CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 9, 2014
From	Ruyi He, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205718
Applicant	Helsinn Healthcare SA
Date of Submission	9/27/2013
PDUFA Goal Date	9/26/2014
Proprietary Name / Established (USAN) names	**AKYNZEO**/Netupitant and Palonosetron HCI Fixed-Dose Combination (FDC) Capsule
Dosage forms / Strength	Capsule: 300 mg netupitant /0.5 mg palonosetron
Proposed Indication(s)	1. prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy; 2. prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
Recommended:	I recommend that NDA 205718 Akynzeo be approved for the indication of 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. Palonosetron prevents nausea and vomiting during the acute phase (first 24 hours after cancer chemotherapy) and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

1. Introduction

The proposed product is a fixed-dose combination of two active substances, netupitant 300 mg and palonosetron 0.5 mg. Netupitant is a novel, potent and selective NK1 receptor antagonist.

Palonosetron is a well-known potent and selective 5-HT3 receptor antagonist. The IV formulation of palonosetron (ALOXI 0.25 mg, NDA 21-372) was approved in the United States in 2003 in the following indications:

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

ALOXI I.V. is also indicated for the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

An oral formulation of palonosetron (ALOXI 0.50 mg, NDA 22-233) was approved in 2008 in the following therapeutic indication:

- Moderately emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses

The characteristics of the drugs support the development as a fixed-dose combination since their mechanism of action is exerted on different neuropathways (5-HT3 receptors and NK1 receptors) and both drugs show a similar pharmacokinetic profile in terms of extended plasma half-life representing a rational and clinically-appropriate choice of antiemetic drugs.

2. Background

Nausea and vomiting are the side effects associated with cancer treatment. 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.

CINV is classified as acute, occurring within the first 24h after chemotherapy, or delayed, occurring after the first 24h, extending until the fifth day. The development of acute emesis is known to largely depend on serotonin (5-HT). 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 pathophysiology of delayed emesis is less understood, and multiple mechanisms may contribute, including substance P. Substance P (SP) belongs to the neurokinin (NK) family of neuropeptides and exerts its biological effects via interaction with the NK1 receptor. The Substance P - NK1 receptor system is one of the best-characterized neurotransmitter pathways in both the central and peripheral nervous systems.

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 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.

Regulatory history

Initial pre-IND discussions began in April 2006. The IND application was submitted to the FDA (IND 73,493) in September 2006. Since that time, the development program to support the registration of this combination product in the target indications has been extensively discussed and agreed upon between the Agency (including the Office of Medical Policy - OMP) and Helsinn in a number of meetings and correspondence exchanges including Special Protocol Assessment procedures.

To address FDA's requests, and to provide adequate safety and efficacy data in support of the registration in the target indication, the sponsor performed following efficacy and safety trials:

• NETU-07-07 (HEC)

• PALO-10-01 (HEC)

• NETU-08-18 (MEC)

• NETU-10-29 (MEC and HEC)

Study PALO-10-01 provides proof of oral palonosetron efficacy in HEC setting and supports the use of PALO oral as the comparator instead of PALO (b) (4) Study NETU-07-07 demonstrates the contribution of netupitant to the combination of netupitant and palonosetron. NETU-08-18 demonstrates pivotal evidence of efficacy MEC (ASCO reclassified AC regimen as HEC in 2011), NETU-10-29 provides safety receiving repeat cycles of MEC and HEC.

The key highlights of the regulatory history are summarized below.

- FDA agreed that single cycle study NETU-07-07 (HEC) and trial PALO-10-01 (HEC; an oral Aloxi 0.5 mg vs I.V. Aloxi 0.25 mg non-inferiority trial) would be acceptable to support efficacy of the Combination for the prevention of acute and delayed CINV-HEC, provided their outcomes are positive.

- FDA agreed with protocol NETU-08-18 submitted for FDA SPA review on September 21, 2010 (Serial #023), in support of the MEC target indication. Specifically, the target patient population, the primary study objective, the primary and key secondary efficacy endpoint, the sample size, the multiplicity handling strategy, the randomization scheme and the primary efficacy analysis were acceptable. FDA confirmed that if NETU-08-18 (MEC) repeat cycle efficacy data are favorable for the Combination, these MEC repeat cycle efficacy results would be suitable to support inclusion of "repeat course" wording in both the MEC and HEC the target indications. Regarding safety, repeat cycle safety assessments and analyses as well as DSMB Charter were also considered acceptable.

- FDA agreed with protocol PALO-10-01 submitted for FDA SPA review on September 21, 2010 (Serial #024), in support of the HEC target indication. Specifically, the target patient population, the primary study objective, the primary and secondary efficacy endpoint, the sample size, the randomization scheme and the non-inferiority margin (based on a 99% confidence interval) were acceptable. FDA agreed on the analysis populations and commented that, since the FAS and PP populations would be the primary efficacy analysis populations, the ITT sensitivity analysis will be an important review component for assessing non-inferiority. FDA also added that the analyses on the primary efficacy endpoint and for assay sensitivity were acceptable and that the statistical analysis plan for sensitivity analysis should replicate the primary analysis and present confidence intervals for the treatment differences. Additional sensitivity analyses may be explored during the review. The safety assessment was acceptable.

- Regarding NETU-10-29, FDA agreed with trial design in the advice letter dated November 19, 2010. Specifically, the patient population (MEC and HEC patients), the primary objective of safety and tolerability, the active control regimen, the safety endpoints, safety population and analysis were acceptable for obtaining repeat cycle safety data. FDA recommended the Sponsor make every effort to enroll patients receiving repeat dose anthracycline-containing therapy; FDA also recommended the Sponsor stratify randomization by chemotherapy type (MEC or HEC) to achieve a 3:1 balance within each stratum at randomization.

- In Pre-NDA meeting dated April 16, 2013, FDA noted that given the continual evolution of opinions in clinical medicine, the Division is moving beyond 'HEC' and 'MEC' classification in antiemetics indications. Sponsor stated to be quite concerned about the possibility of FDA changing the definition of the target indications since it can have substantial impact on drug use, that the MEC and HEC indications were the basis for the phase 2/3 efficacy program as agreed with FDA during the SPA process, and the MEC and HEC indications follow FDA precedent indications. FDA acknowledged Sponsor's feedback that Helsinn would like to maintain the original target indications. FDA indicated that the approved label will describe the chemotherapy regimens that were studied, and that wording of the indications will be a review issue.

Please refer to Dr. Nancy Snow's complete review dated July 9, 2014.

3. CMC/Device

Dr. Raymond Frankewich, Dr. Hitesh Shroff and Dr. Nina Ni are the CMC reviewers for this NDA and they concluded in the review that the applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Office of Compliance for the manufacturing facilities has made a final "Acceptable" recommendation based on e-mail communication dated July 23, 2014. ONDQA's memo will go into DARRTS once the labeling is done. There is no unsolved CMC issue currently. They have no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Based on the review, information from DMF 26715 and DMF 16063 held by Helsinn Advanced Synthesis SA, was reviewed for this NDA and found they are adequate.

The drug product consists of a Size 0 hard gelatin capsule containing three 100 mg immediate-release tablets containing 100 mg netupitant, and one soft gelatin capsule (softgel) containing (b) (4) (b) (4) 0.50 mg of palonosetron (0.56 mg of palonosetron hydrochloride). Thus the dosage delivered by one capsule of the drug product is 300 mg netupitant and 0.5 mg palonosetron.

The purity of the starting materials are adequately controlled by the specifications given, based on the Dr. Frankewich's review.

Please refer to Dr. Frankewich's review dated May 30, 2014.

4. Nonclinical Pharmacology/Toxicology

Dr. Ke Zhang is the reviewer and Dr. David Joseph is the team leader for this NDA and they concluded in the review that the applicant has provided sufficient information. From a nonclinical standpoint, this NDA should be approved for the proposed indication.

Based on Dr. Zhang's review, netupitant alone was tested in oral toxicity studies of up to 26 weeks in rats and 9 months in dogs. Treatment with netupitant induced phospholipidosis at doses of 10 mg/kg/day or higher in both rats and dogs. The clinical significance of phospholipidosis in these studies is not clear. The calculated animal to human AUC multiples for netupitant based on the AUC values at 10 mg/kg/day in both rats and dogs ranged from 0.4 to 1.8. Oral toxicity studies with the combination of netupitant and palonosetron were performed in rats and dogs for up to 13 weeks. The combination did not produce any additional toxicity as compared with either drug tested alone.

Netupitant was negative in the Ames test, mouse lymphoma cell mutation assay, and *in vivo* rat micronucleus test. Long-term studies in animals to evaluate the carcinogenic potential of netupitant are not needed to support approval for the proposed indication. Therefore, no carcinogenicity studies with netupitant were conducted.

Daily oral administration of netupitant at 10 mg/kg/day and higher during the period of organogenesis increased the incidence of external and skeletal abnormalities in rabbit fetuses. These abnormalities included positional abnormalities in the limbs and paws, and fused sternebrae.

Dr. Zhang indicated that an oral toxicity study with netupitant alone of at least 8 weeks duration in juvenile rats is needed to support the proposed pediatric clinical efficacy study in patients age 0 to < 17 years. The juvenile rat study should include evaluation of developmental parameters, neurobehavioral effects, and fertility. The sponsor should submit the juvenile rat study protocol for review and evaluation prior to initiation of this study. The sponsor's proposed timeline for the pediatric study plan should be adjusted according to these recommendations.

Please refer to Dr. Zhang's review dated June 19, 2014.

Dr. Abigail Jacobs concurred that there are no pharm/tox approval issues, concurred with the pregnancy category of C for the combination of netupitant and palonosetron on her Memo dated 6/18/14.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Insook Kim and Dilara Jappar are the reviewers and Dr. Sue-Chih Lee is the team leader for this NDA and they concluded in the review that the applicant has provided sufficient information. From a clinical pharmacology standpoint, they recommend that this NDA be approved for the proposed indication.

They recommend following post-marketing studies to improve the labeling of AKYNZEO.

- In vivo drug interaction study to evaluate the duration of inhibitory effects of AKYNZEO on CYP3A4 enzyme activity beyond 4 days after single dose administration of AKYNZEO.

Rationale: Co-administration of a single dose of netupitant increased the exposure to dexamethasone, a substrate of CYP3A4 by 1.7-fold on Day 1 and up to 2.4-fold on Day 2 and Day 4. The potential inhibitory effect of netupitant on CYP3A4 was not studied beyond Day 4. Given AKYNZEO will be used in patients who require multiple medications for underlying disease treatment as well as supportive care, a study is necessary to provide adequate information for use of AKYNZEO with concomitant medications that are CYP3A4 substrates.

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

Rationale: The potential of netupitant being a substrate for P-gp in ATPase activation assay suggested that netupitant is likely a substrate for P-gp. However, information is lacking

whether netupitant is a substrate for P-gp on bi-directional transport assay system, which is considered a confirmatory study.

The sponsor informs us that the study is finished and the final study report will be submitted in October 2014. That is acceptable.

Please refer to Dr. Kim's addendum review dated June 27, 2014.

Based on Dr. Kim's review, clinical pharmacology and biopharmaceutics findings are summarized as followings.

Exposure (Dose)-Response Relationship
In a dose-finding study (NETU-07-07), the proportion of patients with complete response (CR) was compared between palonosetron monotherapy at 0.5 mg and the combinations of 0.5 mg palonosetron with netupitant at three different doses i.e.100 mg, 200 mg, and 300 mg. The CR rate was evaluated during the 0-24 h (acute phase), 24-120 h (delayed phase) and 0-120 h (overall phase) after the administration of chemotherapeutics. The study was designed to show the difference between the combination therapy and palonosetron alone but not between doses.

No evident dose-response relationship was observed among doses for the CR rate in the delayed and overall phases. Compared to palonosetron monotherapy, all three combinations of palonosetron and netupitant showed statistically significant difference in the proportion of patients with CR during the delayed and overall phases. On the other hand, only the combination with 300 mg netupitant showed statistically significant difference for the CR rate in the acute phase in comparison to palonosetron monotherapy. The combination with netupitant 300 mg showed a numerically higher CR rate for the acute phase CINV than lower doses. Therefore, the combination of 0.5 mg palonosetron and 300 mg netupitant was selected for phase 3 clinical trials.

Effects on QTc interval
To assess the potential effect of the combination therapy, a thorough QT study was conducted at doses up to 600 mg NETU in combination with 1.5 mg PALO in healthy subjects. No significant QTc interval prolongation was observed when single dose 600 mg NETU and 1.5 mg PALO was co-administered4. Consistently, the exposure-response relationship was not evident between ddQTcF and concentrations of NETU and its metabolites as well as concentrations of PALO and its metabolites. No significant effect of PALO on the QTc interval was consistent with the previous report of no effect of PALO on the QTc doses up to 2.25 mg after intravenous administration.

The supratherapeutic dose in this study provides the safety margin of 2 fold for netupitant and 3 fold for palonosetron. The supratherapeutic dose provided higher Cmax and similar AUC for NETU in patients with moderate hepatic impairment.

Pharmacokinetic/ Biopharmaceutics Properties
AKYNZEO

After single dose administration of AKYNZEO in healthy subjects, the peak plasma concentrations for netupitant and palonosetron were reached in about 5 hours. Concomitant food did not significantly affect the systemic exposure to netupitant and palonosetron. In cancer patients, the rate and extent of absorption of netupitant and palonosetron were similar to those in healthy subjects.

