (1 μM)
human MDR1	VT-HTS MDR1-K-NMQ	50	3	NMQ (2 μM)	Verapamil (100 μM)

Treatment groups in BSEP VT transport inhibition assays:

Treatment groups in the 96-well plate format	No. of wells
Fosnetupitant in the respective VT buffer with 1% DMSO (0.03, 0.08, 0.25, 0.74, 2.22, 6.67 and 20 μM) with ATP	3 per TA concentration
Fosnetupitant in the respective VT buffer with 1% DMSO (0.03, 0.08, 0.25, 0.74, 2.22, 6.67 and 20 μM) with AMP	3 per TA concentration
1% DMSO control with ATP	3
1% DMSO control with AMP	3
Reference inhibitor in the respective VT buffer with 1% DMSO with ATP	3
Reference inhibitor in the respective VT buffer with 1% DMSO with AMP	3

Treatment groups in BCRP and MDR1 VT transport inhibition assays:

Treatment groups in the 96-well plate format	No. of wells
Fosnetupitant in the respective VT buffer with 1% DMSO (0.07, 0.21, 0.62, 1.85, 5.56, 16.67 and 50 μM) with ATP	3 per TA concentration
Fosnetupitant in the respective VT buffer with 1% DMSO (0.07, 0.21, 0.62, 1.85, 5.56, 16.67 and 50 μM) with AMP	3 per TA concentration
1% DMSO control with ATP	3
1% DMSO control with AMP	3
Reference inhibitor in the respective VT buffer with 1% DMSO with ATP	3
Reference inhibitor in the respective VT buffer with 1% DMSO with AMP	3

Controls: incubation with AMP, incubation with probe substrate (solvent only), and reference inhibitor (positive control).

Results:

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Inhibition results				
Transporter and assay type	Probe substrate	IC ₅₀ (μM)	Maximum inhibition at the highest tested concentration (% of control)	Effect of reference inhibitors (% of control)
BSEP VT	TC (2 μM)	NA	NIO up to 20 μM	91% (Cyclosporin A)
BCRP VT	E3S (1 μM)	NA	NIO up to 50 μM	98% (Ko 134)
MDR1 VT	NMQ (2 μM)	NA	47% at 50 μM	92% (Verapamil)

VT: vesicular transport assay, UPT: uptake assay

NA: Not applicable. NIO: No interaction observed.

Conclusion:

- Fosnetupitant is an inhibitor of the MDR1-mediated NMQ transport in vesicular assay with the maximum inhibition of 47 % at 50 μM.
- Fosnetupitant did **not** inhibit the BSEP-mediated taurocholate and BCRP-mediated E3S accumulation in vesicular transport inhibition assays up to 20 and 50 μM, respectively.

Uptake transporters

Test system for uptake transporter (UPT) inhibition and substrate assay: CHO, MDCKII, or HEK293 cells expressing the respective uptake transporters.

Transporter	Applying assay protocol	Incubation time (min)	Probe substrate	Reference inhibitor
human MATE1	UPT-MDCKII-MATE1-metformin	15	Metformin (10 μM)	Pyrimethamine (1 μM)
human OAT1	UPT-CHO-OAT1-Tenofovir	10	Tenofovir (5 μM)	Probenecid (200 μM)
human OAT3	UPT-HEK293FT-OAT3-MTX	3	Methotrexate (1 μM)	Probenecid (300 μM)
human OATP1B1	UPT-HEK293-OATP1B1-E ₂ 17βG	3	E ₂ 17βG (1 μM)	Rifampicin (50 μM)
human OATP1B3	UPT-HEK293-OATP1B3-CCK8	10	CCK-8 (0.1 μM)	Rifampicin (50 μM)
human OCT1	UPT-CHO-OCT1-Metf	20	Metformin (10 μM)	Verapamil (100 μM)
human OCT2	UPT-CHO-OCT2-Metf	10	Metformin (10 μM)	Verapamil (100 μM)

Treatment groups in UPT inhibition assay:

Treatment groups in the 96-well plate format	No. of wells
Fosnetupitant in HK buffer with 1% DMSO (0.41, 1.2, 3.7, 11, 33, 100 and 300 μM) in transfected cells	3 per TA concentration
Fosnetupitant in HK buffer with 1% DMSO (0.41, 1.2, 3.7, 11, 33, 100 and 300 μM) in control cells	3 per TA concentration
1% DMSO control in transfected cells	3
1% DMSO control in control cells	3
Reference inhibitor in HK buffer with 1% DMSO in transfected cells	3
Reference inhibitor in HK buffer with 1% DMSO in control cells	3

Treatment groups in UPT substrate assay (i.e. fosnetupitant as an OATP1B1/OATP1B3 substrate):

Treatment groups in the 24-well plate format	No. of wells
Fosnetupitant at two concentrations (1 and 10 μM) and two incubation times (2 and 20 min) in triplicate in transporter expressing cells	12
Fosnetupitant at two concentrations (1 and 10 μM) and two incubation times (2 and 20 min) in triplicates in control cells	12
Initial concentration values in triplicate	6
Fosnetupitant at one concentration (1 μM) and one incubation time (20 min) in the absence of the reference inhibitor of the given transporter in triplicates in transporter transfected and control cells	6
Fosnetupitant at one concentration (1 μM) and one incubation time (20 min) in the presence of the reference inhibitor of the given transporter in triplicates in transporter transfected and control cells	6
Initial concentration values in triplicate	6

Reference inhibitor: rifampicin 50 μM

Results – inhibition:

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Inhibition results				
Transporter and assay type	Probe substrate	IC ₅₀ (μM)	Maximum inhibition at the highest tested concentration (% of control)	Effect of reference inhibitors (% of control)
MATE1 UPT	Metformin (10 μM)	29.48	79% at 300 μM	96% (Pyrimethamine)
OAT1 UPT	Tenofovir (5 μM)	NA	NIO up to 300 μM	97% (Probenecid)
OAT3 UPT	Methotrexate (1 μM)	NA	NIO up to 300 μM	98% (Probenecid)
OATP1B1 UPT	E ₂ 17βG (1 μM)	19.01	91% at 300 μM	100% (Rifampicin)
OATP1B3 UPT	CCK-8 (0.1 μM)	17.37	96% at 300 μM	100% (Rifampicin)
OCT1 UPT	Metformin (10 μM)	NA	44% at 300 μM	100% (Verapamil)
OCT2 UPT	Metformin (10 μM)	NA	NIO up to 300 μM	96% (Verapamil)

VT: vesicular transport assay, UPT: uptake assay
 NA: Not applicable. NIO: No interaction observed.

Conclusion - inhibition:

- Fosnetupitant is an inhibitor of the MATE1-mediated metformin transport (IC₅₀: 29.48 μM), the OATP1B1-mediated E₂17βG transport (IC₅₀: 19.01 μM) and the OATP1B3-mediated CCK-8 transport (IC₅₀: 17.37 μM).
- Fosnetupitant is a weak inhibitor of OCT1-mediated metformin transport, with the maximum inhibition of 44 % at 300 μM.
- Fosnetupitant did **not** inhibit the OAT1-mediated tenofovir transport, the OAT3-mediated methotrexate transport and the OCT2-mediated metformin transport up to 300 μM.

Results – substrate of OATP1B1 and OATP1B3

Transporter	Fold accumulation					
	1 μM		10 μM		Follow-up assay (1 μM/20min)	
	2min	20min	2min	20min	-rifampicin	+rifampicin
OATP1B1	3.65	12.77	3.93	10.53	8.77	0.91
OATP1B3	3.20	8.64	1.90	5.59	8.72	0.83

Conclusion – substrate of OATP1B1 and OATP1B3:

- Fosnetupitant is likely to be a substrate for both OATP1B1 and OATP1B3 uptake transporters.

In vitro CYP P450 inhibition potential of fosnetupitant: PNET-15-49

Title: Pronetupitant Phosphate: Determination of the Potential Inhibition (IC₅₀) of the Main Isoforms of CYP450, Determination of Microsomes Binding and Determination of Microsomes Stability.

Study Design

The concentrations of fosnetupitant were 0.3, 1, 3, 10, 30, 100, 300, and 1000 µM.

The test system was pooled human liver microsome (HLM). A pool of microsomes prepared from 50 individual donors were used.

The quantity of CYP specific substrate metabolites produced during the incubation with and without the compound was evaluated in triplicate. In addition, positive controls with CYP specific isoform inhibitors, were included into each experiment. All incubations were performed under linear conditions with respect to time, protein concentration and amount of product formed.

Individual CYP enzyme testing conditions are provided below.

CYP1A2 incubation: the substrate was Tacrine 6 µM, the positive control was α-Naphthoflavone (0.01, 0.1, 0.3 µM), the protein concentration was 0.1 mg/mL. The incubation was carried out at 37°C, shaking, for 10 minutes.

CYP2B6 incubation: Bupropion 43 µM was used as probe substrate solution and Ticlopidine (0.1, 1, 3 µM) as positive control with the protein concentration of 0.1 mg/mL. The incubation was carried out, at 37°C, shaking, for 20 minutes.

CYP2C8 incubation: the substrate was Paclitaxel 14 µM, the positive control Quercetine (0.6, 6, 18 µM), the protein concentration was 0.1 mg/mL. The incubation was carried out at 37°C, shaking for 20 minutes.

CYP2C9 incubation: the substrate was Diclofenac 7 µM, the positive control was Sulfaphenazole (0.1, 1, 3 µM), the protein concentration was 0.1 mg/mL and the incubation was performed at 37°C, shaking, for 10 minutes.

CYP2C19 incubation: S-mephenytoin 71 µM was used as probe substrate and Ticlopidine (0.1, 1, 3 µM) as positive control with protein concentration of 0.2 mg/mL. The incubation was carried out at 37°C, shaking for 40 minutes.

CYP2D6 incubation: the substrate was Dextromethorphan 5 µM, the positive control was Quinidine (0.01, 0.1, 0.3 µM), the protein concentration was 0.1 mg/mL and the incubation was performed at 37°C, shaking, for 10 minutes.

CYP3A4 (Midazolam) incubation: the probe substrate was Midazolam 2.1 μM , the positive control was Ketoconazole (0.01, 0.1, 0.3 μM). The protein concentration was 0.1 mg/mL. The incubation was carried out at 37°C, shaking, for 10 minutes.

CYP3A4 (testosterone) incubation: the probe substrate was Testosterone 43 μM , the positive control Ketoconazole (0.01, 0.1, 0.3 μM) and the protein concentration was 0.1 mg/mL. The incubation was carried out at 37°C, shaking for 20 minutes.

The reaction was started by addition of 1 mM NADPH. After the reported incubation time, reactions were stopped by adding ice-cold acetonitrile.

Results

Table 42. Descriptive statistics of fosnetupitant IC_{50} towards CYP450 in HLM

Pronetupitant: IC_{50} (μM) summary (μM)				
P450 Enzyme	Enzyme Reaction	IC_{50} (μM)	95% C.I.	R^2
CYP1A2	Tacrine-1-hydroxylation	208.40	121.7 to 357.0	0.9
CYP2B6	Bupropion hydroxylation	106.8	78.37 to 145.6	1.0
CYP2C8	Paclitaxel 6-hydroxylation	56.7	39.42 to 81.42	1.0
CYP2C9	Diclofenac 4'-hydroxylation	27.9	22.33 to 34.83	1.0
CYP2C19	S-mephenytoin 4'-hydroxylation	46.1	27.66 to 76.84	1.0
CYP2D6	Dextromethorphan O-demethylation	217.2	131.8 to 358.0	1.0
CYP3A4 midazolam	Midazolam 1'-hydroxylation	196.8	96.59 to 400.8	0.96
CYP3A4 testosterone	Testosterone 6 β -hydroxylation	299.2	251.7 to 355.6	0.93

Table 43. Descriptive statistics of positive controls IC₅₀ towards CYP450 in HLM

Positive Controls: IC ₅₀ (µM) summary				
P450 Enzyme	Positive control	IC ₅₀ (µM)	95% C.I.	R ²
CYP1A2	α-naphthoflavone	0.023	0.018 to 0.030	1.0
CYP2B6	Ticlopidine	0.07	0.066 to 0.076	1.0
CYP2C8	Quercetin	1.0	0.73 to 1.44	1.0
CYP2C9	Sulfaphenazole	1.1	0.93 to 1.39	1.0
CYP2C19	Ticlopidine	0.93	0.79 to 1.09	1.0
CYP2D6	Quinidine	0.086	0.076 to 0.098	1.0
CYP3A4 (midazolam)	Ketoconazole	0.07	0.061 to 0.071	1.0
CYP3A4 (testosterone)	Ketoconazole	0.01	0.0131 to 0.014	1.0

Conclusions

In the range of concentrations tested (0.3-1000 µM), pronetupitant showed moderate to weak inhibition potential towards CYP2C9 (IC₅₀ = 27.9 µM), CYP2C19 (IC₅₀ = 46.1 µM), CYP2C8 (IC₅₀ = 56.7 µM), CYP2B6 (IC₅₀ = 106.8 µM), CYP1A2 (IC₅₀ = 208.4 µM), CYP2D6 (IC₅₀ = 217.2 µM) and CYP3A4 (IC₅₀ = 196.8 µM and 299.2 with midazolam and testosterone substrates, respectively).

Reviewer's comment: Refer to Section 4.3 for evaluation of in vivo DDI potential using PBPK.

In vitro time-dependent inhibition potential of CYP3A and CYP2C9: PNET-15-81

Title: Pronetupitant Phosphate: Determination of the potential Time-Dependent Inhibition of CYP3A4 and CYP2C9

Study Design

Pooled human liver microsomes (HLM) used in this study. A pool of microsomes prepared from 50 individual donors was used.

Verapamil (CYP3A4) and tienilic acid (CYP2C9) were used as positive controls in the assay.