No significant PK interactions between netupitant and palonosetron were observed.

Netupitant
Distribution
Population PK analysis indicates that the apparent central and peripheral volume of distribution (Vz/F) was estimated to be 486 L and 1170 L, respectively. Human plasma protein binding of netupitant is greater than 99.5% at drug concentration ranging from 10-1300 ng/ml and protein binding of its major metabolites (M1, M2 and M3) are greater than 97% at drug concentrations ranging from 100 to 2000 ng/mL.

Metabolism
In in vitro studies netupitant is metabolized mainly by CYP3A4 and by CYP2C9 and CYP2D6 to a lesser degree. Three major metabolites were identified desmethyl derivative, M1; N-oxide derivative, M2; OH-methyl derivative, M3 in vivo and were all shown to bind to human substance P/neurokinin 1 (NK1) receptor in vitro. Mean AUC for metabolites M1, M2, and M3 was 29%, 14% and 33% of netupitant, respectively.

Elimination
In cancer patients, the apparent median elimination half-life of netupitant was 88 hours and the estimated median systemic clearance was 20.5 L/h based on population PK analysis.
Upon oral administration of labeled netupitant, about 50% and 75% of the administered radioactive dose was recovered from the excreta (urine and feces) collected over 120 h and 336 h (2 weeks), respectively. Over 2 weeks the total of 3.95 % and 70.7 % of the radioactive dose was recovered in urine and feces, respectively. The mean fraction of oral dose of netupitant excreted unchanged in urine was less than 1 % suggesting renal clearance is not a significant elimination route for netupitant.

Specific populations
Currently no dosage adjustment for palonosetron is recommended by renal or hepatic impairment.

Age
In cancer patients population PK analysis indicated that age (within the range of 29 to 75 years old) did not influence the pharmacokinetics of netupitant or palonosetron.

Gender
The Cmax for netupitant was 35 % higher in females than in males but the AUC was similar between males and females. For palonosetron 25-35% higher AUC and Cmax were observed in female subjects than in male subjects consistently with the previous observation.

Hepatic Impairment
In patients with mild or moderate hepatic impairment, the mean Cmax for netupitant was about 30% higher and the mean AUC0-∞ was 56% and 107% higher, respectively than in healthy subjects. The Cmax for netupitant in two patients with severe hepatic impairment was 63% and 463% higher compared to the mean Cmax in healthy subjects.

In patients with mild or moderate hepatic impairment, the mean Cmax for palonosetron was about 35-40% higher and the mean AUC0-∞ was 35% and 55% higher, respectively than in healthy subjects.

Renal Impairment
There was no dedicated PK study to evaluate the effect of renal impairment on PK of netupitant. On the other hand, no significant effect of CLCR on PK of netupitant was noted in the population PK analysis while the effect of CLCR was noted for palonosetron consistently with the current labeling for palonosetron. The pharmacokinetics has not been studied in subjects with end-stage renal disease for either palonosetron or netupitant.

In vitro studies for evaluation of drug interaction potential assessment
CYP inhibition:
In *in vitro* studies, netupitant and its metabolite M1 are inhibitors of CYP3A4. Netupitant did not inhibit CYP1A2, CYP2C19, and CYP2D6 *in vitro*. *In vivo* drug interactions via inhibition of CYP2B6, 2C8 and 2C9 at the clinical dose of 300 mg are unlikely based on weak inhibition of toward these enzymes in *in vitro* studies.

M1 showed inhibition toward CYP2B6, 2C8, 2D6, and 3A4, and weak inhibition toward CYP 1A2, 2C9, 2C19. However, since Cmax/Ki >0.1 for only CYP3A4, *in vivo* drug interaction via M1 inhibition toward CYP enzyme is unlikely except for CYP3A4.

M2 and M3 showed weak inhibition toward all major CYP enzymes. Since Cmax/Ki<0.1 for all enzymes, *in vivo* drug interaction via M2 or M3 inhibition individually toward CYP enzyme is unlikely.

CYP induction:
Netupitant up to 20 μM and its metabolites (M1, M2 and M3) up to 2 μM are not inducers of CYP1A2, CYP2C9, CYP2C19 and CYP3A4. The sponsor did not evaluate the potential of netupitant and its metabolites to induce CYP2B6.

Transporters:
Netupitant is an inhibitor of P-gp and BCRP transporters based on *in vitro* studies. Potential of netupitant being a substrate for P-gp was not evaluated adequately. In addition, M2 is shown to be a substrate for P-gp.

In vivo drug interactions
(A) Effect of other drugs on the PK of netupitant and palonosetron
CYP3A4 inhibitor: Co-administration of AKYNZEO with ketoconazole increased the mean

Cmax and AUC of netupitant by 25% and 140%, respectively compared to those after administration of AKYNZEO without ketoconazole. Co-administration of ketoconazole increased the mean AUC and Cmax for palonosetron was about 10-15%.

CYP3A4 inducer: Co-administration of AKYNZEO with rifampicin decreased the mean Cmax and AUC of netupitant by 62%, and 82%, respectively compared to those after AKYNZEO alone.

Co-administration of rifampicin decreased the mean Cmax and AUC of palonosetron by 15% and 20%, respectively. Use of AKYNZEO in patients who have been on CYP3A4 inducers at the time of AKYNZEO administration is not recommended to ensure the efficacy of combination therapy.

(B) Effect of netupitant or Akynzeo on PK of other drugs
Drugs that are CYP3A4 substrates
Netupitant component of AKYNZEO is a moderate CYP3A4 inhibitor and the increase in the systemic exposure to concomitant drugs that are CYP3A4 substrates was observed to a various degree when AKYNZEO or netupitant alone was co-administered. The significant inhibitory effect was shown for 4 days. While there is no study done beyond 4 days, the inhibitory effect on CYP3A4 is estimated to last at least for 6 days after single dose administration of AKYNZEO.

Dexamethasone:
The potential effect of netupitant on PK of dexamethasone, a CYP3A4 substrate was studied. Palonosetron is not an inhibitor of CYP3A4; therefore, its effect was not studied. The coadministration of a single dose of netupitant (300 mg) with oral dexamethasone regimen (20 mg on Day 1, followed by 8 mg b.i.d. from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a dose-dependent manner. When netupitant was co administered on Day 1, the mean AUC of dexamethasone was increased by 1.7-fold on Day 1 and up to 2.4-fold on Day 2 and Day 4. The potential inhibitory effect of netupitant on CYP3A4 was not studied beyond Day 4.

Chemotherapeutics
The systemic exposure to intravenously given chemotherapeutic agents (docetaxel, etoposide,) that are metabolized by CYP3A4 was increased to a different degree (10-49%) when AKYNZEO was co-administered than when chemotherapeutic agents were coadministered with palonosetron alone in cancer patients.

When co-administered with AKYNZEO the mean Cmax and AUC of intravenously administered docetaxel were 49% and 35% higher, respectively. The systemic exposure to intravenously administered etoposide and cyclophosphamide was also increased when AKYNZEO was coadministered by 10-28%.

No clear safety signal was identified when AKYNZEO was co-administered with chemotherapeutic agents (docetaxel, etoposide) as stated in Dr. Snow’s review.

Please refer to Dr. Kim's review dated May 30, 2014.

6. Clinical Microbiology

NA

7. Clinical/Statistical- Efficacy

Dr. Yeh-Fong Chen is the stat reviewer and Dr. Freda Cooner is the stat team leader for this NDA and they concluded in the review that Study NETU-08-18 supports the use of the combination product (PALO+NETU) for the indication and Study PALO-10-01 supports the use of PALO oral as the comparator (b) (4) Although Study NETU-07-07 demonstrates favorable results on the CR in the delayed phase endpoint to support the efficacy claims of the PALO+NETU for the CINV indication, during the data monitoring after the trial had been completed, the sponsor identified a Russian site (#120) with a relatively large number of protocol violations. Therefore, they performed re-analyses by completely excluding that site from the final analysis. To further assess the study drug's efficacy by exploring the extent of the usage of the Russian Site #120 data in the final analysis, the FDA requested the sponsor to perform different types of reanalyses by either including the data in Site #120 but treating the patients who had major or any protocol violations as treatment failures or excluding them from the analysis. Dr. Chen confirmed the sponsor's re-analysis results and concluded that the data of NETU-07-07 is supportive of the efficacy of the study drug, i.e., palonosetron plus netupitant 300 mg, although not all of the re-analysis results showed significant findings based on the Holm-Bonferroni multiplicity adjustment method.

Dr. Snow stated in her addendum dated September 6, 2014 that only three major violations with occurred in the palonosetron 0.5 mg and netupitant 300 mg arm, and involved administration of ondansetron on the date of study drug administration. Another three major violations in the palonosetron 0.5 mg arm involved administration of ondansetron on the day of study drug administration. She does not believe these impacted the final efficacy conclusion because equal numbers of violations occurred in both arms and any impact would be balanced between arms. In addition, ondansetron and palonosetron are the same class of drug, a serotonin-3 (5-HT3) receptor antagonist. Because both drugs act on the same receptor, using both drugs on the same day may not increase efficacy.

Dr. Cooner in her stat team leader review dated July 4, 2014 also confirmed that Study NETU-07-07 supports the efficacy of the netupitant 300 mg and palonosetron 0.5 mg fixed-dose combination (FDC) compared to oral palonosetron 0.5 mg alone, based on CR in the delayed (25-120 hours), acute (0-24 hours), and overall (0-120 hours) phases after the start of HEC. Study PALO-10-01 demonstrates that oral palonosetron 0.5 mg is noninferior to intravenous (IV) palonosetron 0.25 mg on the primary efficacy endpoint of CR following HEC, and so is acceptable as the comparator in Study NETU-07-07. Study NETU-08-18 shows that the netupitant 300 mg and palonosetron 0.5 mg FDC improves CR in all three phases after the start of chemotherapies compared to oral palonosetron 0.5 mg alone. She concluded that as stated in the primary stat review, with the collective evidence from these three efficacy studies,

the netupitant 300mg and palonosetron 0.5 mg FDC shows benefit in the prevention of both acute and delayed CINV as assessed by the efficacy endpoint of CR.

Dr. Nancy Snow is the primary medical reviewer for this NDA. She concluded that data from 4 Phase 2/3 trials support the conclusion that the benefits of Akynzeo 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, outweigh the risks. I concur. In the following section, I will summary the main efficacy results from 4 key clinical trials.

Proof of efficacy in the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy is demonstrated through the results in three trials (NETU-07-07, NETU-08-18 and NETU-10-29). Study NETU-07-07 demonstrates the contribution of netupitant to the combination of netupitant and palonosetron in HEC. NETU-08-18 demonstrates pivotal evidence of efficacy MEC (ASCO reclassified AC regimen as HEC in 2011), NETU-10-29 provides safety receiving repeat cycles of MEC and HEC. Study PALO-10-01 provides proof of oral palonosetron efficacy in HEC setting. Table 1 provides an overview of the key features of the four important clinical trials conducted in the program.

Table 1 Overview of Clinical Trials Providing Efficacy Data for the Netupitant/Palonosetron FDC Program

Trial No.	Design	No. of Patients randomized/treated/FAS	Duration	Indication	Primary Endpoint	Role of Study for efficacy demonstration
NETU-07-07	Double-blind, randomized (1:1:1:1:1) parallel group	PALO oral 136/136/136* PALO + NETU 100 135/135/135* PALO +NETU 200 142/138/137* PALO +NETU 300 143/136/135* Aprepitant +Onda 138/134/-- Total 694/679/543*	Single-cycle	HEC	CR Overall phase (0-120 hr)	Netupitant dose selection/Pivotal evidence of NETU+PALO efficacy in HEC
NETU-08-18	Double-blind, randomized (1:1) parallel group	PALO oral 726/725/725 FDC 729/725/724 Total 1455/1450/1449	Single and Multiple cycles	MEC	CR Delayed phase (25-120 hr)#	Pivotal evidence of FDC efficacy in MEC

NETU-10-29	Double-blind, randomized (3:1) parallel group	FDC 309/308/309 Aprepitant + PALO oral 104/104/103 Total 413/412/412	Multiple cycles	MEC and HEC	Safety	Supportive evidence of FDC efficacy in MEC and HEC
PALO-10-01	Double-blind, randomized (1;1) parallel group	PALO oral 371/370/369 PALO IV 372/369/369 Total 743/739/738	Single-cycle	HEC	CR Acute phase (0-24 hr)	Evidence of efficacy of PO palonosetron alone in HEC

*For NETU-07-07 the numbers of patients are randomized/number treated/MFAS
# Key secondary endpoints: CR acute phase (0-24 hr), overall phase (0-120 hr)
FDC= Netupitant/Palonosetron Combination Fixed-Dose Capsule (palonosetron 0.50 mg/netupitant 300 mg)
Dexamethasone was included in all dose regimens.
PALO= Palonosteron; NETU= Netupitant; Onda= Ondansetron

Patient Population

All patients in the FDC efficacy and safety development program were adult male or female patients ≥18 years of age who were scheduled to receive chemotherapy as specified by each individual protocol (HEC or MEC, and repeated or single courses). Participants were chemotherapy naïve, defined as having no prior history of cytotoxic chemotherapy, scheduled to receive:

- NETU-07-07; highly emetogenic cisplatin-based chemotherapy (cisplatin dose: >50 mg/m2) over 1-4 hours to be administered alone or in combination with other chemotherapy agents;

- NETU-08-18; an anthracycline and cyclophosphamide containing MEC regimen [cyclophosphamide I.V. (500 to 1500 mg/m2) and I.V. doxorubicin (≥40 mg/m2) or cyclophosphamide I.V. (500 to 1500 mg/m2) and I.V. epirubicin (≥60 mg/m2)]; In 2011 the American Society of Clinical Oncology (ASCO) changed its classification system and re-classified an AC regimen as HEC. This re-classification was based on a search of the medical literature and analysis of 37 trials meeting prespecified inclusion and exclusion criteria. The conclusion of the review was that an AC regimen causes vomiting in 85% of patients not receiving antiemetic prophylaxis, which was so close to the HEC cutoff of 90%.

- NETU-10-29; either MEC (any single I.V. dose of one or more of the following agents: oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamide I.V. <1500 mg/m2, cytarabine I.V. > 1 g/m2, azacidine, alemtuzumab, bendamustine or clofarabine) or HEC (any single I.V. dose of one or more of the following agents: cisplatin, mechlorethamine, streptozocin, cyclophosphamide ≥1500 mg/m2, carmustine, dacarbazine).

- PALO-10-01; highly emetogenic cisplatin-based chemotherapy (cisplatin dose: ≥70 mg/m2 over 1-4 hours either alone or in combination with other chemotherapy agents).

Among other inclusion/exclusion criteria, patients could not participate in the study if they were scheduled to receive any emetogenic chemotherapy other medications, including but not limited to anti-emetics, as disallowed by the protocol, had other medical conditions specified in the protocols (including but not limited to symptomatic primary or metastatic central nervous system malignancy, history or predisposition to cardiac conduction abnormalities, severe cardiovascular disease), or any uncontrolled medical condition that, in the opinion of the investigator, may have confounded the results of the study or posed unwarranted risk in administering the study medication. Females could not be pregnant or lactating.

Demographics and Baseline Characteristics
Demographics and important baseline characteristics in cycle 1 for the combination studies are provided in Table 2. (PALO-10-01 is not included here since it did not evaluate the combination directly.) The mean age and ranges were similar across the studies and all demographics were balanced across treatment groups within the trials. Differences in the patient demographics between studies are due to the different types of cancer under treatment and the resultant chemotherapy regimens (HEC versus MEC).

> Across all treatment groups, there were more women (98.1%) in NETU-08-18 compared to NETU-07-07 (43%) and NETU-10-29 (50%) because NETU-08-18 was primarily a breast-cancer based trial. The overall mean age (54-57 years) and age ranges were similar across all the trials. There was more racial diversity in NETU-08-18 and NETU-10-29 as they were global trials, whereas NETU-07-07 was conducted in Russia and Ukraine. Regardless, the majority of patients in the development program were White.

Table 2: Patient Demographics- Cycle 1 – All Netupitant/Palonosetron Trials (Safety population)

	NETU-07-07 (N=679) HEC	NETU-08-18 (N =1450) MEC	NETU-10-29 (N=412) HEC/MEC
Gender , n (%)			
Male	387 (57)	28 (1.9)	206 (50)
Female	292 (43)	1422 (98.1)	206 (50)
Age (years)			
Mean (SD)	54.4 (9.79)	53.9 (10.65)	56.6 (10.76)
Median	55	54	58
Range	19-82	22-79	21-80
Race , n (%)			
White	678 (99.9)	1153 (79.5)	345 (83.7)
Black	-	4 (0.3)	3 (0.7)
Asian	1 (0.1)	204 (14.1)	64 (15.5)
Hispanic	-	82 (5.7%)	-
Other	-	7 (0.5)	-
ECOG performance status , n (%)			
Grade 0	-	1006 (69.4)	196 (47.6)
Grade 1	-	437 (30.1)	209 (50.7)
Grade 2	-	7 (0.5)	7 (1.7)
Karnofsky performance status , n (%)			
70%	17 (2.5)	-	-
80%	197 (29.0)	-	-
90%	397 (58.5)	-	-
100%	68 (10.0)	-	-

Source: CSRs [Module 5.3.5.1, NETU-07-07, Tables 11 and 12, NETU-08-18 Tables 7 and 8; NETU-10-29 Tables 8 and 9] and [Module 2.7.3, Section 6.1]

Eastern Cooperative Oncology Group Performance Status:

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.

Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.

Grade 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

Karnofsky Performance Status Scale:

100% The subject has no complaints and is without evidence of disease.

90% The subject has minor signs/symptoms, but is able to carry out his or her normal activities.

80% The subject demonstrates some signs/symptoms and requires some effort to carry out normal activities.

70% The subject is able to care for self, but is unable to do his or her normal activities or active work.

Abbreviations: ECOG=Eastern Cooperative Oncology Group; FDC=Fixed Dose Combination; max=maximum; min=minimum; N=Number of patients in group; n=number of patients with data; SD=Standard Deviation.

Primary and Main Secondary Endpoints

The clinical development program addressed primary efficacy in terms of Complete Response defined as no emetic episodes and no rescue medication in all trials. Primary and main secondary endpoints for each of the 3 studies are shown in Table 3.

Table 3: Primary and Main Secondary Endpoints in Clinical Trials

Trial Number	Primary Endpoint	Main Secondary Endpoint (s)
NETU-07-07*	Complete Response: overall phase	Complete response: acute phase Complete response: delayed phase
NETU-08-18	Complete Response: delayed phase Cycle 1	Complete response: acute phase at Cycle 1** Complete response: overall phase at Cycle 1**
NETU-10-29	Safety	Complete response: acute, delayed and overall phases
PALO-10-01	Complete Response: acute phase	Complete response: delayed and overall phase

Source: Module 5.3.5.1 [NETU-07-07, Section 9.7.1.4; NETU-07-07 Addendum 1, Section 10; NETU-08-18, Section 9.7.1.4, NETU-10-29, Section 9.7.1.4]
Acute phase = 0-24 h; Delayed phase = 25-120 h; Overall phase = 0-120 h
*Addendum 1 to the NETU-07-07 CSR was conducted at the request of the US FDA to provide a post-hoc analysis of CR in the delayed phase as primary efficacy variable using Cochran-Mantel-Haenszel (CMH) test stratified for gender. A hierarchical procedure evaluated delayed, followed by acute and overall CR.
** Considered as key secondary; in NETU-08-18, a hierarchical procedure evaluated delayed, followed by acute and overall CR.

Efficacy Results

Selected efficacy results in cycle 1 are presented for the three netupitant-palonosetron clinical trials performed in this program. As described previously, NETU-07-07 is considered pivotal for the efficacy in HEC; while trial NETU-08-18 provides pivotal evidence of efficacy in patients receiving MEC. NETU-08-18 had single and multiple cycle phases whereas NETU-07-07 was single cycle only. Study NETU-10-29 contains both MEC and HEC patients, and was primarily a safety trial in single and multiple cycles with supportive efficacy data.

Primary and Main Secondary Efficacy Endpoints
Complete Response

Despite the differences in complete response rate, as expected considering the difference in design and patient populations involved in the trials, there was a consistent benefit of the netupitant 300 mg plus palonosetron 0.50 mg compared to palonosetron 0.50 mg alone.

The complete response rates for NETU 07-07 are provided in Table 4.

Table 4: Complete Response Rates for NETU 07-07

	PALO alone (N=136)	PALO + NETU100 mg (N=135)	PALO + NETU200 mg (N=137)	PALO + NETU 300 mg (N=135)
Overall (0-120 hours)				
Number (%) of Patients	104 (76.5)	118 (87.4)	120 (87.6)	121 (89.6)
Difference from palonosetron alone (%) with 95% CI		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 21.9)
p-value[1]		0.018	0.017	0.004

	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 palonosetron alone (%), [95% CI]	-	10.2 [1.9, 18.6]	11.1 [2.9, 19.3]	10.2 [1.9, 18.6]
p-value[1]	-	0.018	0.010	0.018
Acute phase (0-24 hours)				
Number (%) of patients	122 (89.7)	126 (93.3)	127 (92.7)	133 (98.5)
Difference from palonosetron alone (%), [95% CI]	-	3.6 [-3.0, 10.2]	3.0 [-3.7, 9.7]	8.8 [3.3, 14.3]
p-value[1]	-	0.278	0.383	0.007

Source: [Module 5.3.5.1, NETU-07-07 Table 18]
[1]p-value from logistic regression analysis including gender as covariate

Dr. Snow stated in her addendum dated September 6, 2014 that only three major violations with occurred in the palonosetron 0.5 mg and netupitant 300 mg arm, and involved administration of ondansetron on the date of study drug administration. Another three major violations in the palonosetron 0.5 mg arm involved administration of ondansetron on the day of study drug administration. She does not believe these impacted the final efficacy conclusion because equal numbers of violations occurred in both arms and any impact would be balanced between arms. In addition, ondansetron and palonosetron are the same class of drug, a serotonin-3 (5-HT3) receptor antagonist. Because both drugs act on the same receptor, using both drugs on the same day may not increase efficacy. I concur with her conclusion and above analyses did not exclude those patients with violations.

To further assess the study drug's efficacy by exploring the extent of the usage of the Russian Site #120 data in the final analysis, the FDA requested the sponsor to perform different types of reanalyses by either including the data in Site #120 but treating the patients who had major or any protocol violations as treatment failures or excluding them from the analysis. Dr. Chen confirmed the sponsor's re-analysis results and concluded that the data of NETU-07-07 is supportive of the efficacy of the study drug, i.e., palonosetron plus netupitant 300 mg, although not all of the re-analysis results showed significant findings based on the Holm-Bonferroni multiplicity adjustment method. See Dr. Chen's review in detail.

The complete response rates of NETU 08-18 are provided in Table 5.

Table 5: Complete Response Rates of NETU 08-18

	NETU/PALO FDC (N=724)	PALO alone (N=725)
Delayed		
Responder, n (%)	557 (76.9)	504 (69.5)
Difference from palonosetron alone, %	7.4	
CMH OR (95% CI)	1.48 (1.16; 1.87)	
p-value[a]	0.001	
Acute		
Responder, n (%)	640 (88.4)	616 (85.0)
Difference from palonosetron alone, %	3.4	
CMH OR (95% CI)	1.37 (1.00; 1.87)	
p-value[a]	0.047	
Overall		
Responder, n (%)	538 (74.3)	483 (66.6)
Difference from palonosetron alone, %	7.7	
CMH OR (95% CI)	1.47 (1.17; 1.85)	
p-value[a]	0.001	

(a) p-value from CMH test, stratified by age class and region.

PALO-10-01 is a single dose, multicenter, randomized, double blind, double dummy, parallel group study to assess the efficacy and safety of oral palonosetron 0.50 mg compared to I.V. palonosetron 0.25 mg administered with dexamethasone for the prevention of chemotherapy induced nausea and vomiting in cancer patients receiving highly emetogenic cisplatin based chemotherapy. The primary study objective was to demonstrate the non-inferiority of single dose of oral palonosetron 0.50 mg versus single dose of I.V. palonosetron 0.25 mg in terms of percentage of patients with CR during the acute phase (0-24 hours) in the HEC setting. An oral formulation of ALOXI 0.5 mg was approved in 2008 (NDA 22-233) for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. The efficacy of oral palonosetron 0.5 mg had not been evaluated in cancer patients receiving highly emetogenic chemotherapy. The role of Study PALO-10-01 is to demonstrate that oral palonosetron 0.5 mg:

- contributes to the FDC efficacy in the HEC setting since oral ALOXI® 0.5 is registered for the prevention of acute CINV induced by MEC only;
- is efficacious in acute HEC and thereby support its use as active comparator in NETU-07-07.

The percentage of patients with CR in the acute phase was 89.4% in the oral palonosetron group and 86.2% in the I.V. palonosetron group. The stratum-adjusted Cochran-Mantel-Haenszel method for difference in proportions, stratified by gender and region, with associated two-sided 99% CI was used for non-inferiority testing. The difference in proportion between the oral and I.V. palonosetron groups was 3.21% (99% CI: -2.74% to 9.17%). Non-inferiority of oral palonosetron versus I.V. palonosetron was demonstrated 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 set at -15%.

Table 6: Non-Inferiority Based on Complete Response in the Acute Phase – FAS (PALO-10-01)

	Oral PALO (N=369)	I.V. PALO (N=369)
Acute phase (0-24 hours)		
Responder, n (%)	330 (89.4)	318 (86.2)
95% CI[a]	[85.9; 92.2]	[82.3;89.3]
Risk difference, % (99% CI)[b]	3.21 (-2.74; 9.17)	

Source: [Module 5.3.5.1, PALO-10-01, Table 13].
a 95% CI using Wilson score method.
b Stratum-adjusted Cochran-Mantel-Haenszel method for difference in proportions, stratified by gender and region according to Koch et al. and O'Gorman et al.
The non-inferiority margin is set to -15%.
Abbreviations: CI=Confidence Interval; I.V.=intravenous; N=Number of patients in group; n=number of patients with data; PALO=Palonosetron.