In the first step, the pre-incubation step, pronetupitant (0.3, 1, 3, 10, 30, 100 and 300 μM), verapamil (0.25, 2.5, 5, 15, 50 and 150 μM), tienilic acid (0.1, 0.3, 1, 3, μM) and the solvent control (i.e. absence of compound) were incubated up to 30 minutes in buffer at the microsomal protein concentration of 1 mg/mL.

In the second step, at different times (0, 5, 10, 20 and 30 minutes) an aliquot of the preincubation mixtures was diluted 10-fold in a buffer mixture containing specific substrates of CYP3A4 and CYP2C9 (midazolam, 8.4 μM and diclofenac, 28 μM , respectively). These incubation mixtures, with a final microsomes concentration of 0.1 mg/mL, were added with NADPH (2 mM).

After 10 minutes shaking at 37°C the incubation reactions were stopped by adding ice-cold acetonitrile.

The quantity of metabolites produced during incubation (1-HO-midazolam or 4-HO-diclofenac) was evaluated in triplicate.

Fosnetupitant of 1000 μM dose: Time dependent inhibition potential of CYP3A and was also determined.

Results: An IC_{50} shift (ratio of the $\text{IC}_{50\text{s}}$ at $t=0$ and $t=30$ min) of > 1.5 with a 30 minutes of pre-incubation time is considered as time-dependent inhibitors. IC_{50} shift was determined for concentration up to 300 μM .

Table 44. CYP3A4 $\text{IC}_{50\text{s}}$ of pronetupitant and verapamil after a pre-incubation time of 0, 5, 10, 20 and 30 minutes and the IC_{50} shift ratios estimated after 30 minutes of pre-incubation.

Pronetupitant and verapamil CYP3A4 IC_{50}^* (μM)						IC_{50} Shift Ratio
	T = 0	T = 5'	T = 10'	T = 20'	T = 30'	T = 30'
Pronetupitant	55.5	45.8	47.7	43.7	39.1	1.42
Verapamil	13	8.66	4.20	1.28	0.55	23.6

*Values are mean of three replicates (incubations).

Table 45. IC₅₀ values of pronetupitant and tienilic acid for CYP2C9 after a pre-incubation time of 0, 5, 10, 20 and 30 minutes and the IC₅₀ shift ratios estimated after 30 minutes of pre-incubation.

Pronetupitant and tienilic acid: CYP2C9 IC ₅₀ * (µM)						IC ₅₀ Shift Ratio
	T = 30'	T = 5'	T = 10'	T = 20'	T = 30'	T = 30'
Pronetupitant	28.1	23.8	24.0	32.6	39.3	0.72
Tienilic acid	0.181	0.046	0.047	0.041	0.032	5.71

* Values are mean of three replicates (incubations)

Reviewer's comment: The first T=30' in the table should be T=0'.

Fosnetupitant of 1000 µM dose: Time dependent inhibition potential of CYP3A and was also determined. However, IC₅₀ shift was **not** determined.

Table 46. CYP3A4 and CYP2C9 % of activity remaining and % of activity loss after pre-incubation with pronetupitant (1000 µM with a pre-incubation time of 0, 5, 10, 20 and 30 minutes

Pre-incubation Time	Remaining activity (%)					Activity loss (%)
	T = 0	T = 5'	T = 10'	T = 20'	T = 30'	T = 30'
CYP3A4	57.7	48.9	53.3	39.0	21.3	63.0
CYP2C9	10.3	5.47	3.61	0.77	0.20	98.0

Reviewer's comment: This concentration (Fosnetupitant of 1000 µM) data point was studied together with other concentration time points (fosnetupitant 0 – 300 µM) with the same positive controls for CYP3A and CYP2C9. However, data generated from 1000 µM was not used to calculate IC₅₀ values and IC₅₀ shift.

The sponsor stated that including the inhibition data obtained with all the fosnetupitant concentrations tested (0.3 - 1000 µM), the calculation of the IC₅₀s using Graph Pad Prism software was unreliable (CYP3A4) or even impossible (CYP2C9). Refer to Response to IR (SDN28). Given that a) no TDI observed from 0-300 µM range and b) 1000 µM is 100X the C_{max} obtained from proposed therapeutic dose, the sponsor's justification is reasonable.

Conclusions

In the concentrations range from 0.3 to 300 µM, up to 30 minutes of pre-incubation time, pronetupitant did not show potential TDI effect towards CYP3A4 and CYP2C9. At 1000 µM, pronetupitant showed time-dependent inhibition.

Reviewer's comment: 1000 μM is about 100 times the C_{max} (9.2 μM) achieved in humans following single dose of IV infusion. Thus, time-dependent inhibition of CYP3A and CYP2C9 is minimal at the therapeutic dose.

Palonosetron as a substrate or inhibitor of transporters: PALO-15-28

Reviewer's comment: This study report was submitted to SDN28.

Title: In vitro Interaction Studies of Palonosetron with human BSEP, BCRP and MDR1 Efflux (ABC) Transporters, and with human MATE1, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters

Methods

Palonosetron concentrations used in the transporter assays:

Test article	Transporter	Assay	Palonosetron concentration range	
			Inhibition assay	Substrate assay
Palonosetron	BCRP	MDCKII-ML inhibition and substrate	5 μM	0.05, 0.5, 5 and 50 μM
	MDR1			
	BCRP	VT inhibition assay	0.14, 0.41, 1.2, 3.7, 11, 33 and 100 μM	-
	BSEP			
	MDR1			
	MATE1	UPT inhibition and substrate	0.14, 0.41, 1.2, 3.7, 11, 33 and 100 μM	0.05, 0.5, 5 and 50 μM
	MATE2-K			
	OAT1			
	OAT3			
	OATP1B1			
	OATP1B3			
	OCT1			
OCT2				

Test system for vesicular (VT) transport inhibition: Vesicular transport assays were performed with inside-out membrane vesicles prepared from cells overexpressing human ABC transporters. The transporter has been expressed by SOLVO Biotechnology in insect (*Trichoplusia ni* [Hi5] ovarian cells) and mammalian (K and M) cells. Hi5 (BSEP) cells were infected with recombinant baculovirus as a means of achieving the overexpression of the selected transporter. The mammalian cells were chemically selected for (BCRP and MDR1) the ABC transporter of interest.

Transporter	Applying protocol	Protein content/well (μg)	Incubation time (min)	Probe substrate	Reference inhibitor
human BCRP	VT-HTS-BCRP-M-E3S	25	1	E3S (1 μM)	Ko134 (1 μM)
human BSEP	VT-HTS-BSEP-Hi5-TC	50	5	TC (2 μM)	Cyclosporin A (20 μM)
human MDR1	VT-HTS MDR1-K-NMQ	50	3	NMQ (2 μM)	Verapamil (100 μM)

Treatment groups in VT transport inhibition assays:

Treatment groups in the 96-well plate format	No. of wells
Palonosetron in the respective VT buffer with 1% DMSO (0.14, 0.41, 1.2, 3.7, 11, 33 and 100 μM) with ATP	3 per TA concentration
Palonosetron in the respective VT buffer with 1% DMSO (0.14, 0.41, 1.2, 3.7, 11, 33 and 100 μM) with AMP	3 per TA concentration
Solvent control with ATP	3
Solvent control with AMP	3
Reference inhibitor in the respective VT buffer with 1% DMSO with ATP	3
Reference inhibitor in the respective VT buffer with 1% DMSO with AMP	3

Controls: incubation with AMP, incubation with probe substrate (solvent only), and reference inhibitor (positive control).