Secondary Efficacy Endpoints

DGIEP requested a SEALD consult regarding sponsor's nausea assessment. According to the review from Dr. Paivi Miskala (SEALD reviewer) and Dr. Elektra Papadopoulos (SEALD team leader), sponsor assessed average nausea severity in the past 24 hours using a 100mm visual analog scale where 0 indicates "no nausea" and 100 indicates "nausea as bad as it could be". This assessment is used as part of combination endpoints and as stand-alone endpoints in sponsor's trials. Key issues regarding the nausea assessment are as follows:

- The endpoints which were not included in the multiplicity adjustment of the statistical analysis plan do not provide conclusive evidence of treatment benefit (b) (4)
- Sponsor's instrument measures average nausea severity, not worst nausea severity in the past 24 hours. This could be problematic since the sponsor is defining "no nausea" as maximum nausea severity < 5 mm as measured on the VAS and "no significant nausea" as maximum nausea severity < 25 mm (maximum refers to maximum average severity of nausea recorded within the time interval to be analyzed, i.e., within overall phase 0-120 hours, acute phase 0-24 hours, delayed phase 25-120 hours,). With average nausea measurement there is no guarantee that maximum average nausea severity was <5 mm in any given day because we are measuring an average, not the worst experience patient had with nausea. For example, it is possible that a patient had nausea > 5mm part of the day, but could have an average nausea measurement of <5 for the day. There is a similar issue with "no significant nausea" cutpoint of < 25 mm using average nausea measurement; it is possible that a patient had significant nausea at some point during the day, but could end up with an average < 25 mm for the day. (b) (4)
- Nausea endpoints cannot be interpreted without information on rescue medication use to ensure that any improvement in nausea is not due to rescue medication use.

- In general, using a 100 mm visual analog scale is acceptable, but one should keep in mind that a visual analog scale may give a false sense of precision.
- Submission did not include information if any validation or translation/cultural adaptation work was done for the nausea assessment.

I concur with her assessments and recommend (b) (4)

Efficacy Results in Multiple Cycles
Two trials collected efficacy data over multiple cycles of chemotherapy (NETU-08-18 in MEC and safety study NETU-10-29 in MEC and HEC).

For both studies, the complete response rates were similar in the multiple cycles compared to cycle 1. During the multiple-cycle portion of NETU-08-18, in each phase up to cycle 6, the CR rates were consistently higher for the FDC than for palonosetron alone. However, there is dimishment the further out in cycles 5 and 6 which is difiicult to interpret given the substantial decrease in the population left at those cycles. Also, the absolute rates by cycle for netupitant arm remain stable by cycle; the palo alone arm has the increase in rates over the cycles. Therefore, the efficacy is stable.

Table 7: Complete Response in the Delayed, Acute and Overall Phases by Cycle of the Multiple-Cycle Extension – FAS (Extension) (NETU-08-18)

	NETU/PALO FDC (N=635)		PALO alone (N=651)		Difference (NETU/PALO FDC – PALO alone)	
Responder in:	**n (%)**	**[95%CI[a]]**	**n (%)**	**[95%CI[a]]**	**(%)**	**[95%CI[b]]**
Cycle 2, n	**635**		**651**			
Cycle 2 delayed phase	519 (81.7)	[78.5;84.5]	448 (68.8)	[65.2;72.3]	12.9	[8.2;17.5]
Cycle 2 acute phase	571 (89.9)	[87.3;92.0]	545 (83.7)	[80.7;86.4]	6.2	[2.5; 9.9]
Cycle 2 overall phase	510 (80.3)	[77.0;83.2]	434 (66.7)	[63.0;70.2]	13.6	[8.8;18.4]
Cycle 3, n	**598**		**606**			
Cycle 3 delayed phase	509 (85.1)	[82.0;87.7]	451 (74.4)	[70.8;77.7]	10.7	[6.2;15.2]
Cycle 3 acute phase	548 (91.6)	[89.1;93.6]	508 (83.8)	[80.7;86.5]	7.8	[4.1;11.5]
Cycle 3 overall phase	501 (83.8)	[80.6;86.5]	426 (70.3)	[66.5;73.8]	13.5	[8.8;18.1]
Cycle 4, n	**551**		**560**			
Cycle 4 delayed phase	471 (85.5)	[82.3;88.2]	433 (77.3)	[73.7;80.6]	8.2	[3.6;12.7]
Cycle 4 acute phase	504 (91.5)	[88.8;93.5]	486 (86.8)	[83.7;89.3]	4.7	[1.0; 8.4]
Cycle 4 overall phase	462 (83.8)	[80.5;86.7]	418 (74.6)	[70.9;78.1]	9.2	[4.4;13.9]
Cycle 5, n	**272**		**249**			
Cycle 5 delayed phase	233 (85.7)	[81.0;89.3]	199 (79.9)	[74.5;84.4]	5.7	[-0.7;12.3]
Cycle 5 acute phase	242 (89.0)	[84.7;92.2]	214 (85.9)	[81.1;89.7]	3.0	[-2.7; 8.8]
Cycle 5 overall phase	225 (82.7)	[77.8;86.7]	193 (77.5)	[71.9;82.3]	5.2	[-1.6;12.1]
Cycle 6, n	**197**		**191**			
Cycle 6 delayed phase	175 (88.8)	[83.7;92.5]	159 (83.2)	[77.3;87.9]	5.6	[-1.3;12.6]
Cycle 6 acute phase	177 (89.8)	[84.8;93.3]	164 (85.9)	[80.2;90.1]	4.0	[-2.6;10.6]
Cycle 6 overall phase	170 (86.3)	[80.8;90.4]	150 (78.5)	[72.2;83.8]	7.8	[0.2;15.3]

Source: [Module 5.3.5.1, NETU-08-18, Table 27]
a 95% CI using Wilson score method.
b 95% CI using Newcombe-Wilson's method.
Abbreviations: CI=Confidence Interval; FDC=Fixed-Dose Combination; N=Number of patients in group; n=number patients with data; NETU=Netupitant; PALO=Palonosetron.

In NETU-10-29, efficacy data were collected over multiple cycles of chemotherapy. CR rates from cycle 2 through 6 are presented in the table below.

Table 8: Complete Response in Delayed, Acute and Overall Phase (NETU-10-29) FAS

	NETU/PALO FDC (N=309)		Aprepitant +PALO (N=103)		Difference (NETU/PALO FDC – Aprepitant/PALO)	
Responder in:	**n (%)**	**[95%CI[a]]**	**n (%)**	**[95%CI[a]]**	**(%)**	**[95%CI[b]]**
Cycle 2, n	**280**		**96**			
Cycle 2 delayed phase	243 (86.8)	[82.3;90.3]	79 (82.3)	[73.5;88.6]	4.5	[-3.3;14.0]
Cycle 2 acute phase	270 (96.4)	[93.6;98.0]	88 (91.77)	[84.4;95.7]	4.8	[-0.2;12.2]
Cycle 2 overall phase	241 (86.1)	[81.5;89.6]	78 (81.3)	[72.3;87.8]	4.8	[-3.1;14.5]
Cycle 3, n	**259**		**90**			
Cycle 3 delayed phase	237 (91.5)	[87.5;94.3]	79 (87.8)	[79.4;93.0]	3.7	[-2.9;12.5]
Cycle 3 acute phase	249 (96.1)	[93.0;97.9]	86 (95.6)	[89.1;98.3]	0.6	[-3.5;7.2]
Cycle 3 overall phase	235 (90.7)	[86.6;93.7]	78 (86.7)	[78.1;92.2]	4.1	[-2.9;13.1]
Cycle 4, n	**233**		**81**			
Cycle 4 delayed phase	212 (91.0)	[86.6;94.0]	71 (87.7)	[78.7;93.2]	3.3	[-3.7;12.7]
Cycle 4 acute phase	225 (96.6)	[93.4;98.3]	78 (96.3)	[89.7;98.7]	0.3	[-3.7;7.1]
Cycle 4 overall phase	210 (90.1)	[85.6;93.3]	71 (87.7)	[78.7;93.2]	2.5	[-4.6;11.9]
Cycle 5, n	**156**		**57**			
Cycle 5 delayed phase	145 (92.9)	[87.8;96.0]	49 (86.0)	[74.7;92.7]	7.0	[-1.5 ;18.7]
Cycle 5 acute phase	148 (94.9)	[90.2;97.4]	56 (98.2)	[90.7;99.7]	-3.4	[-8.3; 4.6]
Cycle 5 overall phase	143 (91.7)	[86.3;95.1]	49 (86.0)	[74.7;92.7]	5.7	[-2.9; 17.5]
Cycle 6, n	**124**		**44**			
Cycle 6 delayed phase	114 (91.9)	[85.8;95.6]	38 (86.4)	[73.3;93.6]	5.6	[-3.9;19.1]
Cycle 6 acute phase	118 (95.2)	[89.8;97.8]	41 (93.2)	[81.8;97.7]	2.0	[-5.0;13.7]
Cycle 6 overall phase	113 (91.1)	[84.8;95.0]	38 (86.4)	[73.3;93.6]	4.8	[-4.8;18.4]

Source: [Module 5.3.5.1, NETU-10-29, Section 14, Table 14.2.1.1]
a 95% CI using Wilson score method.
b 95% CI using Newcombe-Wilson's method.
Abbreviations: CI=Confidence Interval; FDC=Fixed-Dose Combination; N=Number of patients in group; n=number patients with data; NETU=Netupitant; PALO=Palonosetron.

In summary, efficacy of the FDC was maintained over multiple chemotherapy cycles supporting the use of the FDC in initial and repeat cycles of HEC and MEC in cancer patients.

Conclusions for Efficacy Results
I concur with the efficacy conclusions evaluated by Dr. Snow (medical reviewer), Dr. Chen (Stat reviewer) and Dr. Cooner (Stat team leader) that the netupitant-palonosetron Combination Capsule development program has established the efficacy of this fixed dose combination in patients receiving chemotherapy including HEC.

NETU-07-07 is the efficacy trial in patients receiving HEC. It was conducted in conjunction with PALO-10-01, which aimed to demonstrate the efficacy of oral palonosetron 0.50 mg in the HEC setting. NETU-08-18 is another efficacy trial in patients receiving chemotherapy including MEC (ASCO reclassified AC regimen as HEC in 2011).
All the pivotal efficacy studies reached their objectives.

- NETU-07-07 demonstrated statistical superiority of the netupitant/palonosetron 300 mg/0.5 mg FDC dose group versus oral palonosetron 0.5 mg alone.

- NETU-08-18 demonstrated statistical superiority of the FDC versus oral palonosetron alone in the delayed (p=0.001), acute (p=0.047) and overall (p=0.001) phases at cycle 1.

- PALO-10-01 demonstrated the non-inferiority of oral 0.50 mg versus I.V. 0.25 mg palonosetron since the lower limit of the two-sided 99% CI for the difference in proportions was greater (i.e., closer to zero) than pre-defined non-inferiority margin set at -15% (99% CI: -2.74% to 9.17% from stratum-adjusted CMH method for difference in proportions).

Both NETU-07-07 and NETU-08-18 isolated and demonstrated the contribution of netupitant to the FDC, consistent with regulatory requirements for fixed combination drugs. PALO-10-01 demonstrated the efficacy of oral palonosetron 0.50 mg in the HEC setting in the acute phase. Furthermore, PALO-10-01 demonstrated that oral palonosetron 0.5 mg contributes to the efficacy of the FDC in the HEC setting (oral ALOXI 0.5 mg is registered for the prevention of acute CINV induced by MEC only).

Two trials collected efficacy data over multiple cycles of chemotherapy (NETU-08-18 and NETU-10-29). For both studies, the complete response rates were similar in the multiple cycles up to cycle 6 compared to cycle 1.

Please refer to Dr. Snow's review dated July 10, 2014, Dr. Chen's review dated July 2, 2014 and Dr. Cooner's review dated July 4, 2014.

8. Safety

Exposure

Overall, there were a total of 4331 subjects in the overall safety population. The ISS database contains safety data from 3280 patients with cancer who received at least one dose of the investigational medicinal product or the active comparators during the Phase 2/3 CINV studies (NETU-07-07, NETU-08-18, NETU-10-29, and PALO-10-01); of these patients, 1862 were treated in the Phase 3 multicycle studies. Supporting data are presented from 1051 subjects who received at least one dose of the investigational product in studies of healthy volunteers (N = 702) and studies in special populations (N = 349).

During the development program, a total of 1939 subjects received any dose of netupitant and palonosetron in combination (either as the FDC or extemporaneous formulation), including 1442 patients with cancer participating in Phase 2/3 studies, 393 healthy volunteers and 104 subjects in the special population studies. A total of 1538 subjects and patients were exposed to the netupitant-palonosetron combination (300/0.50 mg) during the clinical program; of these, 1169 patients with cancer received at least one dose while participating in one of the 4 key double-blind Phase 2/3 studies; the remaining subjects were exposed to the proposed market combination dose during Phase 1 studies in healthy volunteers (N = 265) and studies in special populations (N = 104).

Treatment exposure for all single-dose studies shows that the 1939 subjects who were exposed to netupitant-palonosetron combination (any dose) had a total of 5843 exposures and the 1538 subjects exposed to the proposed market dose had 5441 exposures. Treatment exposure (days) in multiple cycle Studies NETU-08-18 and NETU-10-29 in cancer patients shows that the mean (SD)

exposure for the FDC, oral palonosetron and the aprepitant+palonosetron regimen was 4.3 (1.83), 4.1 (1.55) and 14.8 (7.04) days.