Test system for uptake transporter (UPT) inhibition and substrate assay: CHO, MDCKII, or HEK293 cells expressing the respective uptake transporters.

Transporter	Applying assay protocol	Incubation time (min)	Probe substrate	Reference inhibitor
human MATE1	UPT-MDCKII-MATE1-metformin	15	Metformin (10 µM)	Pyrimethamine (1 µM)
human MATE2-K	UPT-MDCKII-MATE2K-metformin	15	Metformin (10 µM)	Pyrimethamine (10 µM)
human OATP1B1	UPT-HEK293-OATP1B1-E ₂ 17βG	3	E ₂ 17βG (1 µM)	Rifampicin (50 µM)
human OATP1B3	UPT-HEK293-OATP1B3-CCK8	10	CCK-8 (0.1 µM)	Rifampicin (50 µM)
human OAT1	UPT-CHO-OAT1-Tenofovir	10	Tenofovir (5 µM)	Probenecid (200 µM)
human OAT3	UPT-HEK293FT-OAT3-MTX	3	Methotrexate (1 µM)	Probenecid (300 µM)
human OCT1	UPT-CHO-OCT1-Metf	20	Metformin (10 µM)	Verapamil (100 µM)
human OCT2	UPT-MDCKII-OCT2-metformin	3	Metformin (10 µM)	Verapamil (300 µM)

Treatment groups in UPT inhibition assay:

Treatment groups in the 96-well plate format	No. of wells
Palonosetron in HK buffer with 1% DMSO (0.14, 0.41, 1.2, 3.7, 11, 33 and 100 µM) in transfected cells	3 per TA concentration
Palonosetron in HK buffer with 1% DMSO (0.14, 0.41, 1.2, 3.7, 11, 33 and 100 µM) in control cells	3 per TA concentration
Solvent control in transfected cells	3
Solvent control in control cells	3
Reference inhibitor in HK buffer with 1% DMSO in transfected cells	3
Reference inhibitor in HK buffer with 1% DMSO in control cells	3

Test system for MDCKII monolayer assay for BCRP or MDR1: The monolayer assays were performed using parental and BCRP or MDR1 transfected MDCKII cell monolayers. MDCKII, MDCKII-BCRP and MDCKII-MDR1 cells were cultured in Dulbecco's Modified Eagle's Medium with 4.5 g/L glucose (DMEM) supplemented with 10% (v/v) fetal bovine serum (FBS) at 37 ± 1 °C in an atmosphere of 95:5 air: CO₂ in cell culture flasks prior to seeding into 24-transwell inserts. Transfected and parental MDCKII cells were cultured on the inserts with 400 µL medium per well on the apical side and 25 mL in a single-well receiver tray for all 24 wells on the basolateral side, for 96 hours. Medium was changed 24 hours before the experiment.

Experimental method for bidirectional transport (substrate assessment): Bidirectional transport of palonosetron was determined through parental, MDCKII-BCRP and MDCKII-MDR1 cell monolayers. Cells were preincubated in assay buffer for 10 minutes to allow cells adjusting to the medium. Assay buffer containing palonosetron at four concentrations (0.05, 0.5, 5 and 50 µM) was then added to the

appropriate apical (400 μ L) or basolateral chamber (800 μ L). The prazosin or digoxin efflux ratio was determined as a positive control for BCRP or MDR1 function.

Applying protocol	Compound	Direction	Concentration	Incubation time (min)
ML-MDCKII-MDR1;BCRP	Palonosetron	A-B/B-A	0.05, 0.5, 5 and 50 μ M	0 and 120
	LY	A-B	40 μ g/mL	120
	LY+Palonosetron (applied apically)	A-B	40 μ g/mL + 50 μ M	120
	Antipyrine	A-B	50 μ M	30
	Digoxin	A-B/B-A	5 μ M	120
	Digoxin+PSC833	A-B/B-A	5 + 10 μ M	120
	Prazosin	A-B/B-A	1 μ M	60
	Prazosin+Ko134	A-B/B-A	1 + 1 μ M	60

Bidirectional transport of palonosetron in parental and MDCKII-MDR1 was determined in the presence and absence of the MDR1 inhibitor PSC833 and verapamil to confirm the specificity of the transport in MDCKII-MDR1 cells. Based on the results of the bidirectional permeability measurement, the transported compound was applied at one selected concentration (5 μ M) and incubation time (120 min). The effect of the reference inhibitors were studied at one concentration (10 μ M PSC833 and 100 μ M verapamil). Assay parameters and treatment groups are shown below.

Applying protocol	Substrate	Direction	Inhibitor	Incubation time (min)
ML-MDCKII-MDR1	Palonosetron (5 μ M)	A-B/B-A	NA	120
	Palonosetron (5 μ M)	A-B/B-A	PSC833 (10 μ M)	120
		A-B/B-A	verapamil (100 μ M)	
	Digoxin (5 μ M)	A-B/B-A	NA	120
		A-B/B-A	PSC833 (10 μ M)	
	Digoxin (5 μ M)	A-B/B-A	verapamil (100 μ M)	120
		A-B/B-A	verapamil (100 μ M)	
	LY (40 μ g/mL)	A-B	NA	120
Antipyrine (50 μ M)	A-B	NA	30	

Determination of the inhibitory potential of palonosetron on the BCRP-mediated prazosin and the MDR1-mediated digoxin transport in the MDCKII-BCRP, MDCKII-MDR1 and MDCKII parental monolayers:

Cells were preincubated in assay buffer for 10 minutes to allow cells to adjust to the medium, then assay buffer with prazosin or digoxin (1/5 μM final concentration) was added to the appropriate apical (400 μL) or basolateral chambers (800 μL). Bidirectional transport of prazosin or digoxin in parental, MDCKII-BCRP and MDCKII-MDR1 cells was determined in the presence and absence of palonosetron. In this inhibitory layout, the reference inhibitor (1 μM Ko134 or 10 μM PSC833) or the test compound (5 μM palonosetron) was added to both chambers of the wells. After incubation (60 min/120 min, at 37 ± 1 $^{\circ}\text{C}$), aliquots (100 μL) were taken from the receptor chambers to determine the amount of translocated prazosin or digoxin. Samples containing prazosin or digoxin were analyzed by scintillation counting. The donor compartments were sampled before and after incubation to determine the initial concentration (C0) and recovery (R) of prazosin or digoxin. Assay parameters and treatment groups are shown below.