Netupitant alone was administered in multiple doses in Studies NETU-08-03 and NP1661 where mean (SD) exposure to study drug was 52.0 (12.68) and 6.7 (1.24) days, respectively.

Patient Disposition

Of the 4366 total randomized patients/subjects, 4331 (100%) were in the safety population. Eighty-one percent (80.7%) completed the studies and 19.3% prematurely discontinued, mostly due to "other" reasons (8.8%), withdrawal by subject (3.8%) and AE (1.8%). The "other" reason was mostly due to patients who discontinued the study due to trial closure (i.e. they completed their ongoing cycle and then did not enter the following cycle they had been scheduled to enter). The Phase 3 protocols were designed to close when the last patient enrolled had completed her/his final chemotherapy cycle. After this time, each patient enrolled in the trial was to complete the current cycle and were not permitted to enter any further cycle.

Across treatments, the premature discontinuation rates were similar (18.4%, 15.2%, 22.1% and 21.0% for the palonosetron, netupitant alone, netupitant-palonosetron and comparator treated subjects). The most frequent reasons for discontinuation were also generally consistent across treatments.

Of the 3280 Phase 2/3 cancer patients treated in the program, 2537 (77.3%) completed their chemotherapy cycles. Overall, 89 patients (2.7%) prematurely discontinued the study after randomization and 652 (19.9%) completed a cycle but did not continue into the next planned cycle. Those who did not continue into the next cycle were categorized as "other" and were largely due to the closing of Phase 3 trials as indicated previously (10.6%; 347 patients). Additional reasons included multiple extension screen failure (3.6%) withdrawal by subject (3.4%) and AE (1.5%). Those who discontinued the trial prematurely in the netupitant-palonosetron group were due to withdrawal by the subject (0.8%; 11 patients) or death (0.6%; 9 patients) and in the palonosetron group were due to death (1.1%; 18 patients) or withdrawal by subject (0.7%; 11 patients) (Table 10).

Table 9: **Disposition of Subjects Phase 2/3 Cancer Patients (Safety Population)**

	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
				Total	IV	Oral	Total	*Aprepitant plus:*		Total	
	100/0.50 (N=135) n (%)	200/0.50 (N=138) n (%)	300/0.50 (N=1169) n (%)	(N=1442) n (%)	0.25 (N=369) n (%)	0.50 (N=1231) n (%)	(N=1600) n (%)	PALO (N=104) n (%)	OND (N=134) n (%)	(N=238) n (%)	(N=3280) n (%)
Completed planned/unplanned chemotherapy cycles	134 (99.3)	137 (99.3)	770 (65.9)	1041 (72.2)	351 (95.1)	957 (77.7)	1308 (81.8)	55 (52.9)	133 (99.3)	188 (79.0)	2537 (77.3)
Completed planned/unplanned chemotherapy cycles but discontinued during additional unplanned cycle	–	–	2 (0.2)	2 (0.1)	–	–	–	–	–	–	2 (0.1)
Other	–	–	1 (0.1)	1 (0.1)	–	–	–	–	–	–	1 (0.0)
Completed a cycle but not continuing in the next planned cycle	–	–	365 (31.2)	365 (25.3)	–	244 (19.8)	244 (15.3)	43 (41.3)	–	43 (18.1)	652 (19.9)
Adverse event	–	–	27 (2.3)	27 (1.9)	–	15 (1.2)	15 (0.9)	8 (7.7)	–	8 (3.4)	50 (1.5)
Death	–	–	4 (0.3)	4 (0.3)	–	1 (0.1)	1 (0.1)	–	–	–	5 (0.2)
Protocol violation	–	–	7 (0.6)	7 (0.5)	–	–	–	1 (1.0)	–	1 (0.4)	8 (0.2)
Lost to follow-up	–	–	5 (0.4)	5 (0.3)	–	2 (0.2)	2 (0.1)	1 (1.0)	–	1 (0.4)	8 (0.2)
Withdrawal by subject	–	–	69 (5.9)	69 (4.8)	–	36 (2.9)	36 (2.3)	6 (5.8)	–	6 (2.5)	111 (3.4)
Lack of efficacy	–	–	1 (0.1)	1 (0.1)	–	3 (0.2)	3 (0.2)	–	–	–	4 (0.1)
Sponsor decision	–	–	1 (0.1)	1 (0.1)	–	–	–	–	–	–	1 (0.0)
Other	–	–	198 (16.9)	198 (13.7)	–	122 (9.9)	122 (7.6)	27 (26.0)	–	27 (11.3)	347 (10.6)
Multicycle screen failure	–	–	53 (4.5)	53 (3.7)	–	65 (5.3)	65 (4.1)	–	–		118 (3.6)
Discontinued after randomization and during any planned chemotherapy cycle	1 (0.7)	1 (0.7)	32 (2.7)	34 (2.4)	18 (4.9)	30 (2.4)	48 (3.0)	6 (5.8)	1 (0.7)	7 (2.9)	89 (2.7)
Adverse event	–	1 (0.7)	3 (0.3)	4 (0.3)	1 (0.3)	4 (0.3)	5 (0.3)	4 (3.8)	–	4 (1.7)	13 (0.4)
Death	1 (0.7)	–	8 (0.7)	9 (0.6)	11 (3.0)	7 (0.6)	18 (1.1)	–	–	–	27 (0.8)
Protocol violation	–	–	1 (0.1)	1 (0.1)	1 (0.3)	3 (0.2)	4 (0.3)	–	–	–	5 (0.2)
Lost to follow-up	–	–	–	–	3 (0.8)	4 (0.3)	7 (0.4)	–	1 (0.7)	1 (0.4)	8 (0.2)
Withdrawal by subject	–	–	11 (0.9)	11 (0.8)	2 (0.5)	9 (0.7)	11 (0.7)	2 (1.9)	–	2 (0.8)	24 (0.7)
Sponsor decision	–	–	–	–	–	1 (0.1)	1 (0.1)	–	–	–	1 (0.0)
Other	–	–	7 (0.6)	7 (0.5)	–	1 (0.1)	1 (0.1)	–	–	–	8 (0.2)
Multicycle screen failure	–	–	2 (0.2)	2 (0.1)	–	1 (0.1)	1 (0.1)	–	–	–	3 (0.1)

PALO = palonosetron; OND = ondansetron;
Source: Modified from (Module 5.3.5.3: ISS Table 1.2.3.1 through Table 1.2.3.4)

Overview of Adverse Events

During cycle 1 in the Phase 2/3 studies, overall 61.7% (2024/3280 patients) reported at least 1 TEAE (the netupitant-palonosetron groups (65.5%, 944/1442 patients) and the palonosetron groups (59.1%, 945/1600 patients)).

Among the patients treated with netupitant-palonosetron, the frequency of patients experiencing at least 1 TEAE ranged from 40.7% (55/135 patients) in the 100/0.50 mg group to 70.0% (818/1169 patients) in the 300/0.50 mg group. In the palonosetron groups, the frequency of TEAEs was 51.8% in the 0.25 mg IV group (191/369 patients) and 61.3% in the 0.50 oral group (754/1231 patients). However, differences in the incidence of events between the treatment groups should be interpreted with some caution due to the small number of patients in some groups, the patients' cancer type, and the concomitant chemotherapy received which differed by study.

Serious TEAEs occurred infrequently in cycle 1 of the Phase 2/3 studies (3.8%, 124/3280), with a higher frequency of patients with SAEs in the palonosetron groups (5.4%, 87/1600) than in the netupitant-palonosetron groups (2.3%, 33/1442) or the comparator groups (1.7%, 4/238).

Of the 1862 patients in the multicycle study safety population, 89.7% (1670/1862) experienced at least 1 TEAE in the two multicycle studies, with a similar frequency across the 3 treatment groups: 90.3% (933/1033 patients) in the netupitant-palonosetron group, 88.6% (642/725 patients) in the palonosetron group, and 91.3% (95/104 patients) in the comparator aprepitant+palonosetron group.

Dr. Snow provided safety evaluation for each individual trial in her review. In the following section, I will provide integrated analyses.

Table 10: Overview of Treatment-Emergent Adverse Events – All Cycles (Phase 3 Multicycle Studies)

	Netupitant-Palonosetron	Palonosetron	Comparator	Total
	300/0.50 mg (N=1033) n (%)	0.50 mg PO (N=725) n (%)	Aprepitant + Palonosetron (N=104) n (%)	(N=1862) n (%)
Number of patients with ≥ 1:				
TEAE	933 (90.3)	642 (88.6)	95 (91.3)	1670 (89.7)
Drug-related TEAE	131 (12.7)	81 (11.2)	6 (5.8)	218 (11.7)
Serious TEAE	85 (8.2)	24 (3.3)	19 (18.3)	128 (6.9)
Drug-related serious TEAE	2 (0.2)	–	–	2 (0.1)
TEAE leading to death	16 (1.5)	2 (0.3)	1 (1.0)	19 (1.0)
TEAE leading to discontinuation	43 (4.2)	18 (2.5)	13 (12.5)	74 (4.0)
Drug-related TEAE leading to discontinuation	1 (0.1)	4 (0.6)	–	5 (0.3)

Source: Module 5.3.5.3, ISS Table 2.2.3

Abbreviations: n (%) = number and percentage of patients affected; TEAE=treatment emergent adverse event.

Common Adverse Events

Phase 2/3 Cancer Patients *Cycle 1*

In the Phase 2/3 studies, the most frequently reported TEAEs (i.e., those reported by > 5% of patients in any treatment group overall) were alopecia, neutropenia, leukopenia, asthenia, headache, fatigue, diarrhea, and decreased appetite. The events reported are consistent with the population evaluated in these trials, as subjects undergoing chemotherapy are expected to have a variety of hematological events, hair loss, general weakness, and GI effects mainly due to the toxic effects of chemotherapy as well as disease-related processes.

Table 11 Patients with Treatment-emergent Adverse Events with an Incidence ≥5% – Cycle 1 Phase 2/3 Cancer Studies, Patients Treated with Netupitant-Palonosetron

	Netupitant-Palonosetron Combination			All Doses
	100/0.50 mg (N=135) n (%)	200/0.50 mg (N=138) n (%)	300/0.50 mg (N=1169) n (%)	(N=1442) n (%)
Number of patients with any TEAE	55 (40.7)	71 (51.4)	818 (70.0)	944 (65.5)
Blood and lymphatic system disorders	14 (10.4)	10 (7.2)	329 (28.1)	353 (24.5)
Leukocytosis	10 (7.4)	7 (5.1)	17 (1.5)	34 (2.4)
Leukopenia	1 (0.7)	2 (1.4)	134 (11.5)	137 (9.5)
Neutropenia	–	–	221 (18.9)	221 (15.3)
Neutrophilia	5 (3.7)	4 (2.9)	7 (0.6)	16 (1.1)
Cardiac disorders	7 (5.2)	11 (8.0)	38 (3.3)	56 (3.9)
Gastrointestinal disorders	16 (11.9)	22 (15.9)	175 (15.0)	213 (14.8)
Constipation	3 (2.2)	4 (2.9)	51 (4.4)	58 (4.0)
Diarrhoea	3 (2.2)	3 (2.2)	27 (2.3)	33 (2.3)
Dyspepsia	3 (2.2)	9 (6.5)	24 (2.1)	36 (2.5)
General disorders and administration site conditions	12 (8.9)	17 (12.3)	181 (15.5)	210 (14.6)
Asthenia	4 (3.0)	12 (8.7)	81 (6.9)	97 (6.7)
Fatigue	6 (4.4)	4 (2.9)	69 (5.9)	79 (5.5)
Infections and infestations	1 (0.7)	–	55 (4.7)	56 (3.9)
Investigations	12 (8.9)	24 (17.4)	108 (9.2)	144 (10.0)
Alanine aminotransferase increased	6 (4.4)	7 (5.1)	25 (2.1)	38 (2.6)
Neutrophil count increased	4 (3.0)	10 (7.2)	6 (0.5)	20 (1.4)
Metabolism and nutrition disorders	10 (7.4)	10 (7.2)	95 (8.1)	115 (8.0)
Decreased appetite	4 (3.0)	5 (3.6)	42 (3.6)	51 (3.5)
Musculoskeletal and connective tissue disorders	1 (0.7)	–	32 (2.7)	33 (2.3)
Nervous system disorders	10 (7.4)	15 (10.9)	115 (9.8)	140 (9.7)
Headache	5 (3.7)	11 (8.0)	80 (6.8)	96 (6.7)
Respiratory, thoracic and mediastinal disorders	8 (5.9)	6 (4.3)	48 (4.1)	62 (4.3)
Skin and subcutaneous tissue disorders	1 (0.7)	3 (2.2)	317 (27.1)	321 (22.3)
Alopecia	–	–	294 (25.1)	294 (20.4)
Vascular disorders	6 (4.4)	5 (3.6)	39 (3.3)	50 (3.5)

Source: Modified from Module 5.3.5.3, ISS Table 2.5.1.1
Abbreviations: n = number of patients; TEAE = treatment emergent adverse event
Note: patients with multiple events counted only once per line.