Monolayer assay	Applying protocol	Substrate	Direction	Inhibitor	Incubation time (min)
MDCKII, MDCKII- BCRP/MDRI	ML-MDCKII- BCRP/MDR1	Prazosin/Digoxin (1/5 μM)	A-B/B-A	NA	60/120
		Prazosin/Digoxin (1/5 μM)	A-B/B-A	Palonosetron: 5 μM	60/120
		Prazosin/Digoxin (1/5 μM)	A-B/B-A	Ko134/ PSC833 (1/10 μM)	60/120
		LY (40 $\mu\text{g}/\text{mL}$)	A-B	NA	120
		Antipyrine (50 μM)	A-B	NA	30

Controls:

- TEER values were determined for each well prior to the experiment with a Volt Ohmmeter (Millicell, Millipore, Billerica MA, or equivalent). Values above 120 $\Omega\text{cm}^2/\text{plate}$ were accepted.
- Monolayer integrity markers included the measurement of LY as low permeability compound. LY values were accepted below 2×10^{-6} cm/s. Antipyrine served as a high permeability marker. The antipyrine values were expected to be around 50×10^{-6} cm/s.
- The efflux ratio of digoxin (positive control for MDR1-mediated active efflux) was accepted when above 3 for the digoxin control. The efflux ratio of digoxin in the presence of the reference inhibitor PSC833 (10 μM) or verapamil (100 μM) was reduced by $> 80\%$.
- The efflux ratio of prazosin (positive control for BCRP-mediated active efflux) accepted when above 3 for the prazosin control. The efflux ratio of prazosin in the presence of the reference inhibitor Ko134 (1 μM) was reduced by $> 80\%$.

Results

Transporter and assay type	Inhibition results			Substrate results	
	Transported probe substrate	Maximum inhibition (% of control)	IC ₅₀ (μM)	Maximum net ER and fold accumulation	Substrate
BCRP VT	E3S (1 μM)	NIO	NA	ND	ND
BCRP ML	Prazosin (1 μM)	NIO	NA	0.37 (at 5 μM)	unlikely
BSEP VT	Taurocholate (2 μM)	NIO	NA	ND	ND
MDR1 VT	NMQ (2 μM)	NIO	NA	ND	ND
MDR1 ML	Digoxin (5 μM)	NIO	NA	3.12 (at 5 μM)	likely
MATE1 UPT	Metformin (10 μM)	93%	2.48	1.14 (at 0.5 μM)	unlikely
MATE2-K UPT	Metformin (10 μM)	89%	11.55	1.30 (at 50 μM)	unlikely
OAT1 UPT	Tenofovir (5 μM)	NIO	NA	1.77 (at 0.05 μM)	unlikely
OAT3 UPT	MTX (1 μM)	61%	74.22	1.26 (at 0.05 μM)	unlikely
OATP1B1 UPT	E ₂ 17βG (1 μM)	NIO	NA	1.74 (0.05 μM)	unlikely
OATP1B3 UPT	CCK-8 (0.11 μM)	30%	NA	1.48 (at 0.05 μM)	unlikely
OCT1 UPT	Metformin (10 μM)	88%	12.01	1.01 (at 5 μM)	unlikely
OCT2 UPT	Metformin (10 μM)	89%	10.44	0.93 (at 50 μM)	unlikely

Net ER: net efflux ratio, ML: monolayer assay, VT: vesicular transport assay, UPT: uptake assay, NIO: No interaction observed; NA: Not applicable; ND: Not determined

Conclusions – Palonosetron as an inhibitor

- Palonosetron is an inhibitor of MATE1, MATE2-K, OCT1, OCT2, OAT3 in a dose-dependent manner.
- Palonosetron (100 μM) inhibited 30% the OATP1B3-mediated CCK-8 transport.
- Palonosetron up to 100 μM is **not** an inhibitor of BCRP, BSEP, MDR1, OAT1, OATP1B1.

Reviewer's comment: In vivo inhibition of MATE1 and MATE2-K by palonosetron is possible as the ratio of $\frac{C_{max,u}}{IC_{50}}$ for MATE1 and MATE2-K is 0.35 and 0.076, respectively. Both ratios are greater than 0.02. The C_{max} of 0.78 ng/mL (2.3 nM) following IV infusion of Akyzneo in cancer patients and fu of 0.38 is used for the calculation.

In vivo inhibition of OCT1, OCT2, and OAT3 is unlikely as the ratios of $\frac{C_{max,u}}{IC_{50}}$ for these transporters are < 0.1. In vivo inhibition of OATP1B3 is also unlikely as $\frac{C_{max}}{IC_{50}} < 0.1$ assuming IC₅₀ is 100 μM, the worst-case scenario.

Since palonosetron has been on the market quite for a while without any major safety concerns, an in vivo study to evaluate the inhibition potential of palonosetron towards MATE1 and MATE2-K is unnecessary. Therefore, a PMC is not issued regarding this.

Conclusions – Palonosetron as a substrate

- Palonosetron is a substrate of MDR1 (p-gp).
- Palonosetron is **not** a substrate of BCRP.
- Palonosetron is **not** a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters.

Reviewer’s comment: Because of IV administration, systemic exposure to palonosetron will not be impacted due to inhibition of MDR1 transporters. The DDI potential between fosnetupitant and P-gp substrates in the GI tract is minimal because fosnetupitant is administered intravenously and eliminated quickly from the systemic circulation. The ratio of the estimated [Iu,in,max] and reported IC50 for P-gp was less than 0.1, where Iu,in,max is the estimated maximum unbound concentration of fosnetupitant at the inlet to the liver, suggesting no DDI potential between fosnetupitant and P-gp substrates in the liver.

***In vitro* metabolism of fosnetupitant**

Refer to Pharm/Tox Review for details of the following studies:

Type of Study	Test System	Method of Administration	Testing Facility	Study Number
Metabolism				
	Human, rat, dog, liver microsomes	<i>in-vitro</i>	(b) (4)	NETU-10-03
	Human, rat, dog, hepatocytes	<i>in-vitro</i>		NETU-10-04
	Human, rat, dog, hepatocytes	<i>in-vitro</i>		NETU-10-18
	Human, S9, lung, liver, kidney, intestine	<i>In vitro</i>		PNET-14-04

4.3. Review of Physiologically Based Pharmacokinetic Modeling (PBPK): PNET-16-29

Objectives

The applicant submitted study report PNET-16-29 entitled ‘quantitative prediction of the potential for pro-netupitant as a perpetrator to cause CYP2C and transporter-mediated drug-drug interactions’ to support the following labeling claim.

(b) (4)

Specifically, the applicant applied physiologically based pharmacokinetic (PBPK) modelling approach to predict in vivo drug-drug interactions (DDIs) between fosnetupitant (also known as pro-netupitant, the perpetrator, IV 260 mg over 30 min) and the following substrates (victims).

- CYP2C19 substrate: omeprazole
- CYP2C9 substrate: S-warfarin
- OATP1B1 and OATP1B3 substrate: rosuvastatin
- P-gp substrate: digoxin

On 9/27/2017, the applicant submitted supporting files for the physiologically based pharmacokinetic (PBPK) model development and model performance assessment for CYP2C9 substrate (S-warfarin), OATP1B1 and OATP1B3 substrate (rosuvastatin), and P-gp substrate (digoxin) (Sequence # 0020).

On 11/9/2017, the applicant submitted re-evaluation of the in vivo drug-drug interaction (DDI) potential between fosnetupitant and CYP2C9 and CYP2C19 isoforms, and P-gp, OATP1B1 and OATP1B3 transporters using basic models recommended in the draft guidance published in October 2017² (Sequence # 0028).

This review aims to evaluate the adequacy of the applicant’s modelling approaches.

Recommendation based on PBPK modeling review

Based on the prediction using basic model approach, the in vivo DDI potential could not be ruled out. Nevertheless, PBPK modeling approach predicted no significant in vivo DDI potential between fosnetupitant and CYP2C9 or CYP2C19 substrates. For transporters, DDIs between fosnetupitant and OATP1B1, OATP1B3, or P-gp substrates are not expected based on both basic model approach and PBPK modeling approach.

1. Based on the basic model recommended in the draft guidance³, the calculated R1 values were 1.04 for CYP2C9 and 1.03 for CYP2C19. Both were slightly higher than the predefined cutoff value of 1.02⁴. The PBPK modeling approach suggested no in vivo pharmacokinetic interaction between fosnetupitant and S-warfarin (CYP2C9 substrate) as well as between fosnetupitant and

² Draft guidance for industry (2017) In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies Guidance for Industry

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>

³ Draft guidance for industry (2017) In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies Guidance for Industry

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>

⁴ R1 is the predicted ratio of the victim drug’s AUC in the presence and absence of an inhibitor for basic models of reversible inhibition.

omeprazole (CYP2C19 substrate) at the recommended dose level (260 mg IV infusion for 30 min).

- For OATP1B1 and OATP1B3 inhibition potential estimation, the calculated R values⁵ were 1.087 for OATP1B1 and 1.095 for OATP1B3. Both were slightly below the cutoff value of 1.1⁶. PBPK modeling approach with sensitivity analysis also suggested negligible in vivo DDIs.
- The DDI potential between fosnetupitant and P-gp substrates in the GI tract is minimal because fosnetupitant is administered intravenously and eliminated quickly from the systemic circulation. The ratio of the estimated $[I_{u,in,max}]$ and reported IC50 for P-gp was less than 0.1, where $I_{u,in,max}$ is the estimated maximum unbound concentration of fosnetupitant at the inlet to the liver⁷, suggesting no DDI potential between fosnetupitant and P-gp substrates in the liver.

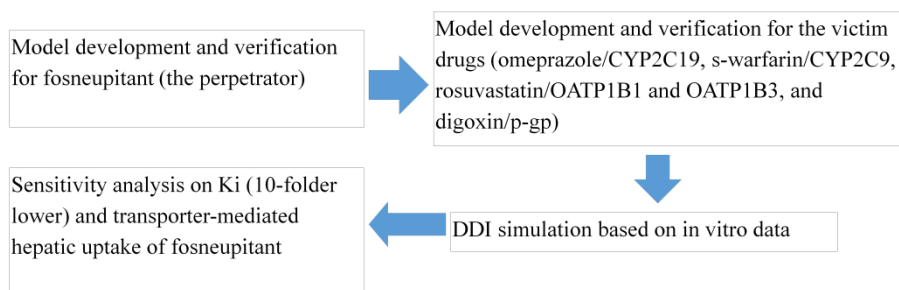
Background

The investigational product is an intravenous fixed dose combination of fosnetupitant and palonosetron HCl (IV NEPA FDC). Fosnetupitant is a water-soluble phosphorylated pro-drug of netupitant rapidly converted to netupitant in vivo following IV administration with mean half-life of approximately 1 hour. The proposed dose of fosnetupitant is 235 mg (equivalent to 260 mg fosnetupitant chloride) IV infusion over 30 min. .

In this submission, the applicant applied physiologically based pharmacokinetic (PBPK) modeling approach to predict in vivo DDIs between fosnetupitant (also known as pro-netupitant, the perpetrator, IV 260 mg over 30 min) and CYP2C9, CYP2C19, OATP1B1, OATP1B3 and P-gp substrates.

Model Development

The models were developed in Simcyp (version 15). A flow chart of modeling strategy is summarized below by the reviewer. The applicant's modeling strategy is appropriate.



Model structures for each compound are summarized below.

Drug name	Description	Model structure	Dosing regimen	Model verification report

⁵ R is the predicted ratio of the victim drug's AUC in the presence and absence of the investigational drug as the inhibitor.

⁶ [Application 210493 - Sequence 0028 - Response to Clinical Pharmacology Information Request - 0028](#)

⁷ See response to information request ([Application 210493 - Sequence 0028 - Response to Clinical Pharmacology Information Request - 0028](#)) about $I_{u,in,max}$ estimation.

Fosnetupitant	Perpetrator	Minimal PBPK model with single adjusting compartment (SAC)	260 mg IV over 30 min	Study PNET-13-63
Omeprazole	CYP2C19 substrate	Minimal PBPK model	Single oral dose 20 mg	⁸
S-warfarin	CYP2C9 substrate	Minimal PBPK model	Single oral dose 10 mg	^{9, 10}
Rosuvastatin	OATP1B1 and OATP1B3 substrate	Full PBPK model	Single oral dose 20 mg	¹¹
Digoxin	P-gp substrate	Full PBPK model	Single oral dose 0.5 mg	¹²

Question based review

When using PBPK modeling to predict the interaction potential of fosnetupitant as an enzyme and transporter perpetrator, the following questions were considered¹³.

1. Can the PBPK model of fosnetupitant (the investigational perpetrator) describe the available clinical PK data using different dosing regimens?

Yes, the proposed fosnetupitant model (a minimal PBPK with a single adjusting compartment (SAC)) can describe the plasma concentration of fosnetupitant at dose levels ranging from 19.5 mg to 390 mg. The applicant verified the simulated PK of fosnetupitant against observed data at a dose level of 260 mg (Figure 20). It was noted that 260 mg was used in the simulation while the proposed recommended dose was 235 mg fosnetupitant (equivalent to 260 mg fosnetupitant chloride), and the model input should be using the corresponding base dose. Nevertheless, the simulated mean C_{max} (6643 ng/mL) and AUC_t (3526 ng*hr/mL) using a dose of 235 mg were closer to the observed C_{max} (mean values ranging from 6414 – 6464 ng/mL, PNET-12-23), and AUC_t (ranging from 2922-2939 ng*hr/mL, PNET-12-23) compared to the simulated values using a dose of 260 mg (Figure 20). The observed fosnetupitant C_{max} and AUC_t were 7367 ng/mL, and 2855 ng*hr/mL, respectively in Study PNET-13-63 (fosnetupitant drug-drug interaction with oral dexamethasone).