Table 12 Patients with Treatment-emergent Adverse Events with an Incidence ≥5% – Cycle 1 Phase 2/3 Cancer Studies, Patients Treated with Palonosetron

	Palonosetron		All Doses
	0.25 mg IV (N=369) n (%)	0.50 mg PO (N=1231) n (%)	(N=1600) n (%)
Number of patients with any TEAE	191 (51.8)	754 (61.3)	945 (59.1)
Blood and lymphatic system disorders	46 (12.5)	284 (23.1)	330 (20.6)
Leukocytosis	4 (1.1)	19 (1.5)	23 (1.4)
Leukopenia	5 (1.4)	101 (8.2)	106 (6.6)
Neutropenia	28 (7.6)	203 (16.5)	231 (14.4)
Neutrophilia	3 (0.8)	13 (1.1)	16 (1.0)
Cardiac disorders	11 (3.0)	30 (2.4)	41 (2.6)
Gastrointestinal disorders	67 (18.2)	169 (13.7)	236 (14.8)
Constipation	20 (5.4)	50 (4.1)	70 (4.4)
Diarrhoea	7 (1.9)	26 (2.1)	33 (2.1)
Dyspepsia	7 (1.9)	14 (1.1)	21 (1.3)
General disorders and administration site conditions	64 (17.3)	169 (13.7)	233 (14.6)
Asthenia	28 (7.6)	94 (7.6)	122 (7.6)
Fatigue	15 (4.1)	51 (4.1)	66 (4.1)
Infections and infestations	7 (1.9)	41 (3.3)	48 (3.0)
Investigations	45 (12.2)	113 (9.2)	158 (9.9)
Alanine aminotransferase increased	9 (2.4)	27 (2.2)	36 (2.3)
Neutrophil count increased	–	5 (0.4)	5 (0.3)
Metabolism and nutrition disorders	30 (8.1)	110 (8.9)	140 (8.8)
Decreased appetite	11 (3.0)	65 (5.3)	76 (4.8)
Musculoskeletal and connective tissue disorders	7 (1.9)	20 (1.6)	27 (1.7)
Nervous system disorders	28 (7.6)	97 (7.9)	125 (7.8)
Headache	21 (5.7)	70 (5.7)	91 (5.7)
Respiratory, thoracic and mediastinal disorders	18 (4.9)	50 (4.1)	68 (4.3)
Skin and subcutaneous tissue disorders	13 (3.5)	273 (22.2)	286 (17.9)
Alopecia	7 (1.9)	259 (21.0)	266 (16.6)
Vascular disorders	13 (3.5)	29 (2.4)	42 (2.6)

Source: Modified from Module 5.3.5.3, ISS Table 2.5.1.2
Abbreviations: n = number of patients; TEAE = treatment emergent adverse event
Note: patients with multiple events counted only once per line.

Table 13 Patients with Treatment-emergent Adverse Events with an Incidence ≥5% – Cycle 1 Phase 2/3 Cancer Studies, Patients Treated with Comparators

System Organ Class/ Preferred Term	Comparator Aprepitant Plus		Total
	Palonosetron (N=104) n (%)	Ondansetron (N=134) n (%)	Aprepitant Plus 5HT3 (N=238) n (%)
Number of patients with any TEAE	64 (61.5)	71 (53.0)	135 (56.7)
Blood and lymphatic system disorders	20 (19.2)	13 (9.7)	33 (13.9)
Leukocytosis	–	6 (4.5)	6 (2.5)
Leukopenia	11 (10.6)	–	11 (4.6)
Neutropenia	12 (11.3)	1 (0.7)	13 (5.5)
Neutrophilia	–	7 (5.2)	7 (2.9)
Cardiac disorders	1 (1.0)	13 (9.7)	14 (5.9)
Gastrointestinal disorders	21 (20.2)	26 (19.4)	47 (19.7)
Constipation	3 (2.9)	5 (3.7)	8 (3.4)
Diarrhoea	7 (6.7)	6 (4.5)	13 (5.5)
Dyspepsia	1 (1.0)	5 (3.7)	6 (2.5)
General disorders and administration site conditions	16 (15.4)	19 (14.2)	35 (14.7)
Asthenia	4 (3.8)	13 (9.7)	17 (7.1)
Fatigue	8 (7.7)	5 (3.7)	13 (5.5)
Infections and infestations	7 (6.7)	1 (0.7)	8 (3.4)
Investigations	13 (12.5)	17 (12.7)	30 (12.6)
Alanine aminotransferase increased	2 (1.9)	6 (4.5)	8 (3.4)
Neutrophil count increased	–	5 (3.7)	5 (2.1)
Metabolism and nutrition disorders	9 (8.7)	13 (9.7)	22 (9.2)
Decreased appetite	4 (3.8)	9 (6.7)	13 (5.5)
Musculoskeletal and connective tissue disorders	7 (6.7)	–	7 (2.9)
Nervous system disorders	6 (5.8)	16 (11.9)	22 (9.2)
Headache	1 (1.0)	12 (9.0)	13 (5.5)
Respiratory, thoracic and mediastinal disorders	8 (7.7)	2 (1.5)	10 (4.2)
Skin and subcutaneous tissue disorders	13 (12.5)	4 (3.0)	17 (7.1)
Alopecia	10 (9.6)	–	10 (4.2)
Vascular disorders	6 (5.8)	5 (3.7)	11 (4.6)

Source: Modified from Module 5.3.5.3, ISS Table 2.5.1.3
Abbreviations: n = number of patients; TEAE = treatment emergent adverse event
Note: patients with multiple events counted only once per line.

For the multicycle Phase 3 studies, TEAEs reported by at least 5% of patients in any treatment group are summarized by system organ class and preferred term in Table 14.

Table 14: Patients with Treatment-emergent Adverse Events with an Incidence ≥5% in Any Treatment Group by Preferred Term – All Cycles (Phase 3 Multicycle Studies)

System Organ Class/ Preferred Term	NETU 300/0.50 mg (N=1033) n (%)	PALO 0.50 mg PO (N=725) n (%)	Comparator Aprepitant+PALO (N=104) n (%)	Total (N=1862) n (%)
Number of patients with any TEAE	933 (90.3)	642 (88.6)	95 (91.3)	1670 (89.7)
Blood and lymphatic system disorders	517 (50.0)	371 (51.2)	48 (46.2)	936 (50.3)
Anaemia	125 (12.1)	60 (8.3)	26 (25.0)	211 (11.3)
Leukopenia	232 (22.5)	173 (23.9)	18 (17.3)	423 (22.7)
Neutropenia	390 (37.8)	317 (43.7)	29 (27.9)	736 (39.5)
Thrombocytopenia	62 (6.0)	17 (2.3)	16 (15.4)	95 (5.1)
Cardiac disorders	74 (7.2)	42 (5.8)	8 (7.7)	124 (6.7)
Gastrointestinal disorders	293 (28.4)	172 (23.7)	38 (36.5)	503 (27.0)
Constipation	75 (7.3)	55 (7.6)	9 (8.7)	139 (7.5)
Diarrhoea	75 (7.3)	30 (4.1)	19 (18.3)	124 (6.7)
Nausea	64 (6.2)	53 (7.3)	11 (10.6)	128 (6.9)
Stomatitis	43 (4.2)	25 (3.4)	6 (5.8)	74 (4.0)
Gen. disorders and administration site conditions	309 (29.9)	194 (26.8)	35 (33.7)	538 (28.9)
Asthenia	138 (13.4)	91 (12.6)	12 (11.5)	241 (12.9)
Fatigue	117 (11.3)	72 (9.9)	15 (14.4)	204 (11.0)
Pyrexia	48 (4.6)	28 (3.9)	10 (9.6)	86 (4.6)
Infections and infestations	153 (14.8)	76 (10.5)	19 (18.3)	248 (13.3)
Investigations	193 (18.7)	117 (16.1)	25 (24.0)	335 (18.0)
Blood creatinine increased	12 (1.2)	4 (0.6)	6 (5.8)	22 (1.2)
Metabolism and nutrition disorders	177 (17.1)	113 (15.6)	19 (18.3)	309 (16.6)
Decreased appetite	71 (6.9)	58 (8.0)	7 (6.7)	136 (7.3)
Hyperglycemia	63 (6.1)	53 (7.3)	3 (2.9)	119 (6.4)
Musculoskeletal and connective tissue disorders	77 (7.5)	38 (5.2)	15 (14.4)	130 (7.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	36 (3.5)	6 (0.8)	7 (6.7)	49 (2.6)
Nervous system disorders	186 (18.0)	126 (17.4)	24 (23.1)	336 (18.0)
Headache	114 (11.0)	89 (12.3)	7 (6.7)	210 (11.3)
Psychiatric disorders	61 (5.9)	31 (4.3)	1 (1.0)	93 (5.0)
Renal and urinary disorders	38 (3.7)	32 (4.4)	12 (11.5)	82 (4.4)
Respiratory, thoracic and mediastinal disorders	91 (8.8)	36 (5.0)	19 (18.3)	146 (7.8)
Cough	35 (3.4)	15 (2.1)	8 (7.7)	58 (3.1)
Skin and subcutaneous tissue disorders	507 (49.1)	414 (57.1)	37 (35.6)	958 (51.5)
Alopecia	475 (46.0)	394 (54.3)	32 (30.8)	901 (48.4)
Vascular disorders	76 (7.4)	41 (5.7)	12 (11.5)	129 (6.9)

n = number of patients; NETU = netupitant; PALO = palonosetron; TEAE = treatment-emergent adverse event
Source: Modified from Module 5.3.5.3, ISS Table 2.3.3

Drug-related Adverse Events

Phase 2/3 Cancer Patients *Cycle 1*

Overall, the percent of patients with at least 1 TEAE assessed as being related to study drugs by the investigator was 9.6% in the netupitant-palonosetron groups, 6.6% in the palonosetron group , and 12.2% in the aprepitant+5-HT3 comparator group (Table 15).

Table 15 Patients with Drug-related Treatment-emergent Adverse Events with an Incidence ≥ 2% – Cycle 1 (Phase 2/3 Cancer Studies)

	Netupitant–Palonosetron (mg)				Palonosetron Alone (mg)			Comparators			All Patients
System Organ Class/ Preferred Term	100/0.50 (N=135)	200/0.50 (N=138)	300/0.50 (N=1169)	Total (N=1442)	IV 0.25 (N=369)	Oral 0.50 (N=1231)	Total (N=1600)	*Aprepitant plus:* PALO (N=104)	OND (N=134)	Total (N=238)	(N=3280)
Number of patients with any drug-related TEAE	18 (13.3)	24 (17.4)	96 (8.2)	138 (9.6)	24 (6.5)	81 (6.6)	105 (6.6)	3 (2.9)	26 (19.4)	29 (12.2)	272 (8.3)
Blood and lymphatic system disorders	2 (1.5)	1 (0.7)	4 (0.3)	7 (0.5)	–	6 (0.5)	6 (0.4)	–	4 (3.0)	4 (1.7)	17 (0.5)
Cardiac disorders	3 (2.2)	3 (2.2)	8 (0.7)	14 (1.0)	2 (0.5)	4 (0.3)	6 (0.4)	–	10 (7.5)	10 (4.2)	30 (0.9)
Bradycardia	1 (0.7)	–	–	1 (0.1)	–	–	–	–	3 (2.2)	3 (1.3)	4 (0.1)
Gastrointestinal disorders	4 (3.0)	9 (6.5)	35 (3.0)	48 (3.3)	11 (3.0)	32 (2.6)	43 (2.7)	2 (1.9)	5 (3.7)	7 (2.9)	98 (3.0)
Constipation	2 (1.5)	2 (1.4)	23 (2.0)	27 (1.9)	9 (2.4)	20 (1.6)	29 (1.8)	–	2 (1.5)	2 (0.8)	58 (1.8)
Dyspepsia	–	4 (2.9)	2 (0.2)	6 (0.4)	–	4 (0.3)	4 (0.3)	1 (1.0)	–	1 (0.4)	11 (0.3)
Investigations	3 (2.2)	5 (3.6)	9 (0.8)	17 (1.2)	5 (1.4)	7 (0.6)	12 (0.8)	–	3 (2.2)	3 (1.3)	32 (1.0)
ALT increased	1 (0.7)	3 (2.2)	3 (0.3)	7 (0.5)	1 (0.3)	2 (0.2)	3 (0.2)	–	2 (1.5)	2 (0.8)	12 (0.4)
AST increased	1 (0.7)	3 (2.2)	1 (0.1)	5 (0.3)	–	2 (0.2)	2 (0.1)	–	2 (1.5)	2 (0.8)	9 (0.3)
Nervous system disorders	4 (3.0)	5 (3.6)	31 (2.7)	40 (2.8)	6 (1.6)	29 (2.4)	35 (2.2)	1 (1.0)	5 (3.7)	6 (2.5)	81 (2.5)
Headache	1 (0.7)	3 (2.2)	28 (2.4)	32 (2.2)	6 (1.6)	26 (2.1)	32 (2.0)	1 (1.0)	3 (2.2)	4 (1.7)	68 (2.1)
Respiratory, thoracic and mediastinal disorders	5 (3.7)	5 (3.6)	7 (0.6)	17 (1.2)	2 (0.5)	6 (0.5)	8 (0.5)	–	–	–	25 (0.8)
Hiccups	5 (3.7)	5 (3.6)	7 (0.6)	17 (1.2)	2 (0.5)	6 (0.5)	8 (0.5)	–	–	–	25 (0.8)

PALO = palonosetron; OND = ondansetron; TEAE = treatment-emergent adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase
Source: Modified from (Module 5.3.5.3: ISS) Table 2.6.7.1, Table 2.6.7.2, Table 2.6.7.3, and Table 2.6.7.4

No clear pattern was seen across the netupitant-palonosetron dose groups or between the 2 palonosetron dose groups in the overall frequency of related TEAEs.