Figure 20: Observed (circle) vs. simulated (solid line) fosnetupitant PK profiles after 260 mg iv infusion over 30 min (source: Figures 3 and 5 in study report PNET-16-29). Left: simulated mean concentration-time profiles (solid lines) vs. mean observed data (solid circles; n=17; Clinical Study PNET-13-63); right: simulated mean concentration-time profile (solid lines) and 5th and 95th percentiles (dashed lines) for the simulated population vs. observed individual concentrations (symbols; n=17; Clinical Study PNET-13-63)

⁸ [Application 210493 - Sequence 0001 - PNET-16-29 - Study Report](#)

⁹ [Application 210493 - Sequence 0020 - Performance Verification Warfarin - V13](#)

¹⁰ [Application 210493 - Sequence 0020 - Performance Verification Warfarin - V15](#)

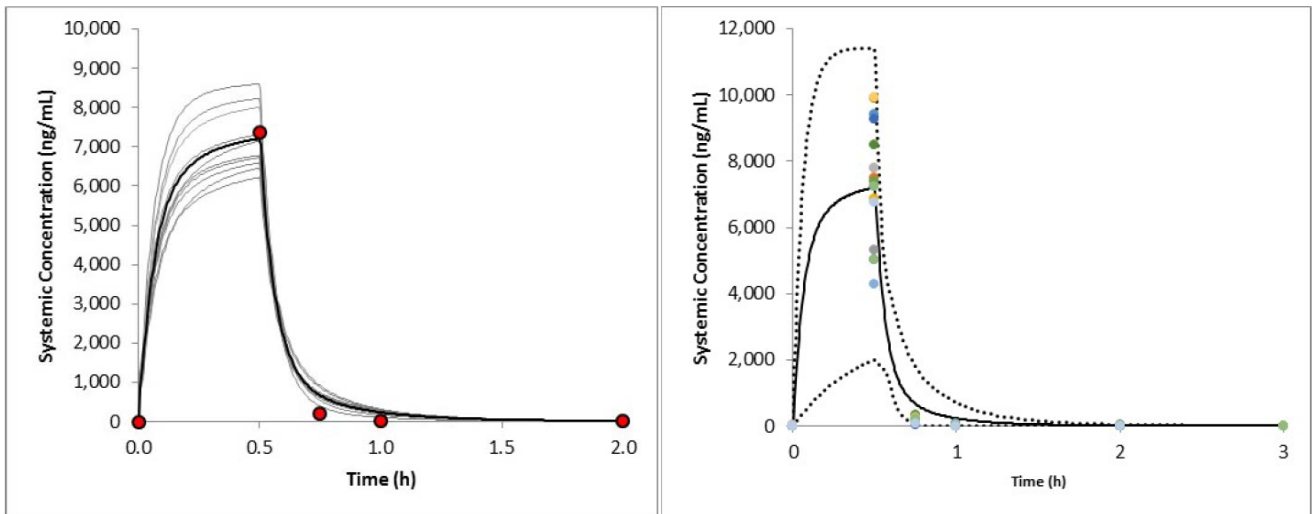
¹¹ [Application 210493 - Sequence 0020 - Performance Verification Rosuvastatin - V15](#)

¹² [Application 210493 - Sequence 0020 - Performance Verification Digoxin - V15](#)

¹³ Draft guidance for industry (2017) In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies

Guidance for Industry

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>



The reviewer performed additional simulations at dose levels ranging from 19.5 mg to 390 mg. As shown in the following figures, the simulated mean C_{max} and AUC_t values were close (with ratio ~0.9-1.3) to the observed mean C_{max} and AUC_t values (study PNET-12-23) (Figure 21 and 22).

Figure 21: Observed vs. simulated fosnetupitant C_{max}, and AUC_t at various doses levels performed by the reviewer

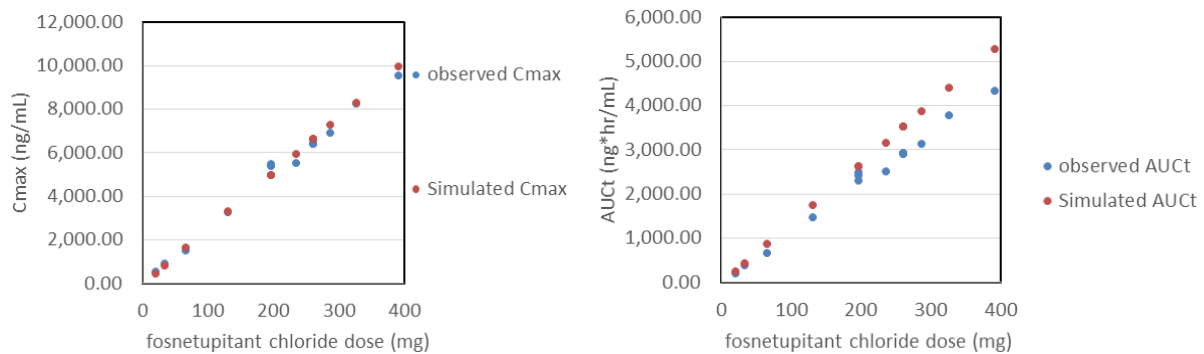
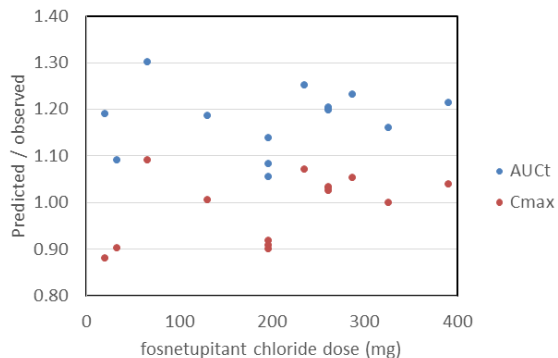


Figure 22: Ratios of simulated fosnetupitant mean PK values / observed fosnetupitant mean PK values at various doses levels performed by the reviewer

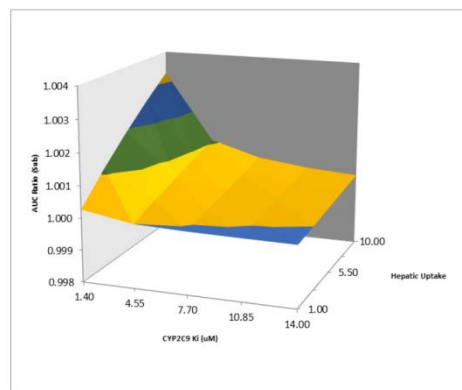


2. **Are index substrate models (CYP 2C9 and CYP2C19) verified with regard to the effect of altered enzyme activity on its PK in humans?**

Yes. S-warfarin and omeprazole are in vivo index substrates of CYP 2C9 and CYP2C19, respectively¹⁴. The applicant verified the index substrate drugs by 1) comparison of simulated vs. observed PK profiles, and 2) comparison of the simulated vs. observed fold change in PK parameters in the absence and presence of other index modulators: fluconazole (a moderate CYP2C9 index inhibitor), and fluvoxamine (a strong CYP2C19 index inhibitor). It was noted that the dose used for fosnetupitant simulation input was 260 mg and the proposed recommended dose was 235 mg fosnetupitant. The model input should be using the corresponding base dose. Nevertheless, the difference will not affect the DDIs conclusions, as the doses used in simulation was higher than the corresponding base dose and simulated mean PK values tend to be higher than observed mean PK values.