The only TEAE PT that was reported in ≥ 2% of patients in any of the 3 treatment groups overall was headache, which occurred in 2.2% (32/1442 patients) in the netupitant-palonosetron groups, 2% (32/1600 patients) in the palonosetron groups, and 1.7% (4/238 patients) in the aprepitant+5-HT_3 comparator group (Module 5.3.5.3: ISS, Tables 2.6.7.1 through 2.6.7.4). Constipation occurred at a frequency of 2.4% after IV palonosetron and 2.0% after the FDC 300/0.50 mg, but was not greater than 2.0% in the overall dose groups.

Assessments for drug-related adverse events were assessed as being related to study drugs by the investigator. Clearly the investigator did not include the most frequently reported TEAEs like alopecia, neutropenia, leukopenia, asthenia, headache, fatigue, diarrhea, and decreased appetite that were consistent with chemotherapy. Although the events reported are consistent with the population evaluated in these trials, as subjects undergoing chemotherapy are expected to have a variety of hematological events, hair loss, general weakness, and GI effects mainly due to the toxic effects of chemotherapy as well as disease-related processes, it is impossible to conclude that study drug (netupitant-palonosetron) does not cause or contribute to some degree of those events. Especially, the study drug may increase the concentration of some chemotherapy agents through drug-drug interaction.

Deaths
Of the 3280 patients in the 4 key Phase 2/3 studies in patients with cancer, 39 patients (1.2%) died on-study. None of the deaths was considered by the investigator to be related to investigational product, with most of the deaths being attributable to disease-related progression or to complications due the toxic effects of chemotherapy.

In the Phase 2/3 studies, 28 patients (0.9%) died during cycle 1, and 11 patients died during the remaining chemotherapy cycles, as follows:

- In cycle 1, of the 28 patients who died, 20 patients out of 1600 (1.3%) had received either IV or oral palonosetron (19 were treated in single-cycle Study PALO-10-01 and 1 in Study NETU-08-18); 8 patients (of 1442 [0.6%]) had received netupitant-palonosetron; no subjects in the aprepitant+5-HT3 group had a fatal TEAE during cycle 1.

- During the remaining cycles (i.e., patients in the Phase 3 multicycle studies), 19 patients died (of 1862 patients treated during the multicycle studies [1.0%]). There did not appear to be an influence of repeated dosing on the incidence of fatal adverse events, as the overall incidence of adverse events resulting in death was similar across chemotherapy cycles (range of incidences: 0.1% [cycle 2 and cycle 4] to 0.4% [cycle 1 and cycle 6]).

In addition to the deaths reported above, there were 5 patients in Study NETU-10-29 who experienced TEAEs with a final fatal outcome, but who were not included in the data as on-study deaths: 3 of these patients (2 in the netupitant-palonosetron group and 1 in the aprepitant+5-HT3 group) died after completion of all chemotherapy cycles to which they were scheduled (i.e., these patients, per protocol, were considered to have completed study); 1 patient withdrew from the study due to an AE (which ultimately had a fatal outcome). Patient 5303/02, a 64-year-old male with metastatic adenocarcinoma of lung and respiratory tract in the aprepitant+palonosetron group, experienced renal insufficiency of moderate intensity on (b) (6) 3 days after the last administration of study drugs. The patient developed severe convulsions on (b) (6) and, despite corrective treatment for the events, the patient's symptoms worsened on (b) (6). The patient exited the study on (b) (6) The patient died on (b) (6) after study end. One patient withdrew from the study due to other reasons (investigator assessment: worsening of global health condition) and died a few days after discontinuation.

Of the remaining patients in the netupitant-palonosetron clinical development program (i.e., healthy volunteers and patients in special population studies), 2 died on-study. Both were cancer patients treated with the netupitant/palonosetron FDC (300/0.50 mg) prior to docetaxel chemotherapy in drug-interaction Study NETU-10-09. Neither death was assessed by the investigator as being related to netupitant/palonosetron FDC. In the first case, the patient (81-year-old male with prostate cancer) was hospitalized because of dehydration, neutropenia, and pneumonia, and died following circulatory and respiratory insufficiency associated to pneumonia. The events were considered to be related (possibly and definitely) to docetaxel. In the second case, the patient (a 63-year-old female with lung adenocarcinoma) was hospitalized after experiencing respiratory failure with dyspnea, and later died after developing severe neutropenia (nonserious) and pulmonary edema. The death was attributed to progression of lung cancer, and was not considered to be related to docetaxel or to investigational product.

In conclusion, a total of 46 patients who participated in the clinical development program had a TEAE that resulted in death; all were cancer patients and none of the deaths was considered related to study medication. Thirty-nine of these patients were participating in the Phase 2/3 studies at the time of their death; 2 were enrolled in a PK chemotherapy interaction trial, and 5 were considered post-study deaths.

Other Serious Events

Phase 2/3 Cancer Patients

Cycle 1

The overall incidence of serious TEAEs during cycle 1 of the Phase 2/3 studies was 3.8%; 2.3% in the netupitant-palonosetron groups, 5.4% in the palonosetron group, and 1.7% in the aprepitant+5-HT_3 group. The most commonly reported events were coded to the system organ classes of blood and lymphatic system disorders (1.2%, overall), GI disorders (0.8%), general disorders and administration site conditions (0.5%), and respiratory, thoracic, and mediastinal disorders (0.5%).

By preferred term, neutropenia and febrile neutropenia were the most commonly reported serious TEAEs; these are known to be frequent events associated with the administration of chemotherapy. Both of these serious TEAEs were reported in the palonosetron (0.9% and 0.6% for neutropenia and febrile neutropenia) and netupitant-palonosetron groups (0.2% and 0.3%, respectively), but not in the aprepitant+5-HT_3 group.

Four patients (< 0.1%) in cycle 1 of the Phase 2/3 studies had serious TEAEs that were considered by the investigator to be related to investigational product: 2 patients in the netupitant-palonosetron groups (events of *loss of consciousness* and *acute psychosis*) and 2 patients in the palonosetron group (0.50 mg PO; events of *abdominal pain* and *constipation* in 1 patient, and *diarrhea* and *asthenia* in 1 patient).

Phase 3 Multicycle Studies

All Cycles

The overall subject incidence of SAEs was 6.9% across all cycles of the Phase 3 multicycle program, with SAEs being reported more frequently for patients in the aprepitant+palonosetron group (18.3%) than in the netupitant-palonosetron (8.2%) or palonosetron groups (3.3%). In general, the most common SAEs were categorized within the system organ classes of blood and lymphatic system disorders (3.1% netupitant-palonosetron; 1.1% palonosetron; 4.8% aprepitant+palonosetron), GI disorders (1.8% netupitant-palonosetron; 0.3% palonosetron; 3.8% aprepitant+palonosetron), and infections and infestations (1.5% netupitant-palonosetron; 0.7% palonosetron; 3.8% aprepitant+palonosetron), consistent with those expected for a population of patients with cancer receiving multicycle chemotherapy.

By preferred term, the most common SAEs (≥ 0.3% overall) observed in patients were febrile neutropenia (1.2%), neutropenia (0.7%), vomiting (0.4%), anemia (0.4%), and leukopenia (0.3%). In the netupitant-palonosetron and palonosetron groups, febrile neutropenia was the most frequently reported SAE (1.5% [16/1033] and 0.8% [6/725], respectively), while anemia was the most frequently reported SAE among patients in the aprepitant+palonosetron group (2.9%; 3/104). For other individual preferred terms, there did not appear to be a pattern observed with respect to the types of SAEs that were reported with greater subject incidence, and the low incidence of each of these SAEs across treatment groups precludes meaningful comparison.

Adverse Events Leading to Withdrawal from the Study

Of the 3280 patients with cancer treated in the Phase 2/3 studies, 24 (0.7%) reported AEs during cycle 1 that resulted in withdrawal from the study. Of these AEs, those that were reported for > 1 patient were neutropenia (3/1169 patients [0.3%]) in the netupitant-palonosetron 300/0.50 mg group, and nausea (2/1231 patients [0.2%]) in the palonosetron 0.50 mg group.

Four subjects (0.1%) experienced AEs leading to withdrawal from the study that, in the opinion of the investigator, were related to investigational product. Of these patients, 2 (of 1442 [0.1%]) had received netupitant-palonosetron (AEs of *loss of consciousness* and *acute psychosis* [both serious]), and 2 (of 1600 [0.1%]) had received palonosetron 0.50 mg only (AEs of *nausea* and *urticaria*).

Assessment of Potential Liver Toxicity

The sponsor provided an expert assessment of potential liver toxicity by (b) (4) I concur with (b) (4) assessment and conclusion.

Study cancer patients with an increase of Aspartate amino transferase (AST), Alanino amino transferase (ALT) more than 3 times the upper normal limit (or both elevated), with an increase of total bilirubin more than 1.5 times the upper normal limit and an increase of Alkaline phosphatase (ALP) more than 1.5 times the upper normal limit have been taken into consideration. A total of 14 patients have been identified in the clinical trials: 7 cases in NETU 07-07, 5 cases in NETU 08-18 and 2 cases in PALO 10-01. In study NETU 10-29 no patients have been identified. Following case evaluations are directly from (b) (4) report.

Case 1) PT ID 129-1503 - female, 54 yrs
Treatment: palonosetron 0.50 mg + netupitant 100 mg + dexamethasone
Cancer type: primary ovarian cancer.
Medical history: Salpingo-oophorectomy and omentectomy in (b) (6)
Liver tests at baseline: ALT 33 U/L (1.1 ULN), AP 125 U/L (1.3 ULN), normal ranges for AST, total bilirubin.

On (b) (6), first cycle of chemotherapy with cisplatin and cyclophosphamide.
On Day 2 post dosing: ALT 279 U/L (9.0 ULN), AST 323 U/L (10.1 ULN), AP 182 U/L (1.9 ULN), total bilirubin 36 micromol/L (1.7 ULN), normal albumin.
On Day 6 post dosing: decrease of ALT 73 U/L (2.4 ULN), AP 124 U/L (1.3 ULN), and return to normal for AST, and total bilirubin with normal albumin.
There is no data on GGT, PTT, INR.
Other co-medications: vitamins.
There is no further laboratory follow-up after Day 6 (last study lab evaluation).
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury: abnormal baseline; acute hepatocellular liver injury without jaundice.

- Grade 1 severity: mild severity;
- No Hy's law case;
- Followed by a rapid improvement.

Role of drugs: probable DILI considering the very close temporal relationship with study drug and chemotherapy administration; among them possible role for cisplatin, cyclophosphamide, netupitant and palonosetron.

Case 2) PT ID 133- 1413 - female, 53 yrs

Treatment: palonosetron 0.50 mg + netupitant 200 mg + dexamethasone

Cancer type: oro-pharyngeal cancer.
Medical history: chronic gastritis, psychiatric disorders.
Liver tests at baseline: normal for ALT, AST, AP, total bilirubin.
On (b) (6), first cycle of chemotherapy with cisplatin and fluorouracil.
On Day 2 post dosing: ALT 150 U/L (4.8 ULN), AST 115 U/L (3.6 ULN), AP 103 U/L (1.1 ULN), total bilirubin 23 micromol/L (1.1 ULN), normal albumin.
On Day 6 post dosing: decrease of ALT 72 U/L (2.3 ULN), slight increase of total bilirubin 28 micromol/L (1.3 ULN), return to normal for AST, AP with normal albumin.
There is no data on GGT, PTT, INR.
Other co-medications: none
Further follow-up: recovery 1 week later.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:

Type and severity of liver injury: acute mixed pattern liver injury (ALT/AP ratio 4.3) without jaundice.
- Grade 1 severity: mild severity;
- No Hy's law case;
- Followed by a rapid improvement.

Role of drugs: probable DILI considering the very close temporal relationship with study drug and chemotherapy administration: among them possible role for cisplatin, fluorouracil, netupitant and palonosetron.

Case 3) PT ID 210-2071 - female, 43 yrs

Treatment: palonosetron 0.50 mg + netupitant 200 mg + dexamethasone

Cancer type: primary ovarian cancer.
Medical history: hystero-salpyngo-oophorectomy in (b) (6)
Liver tests at baseline: normal ranges for ALT, AST, AP, total bilirubin and albumin.
On (b) (6), first cycle of chemotherapy with cisplatin.
On Day 2 post dosing: ALT 399 U/L (12.9 ULN), AST 344 U/L (10.8 ULN), total bilirubin 27 micromol/L (1.3 ULN) with normal AP and normal albumin.
On Day 6 post dosing: decrease of ALT 84 U/L (2.7 ULN), and return to normal for AST, and total bilirubin with normal AP and albumin.
There is no data on GGT, PTT, INR.
Other co-medications: none.
There is no further follow-up after Day 6 (last study lab evaluation).