S-warfarin clearance was modeled by CYP2C9 allelic variants and verified against published in vivo PK data. The DDI model predicted warfarin AUC changes in the absence and presence of fluconazole (a moderate CYP2C9 index inhibitor) were 69%-120% higher than observed AUC changes¹⁵. The uncertainty associated with the Ki (inhibition constant) values were addressed by sensitivity analysis (Figure 23).

Figure 23: Sensitivity analysis to assess the impact of hepatic uptake and CYP2C9 Ki values for fosnetupitant on the predicted DDI with S-warfarin after coadministration of a single oral dose of 10 mg S-warfarin and a single 30-min IV infusion of 260 mg fosnetupitant (source: Figure 9 in study report PNET-16-29)



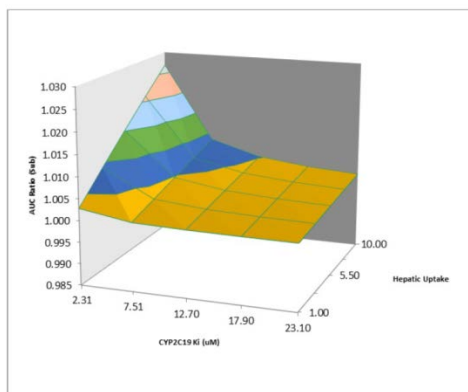
The contribution of CYP2C19 (fmCYP2C19) to the overall clearance of omeprazole in CYP2C19 extensive metabolizer (EM) in vivo was assigned based on literature report (0.80-0.87). In order to describe the observed DDI between fluvoxamine (a strong CYP2C19 index inhibitor) and omeprazole, a Ki values 5-fold lower than the in vitro value was used in the simulation. Nevertheless, sensitivity

¹⁴ FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-1>

¹⁵ [Application 210493 - Sequence 0020 - Performance Verification Warfarin - V15](#)

analysis was performed by the applicant on K_i down to 10-fold lower than the in vitro value and there was no C_{max} and AUC change in the absence and presence of fosnetupitant (Figure 24).

Figure 24: Sensitivity analysis to assess the impact of hepatic uptake and CYP2C19 K_i values for fosnetupitant on the predicted DDI with omeprazole after coadministration of a single oral dose of 20 mg omeprazole and a single 30-min IV infusion of 260 mg fosnetupitant (source: Figure 12 in study report PNET-16-29)



3. Can the proposed PBPK model be used to predict the DDIs between fosnetupitant and OATP1B1, and OATP1B3 substrates?

The basic model approach (Sequence # 0028) suggested no in vivo inhibition potential for OATP1B1 and OATP1B3 substrates. In vivo DDI prediction between fosnetupitant and rosuvastatin (OATP1B1 and OATP1B3 substrate) suggested that there is negligible in vivo inhibition potential.

(b) (4)

The clearance ($Cl_{int,T}$) assigned to each transporter (49% for OATP1B1, 35% for NTCP, and the remaining 16% for OATP1B3)¹⁶ as well as their K_i values may impact the prediction of the DDI between fosnetupitant and rosuvastatin. The applicant evaluated the impact of K_i values on DDI prediction but not $Cl_{int,T}$. The reviewer performed additional simulation to mimic a worst-case scenario where only OATP1B3 (100%) was responsible for uptake as it has lower K_i value, and K_i value was 100- fold lower than the in vitro value (0.087 μM). The predicted ratios of rosuvastatin C_{max} and AUC were about 10% and 1% higher, respectively, when it was coadministered with fosnetupitant, suggesting negligible DDI between fosnetupitant and

¹⁶ Page 8 in [Application 210493 - Sequence 0020 - Performance Verification Rosuvastatin - V15](#)

OATP1B1, and OATP1B3 substrates. As both OATP1B1, and OATP1B3 are influx transporters, inhibition effect does not raise the concern of potentially more liver accumulation.

4. Can the proposed PBPK model be used to predict the DDIs between fosnetupitant and P-gp substrates?

In order to simulate the DDI between fosnetupitant and P-gp substrates in the intestine, a physiologically based model is needed to estimate the fosnetupitant concentration in enterocytes coming from the blood flow. The current fosnetupitant model does not include a physiologically based gastrointestinal tract. Nevertheless, the impact of fosnetupitant on digoxin intestinal efflux should be minimal because fosnetupitant is administered intravenously and eliminated from systemic circulation quickly.

The ratio of the estimated $[I_{u,in,max}]$ and reported IC_{50} for P-gp was less than 0.1, where $I_{u,in,max}$ is the estimated maximum unbound concentration of fosnetupitant at the inlet to the liver, suggesting no DDI potential between fosnetupitant and P-gp substrates in the liver.

Conclusions

- The PBPK modeling approach is appropriate to address the DDIs between fosnetupitant and CYP2C9, CYP2C19 substrates. Therefore, in vivo pharmacokinetic DDIs between fosnetupitant and CYP2C9, CYP2C19 substrates are not expected.
- In vivo DDIs between fosnetupitant and OATP1B1, OATP1B3, or P-gp substrates are not expected based on basic model approach and PBPK modeling approach.

PBPK parameters for fosnetupitant (source: PNET-116-29 study report)

PARAMETER	PRO-NETUPITANT	REFERENCE
MW	689.61	Provided by Helsinn
log P	2.43	Provided by Helsinn
Compound type	Zwitterion	Provided by Helsinn
pKa	2.35, 4.60	Provided by Helsinn
B:P	0.55	Assumed
fu	0.065	<i>In Vitro</i> Report: PNET-15-90
V _{ss} (L/kg)	1.81	Optimised based on data from
V _{SAC} (L/kg)	1.75	Clinical Study Number: PNET-13-63
k _{in} (h ⁻¹)	2.00	
k _{out} (h ⁻¹)	0.01	
CL _{IV} (L/h)	96.6	Clinical Study Number: PNET-13-63
<u>K_i (μM)*</u>		
CYP2C9	14.0	<i>In Vitro</i> Report: PNET-15-49
CYP2C19	23.1	
OATP1B1	9.51	<i>In Vitro</i> Report: PNET-15-27
OATP1B3	8.69	
P-gp	25.0	

* It was assumed that $K_i = IC_{50}/2$.

4.4. QT Study Review

Refer to Interdisciplinary Review Team for QT Studies Consultation: QT Study Review for this NDA in DARRTS dated August 28, 2017.

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

/s/

ELIZABETH Y SHANG
12/15/2017

XINYUAN ZHANG
12/15/2017

YUCHING N YANG
12/15/2017

INSOOK KIM
12/15/2017

HAE YOUNG AHN
12/18/2017