There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury: acute hepatocellular liver injury without jaundice.
- Grade 1 severity: mild severity;
- No Hy's law case;
- Followed by a very rapid improvement.

Role of drugs: probable DILI considering the very close temporal relationship with study drug and chemotherapy administration: among them possible role for cisplatin, netupitant and palonosetron.

Case 4) PT ID 119-1128 - female, 60 yrs

Treatment: palonosetron 0.50 mg + netupitant 300 mg + dexamethasone
Cancer type: nasopharyngeal cancer.
Medical history: chronic gastritis, hypertension, cardiac failure, atherosclerosis, penicillin allergy, urolithiasis and chronic cholecystitis.
Liver tests at baseline: normal ranges for ALT, AST, AP, albumin and total bilirubin.
On (b) (6) first cycle of chemotherapy with cisplatin and fluorouracil.
On Day 2 post dosing: ALT 780 U/L (25.1 ULN), AST 545 U/L (17.0ULN), AP 214 U/L (1.5 ULN), normal total bilirubin and normal albumin.
On Day 6 post dosing: decrease of ALT 189 U/L (6.1ULN), AST 42 U/L (1.3 ULN), and return to normal for AP, with normal total bilirubin and albumin.
There is no data on GGT, PTT, INR.
Other co-medications: enalapril for hypertension since 1997.
There is no further follow-up after Day 6 (last study lab evaluation).
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury: acute hepatocellular liver injury without jaundice.
- Grade 1 severity: mild severity since transaminases elevation was isolated;
- No Hy's law case;
- Followed by a rapid improvement.

Role of drugs: probable DILI considering the very close temporal relationship with study drug and chemotherapy administration: among them possible role for cisplatin, fluorouracil, netupitant and palonosetron.

Case 5) PT ID 132-1682 - female, 58 yrs

Treatment: palonosetron 0.50 mg + netupitant 300 mg + dexamethasone
Cancer type: lung cancer.
Medical history: chronic gastritis, chronic cholecystitis, hysterectomy.
Liver tests at baseline: normal ranges for ALT, AST, AP, and slightly increased total bilirubin to 26 micromol/L (1.2 ULN).
From (b) (6) first cycle of chemotherapy with cisplatin, and etoposide. On Day 2 post dosing: slight isolated increase of ALT to 39 U/L (1.3

ULN), whereas AST, AP and total bilirubin remained normal as well as albumin.
On Day 6 post dosing: further increase of ALT 134 U/L (4.3 ULN), with total bilirubin 35 micromol/L (1.7ULN) whereas AST and AP and albumin were normal.
There is no data on GGT, PTT, INR.
Other co-medications: none.
There is no further follow-up after Day 6(last study lab evaluation).
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury: mild acute hepatocellular liver injury with ALT below 5 ULN without jaundice but just fluctuation of bilirubin which was slightly elevated at baseline.
- Grade 1 severity: mild severity since transaminase elevation was mild with not significant bilirubin variation compared to baseline;
- No Hy's law case;
- No follow-up after the peak value on Day 6.
Role of drugs: possible DILI considering the close temporal relationship with study drug and chemotherapy administration: among them possible role for cisplatin, etoposide, netupitant and palonosetron.

Case 6) PT ID 132-1643 - male, 58 yrs
Treatment: ondansetron + aprepitant + dexamethasone
Cancer type: lung cancer with metastatic lymph nodes.
Medical history: emphysema, asthma, horseshoe kidney, renal cyst, duodenal ulcus, gastroduodenitis, hepatomegaly and gallbladder polyp.
Liver tests at baseline: normal ranges for ALT, AST, AP, total bilirubin, and albumin.
From (b) (6) first cycle of chemotherapy with cisplatin and etoposide. On Day 2 post dosing: increase of ALT to 630 U/L (15.4 ULN), AST 428 U/L (11.3 ULN), AP 167 U/L (1.4 ULN), total bilirubin 26 micromol/L (1.2 ULN), normal albumin.
On Day 6 post dosing: marked decrease with return to normal of all tests: ALT, AST, AP, total bilirubin and normal albumin.
There is no data on GGT, PTT, INR.
Other co-medications: none.
Follow-up: normalization within 4 days.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury: acute hepatocellular liver injury without jaundice.
- Grade 1 severity: mild severity;
- No Hy's law case;
- Recovery within 4 days.
Role of drugs: probable considering the temporal relationship with study drug and chemotherapy administration: among them possible role for cisplatin, etoposide,

aprepitant and ondansetron.

Case 7) PT ID 119-1130 - male, 53 yrs
Treatment: palonosetron 0.50 mg + dexamethasone
Cancer type: pancreatic carcinoma with bone and hepatic metastases.
Medical history: hypertension grade 2, encephalopathy, polyneuropathy, urolithiasis, chronic gastritis and deafness.
Liver tests at baseline: AST, ALT, AP, total bilirubin and albumin in normal ranges.
From (b) (6) first cycle of chemotherapy with cisplatin and etoposide.
On Day 2 post dosing: ALT 458 U/L (11.2 ULN), AST 295 U/L (8.1 ULN), AP 136 U/l (1.2 ULN) total bilirubin 26 micromol/L (1.2 ULN), normal albumin.
On Day 6 post dosing: decrease of ALT 141 U/L (3.4ULN), AST 57 U/L (1.5 ULN), and return to normal for AP and total bilirubin; normal albumin.
There is no data on GGT, PTT, INR.
Other co-medications: none.
There is no further follow-up; the outcome of the event is reported as “recovering”.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury: acute hepatocellular liver injury without jaundice.
- Grade 1 severity: mild severity;
- No Hy’s law case;
- Followed by an improvement.

Role of drugs: probable DILI considering the very close temporal relationship with study drug and chemotherapy administration: among them possible role for cisplatin, etoposide and palonosetron.

Study NETU 08-18 (N= 5 cases).
Case 8) PT ID 4209-01 - male, 61 yrs
Treatment: netupitant 300 mg +palonosetron 0.50 mg + dexamethasone
Cancer type: stomach adenocarcinoma with liver and lung metastases.
Medical history: no data
First cycle from (b) (6)
Course of chemotherapy with pyrimidine analogues (fluorouracil), cyclophosphamide and doxorubicin.
Liver tests at baseline: increase of AST 60 U/L (1.5 ULN), AP 279 U/L (2.2 ULN) with normal ALT, total bilirubin, and albumin.
On Day 2 post dosing: decrease of AP 150 U/L (1.2 ULN), mild increase of total bilirubin 22 micromol/L (1.1 ULN), normal ALT, AST, and albumin.
On Day 6 post dosing: mild increase of ALT 46 U/L (1.1 ULN), AST 52 U/L (1.3 ULN), stable AP 146 U/L (1.1 ULN), limit of normal total bilirubin 21 micromol/L (1.0 ULN), with normal albumin.
Analysis: Very mild changes of liver tests during this cycle.
Cycle 2 on (b) (6)
Liver tests at baseline: AP 273 U/L (2.2 ULN), normal for ALT, AST, total bilirubin.

On Day 2 post dosing: stable AP 267 U/L (2.1 ULN), normal ALT, AST, bilirubin and albumin.
On Day 6 post dosing: decrease of AP 188 U/L (1.5 ULN), limit total bilirubin 22 micromol/L (1.1 ULN), with normal ALT, AST, and albumin.
Analysis: No event in this cycle.
Cycle 3 on (b) (6)
Liver tests at baseline: AST 56 U/L (1.4 ULN), AP 218 U/L (1.7 ULN) normal for ALT, total bilirubin, and albumin.
On Day 2 post dosing: slight increase of AST 95 U/L (2.3 ULN), AP 256 U/L(1.9 ULN), with normal ALT, bilirubin and albumin.
On Day 6 post dosing: increase of AST 137 U/L (3.3 ULN), ALT 83 U/L (2.1 ULN), total bilirubin 28 micromol/L (1.1 ULN), stable AP 229 U/L (1.8 ULN) with normal albumin.
Analysis: Mild liver reaction peaking on Day 6.
Cycle 4 on (b) (6)
Liver tests at baseline: normal for ALT, AST, AP, albumin and total bilirubin.
On Day 2 post dosing: ALT 333 U/L (7.4 ULN), AST 306 U/L (7.5 ULN), AP 303 U/L (2.3 ULN), total bilirubin 32 micromol/L (1.5 ULN), normal albumin.
On Day 6 post dosing: trend to decrease of ALT 248 U/L (5.5 ULN), AST 142 U/L (3.5 ULN), AP 233 U/L (1.8 ULN), contrasting with an increase of total bilirubin 42 micromol/L (2.0 ULN), with normal albumin.
Analysis: Cycle marked by a mixed liver reaction.
Cycle 5 on (b) (6)
Liver tests at baseline: ALT 63 U/L (1.4 ULN), AST 119 U/L (2.9 ULN), AP 202 U/L (1.6 ULN) normal for total bilirubin. This patient was not qualified to receive the fifth course of chemotherapy because of hematological blood test results.
There is no data on GGT, PTT, INR.
Other co-medications: none.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
Patient with baseline anicteric cholestasis observed all along the different cycles.
It is evident a moderate liver reaction during the 3rd cycle and more at the 4th course with a mixed pattern, followed by improvement at each time. The abnormal liver tests results at the screening of the 5th cycle suggest an underlying liver injury.
- Grade 1 severity: mild severity, since transaminases always below 10 ULN - The absence of Hy's law pattern (indeed, despite ALT 5.5 ULN+ bilirubin 2.0 ULN combination, the mixed pattern ALT/AP ratio =3, is not in accordance of the definition);
- Followed by a rapid improvement.
Role of drugs: probable considering the very close temporal relationship with study drug and chemotherapy administration at each cycle: among them possible role for chemotherapy, netupitant and palonosetron.

Case 9) PT ID 5606- 47 - female, 47 yrs

Treatment: palonosetron 0.50 mg + dexamethasone
Cancer type: breast cancer.
Medical history: hypothyroidism, hypertension
First cycle on (b) (6)
Course of chemotherapy with cyclophosphamide and doxorubicin.
Liver tests at baseline: normal ALT, AST, AP, total bilirubin, and albumin. All parameters remained normal on Day 2 post dosing and on Day 6 post dosing.
Cycle 2 on (b) (6)
Liver tests at baseline: normal ALT, AST, AP, total bilirubin, and albumin.
On Day 2 post dosing: isolated increase of AP to 126 U/L (1.2 ULN) with normal ALT, AST, bilirubin and albumin.
On Day 6 post dosing: increase of ALT 332 U/L (7.4 ULN), AP 115 U/L (1.1 ULN) total bilirubin 25 micromol/L (1.2 ULN), with normal albumin; no AST value analyzed.
There is no data on GGT, PTT, INR.
Other co-medications: levothyroxine sodium since 2002, quinapril and bisoprolol since 2010.
Further follow-up: no data after the second cycle as patient discontinued from the study due to Investigator's decision.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
Acute hepatocellular injury without jaundice at the second cycle.
- Grade 1 severity: mild severity with transaminases always below 10 ULN;
- No Hy's law case;
- No follow-up to verify recovery.

Role of drugs: possible DILI considering the time relationship with the study drug and chemotherapy administration and the absence of follow-up: among them possible role for chemotherapy and palonosetron.

Case 10) PT ID 4204- 11 - male, 67 yrs

Treatment: (palonosetron 0.50 mg + dexamethasone)
Cancer type: lung cancer.
Medical history: vascular encephalopathy, hepatic cyst.
First cycle on (b) (6)
Course of chemotherapy with vincristine, cyclophosphamide and doxorubicin.
Liver tests at baseline: normal ALT, AST, AP, total bilirubin and albumin, all parameters remained normal on Day 2 and Day 6 post dosing.
Analysis: Cycle 1 without abnormality of liver tests.
Cycle 2 on (b) (6)
Liver tests at baseline: normal AP, albumin and total bilirubin. No ALT and AST results available.
On Day 2 post dosing: increase of AP 179 U/L (1.4 ULN), total bilirubin 22 micromol/L (1.1 ULN) with normal albumin. No data for ALT and AST.

On Day 6 post dosing: increase of ALT 352 U/L (7.8 ULN), AST 139 U/L (3.4 ULN AP 160 U/L (1.2 ULN), total bilirubin 25 micromol/L (1.2 ULN), with normal albumin.
Analysis: cycle 2 with moderate transaminase elevation.
Cycle 3 on (b) (6)
Liver tests at baseline: normal for AST, ALT, AP, total bilirubin, and albumin.
On Day 2 post dosing: marked increase of ALT 597 U/L (11.0 ULN), AST 400 U/L (9.8 ULN), AP 243 U/L (1.9 ULN), and total bilirubin 57 micromol/L (2.7 ULN) with a slight decrease of albumin 29 g/L.
On Day 6 post dosing: rapid return to normal of ALT, AST, AP, bilirubin, and albumin.
Analysis: marked and transient liver reaction resolving very quickly.
There is no data on GGT, PTT, INR.
Other co-medications: none.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
After the first cycle without liver abnormalities, the second cycle marked by a moderate increase of transaminases without jaundice with rapid recovery, the main liver event occurred during the third cycle with elevated transaminases up to 11 ULN (acute hepatocellular pattern) and increase of bilirubin > 2 ULN.
- Severity grade 2: moderate, with pattern of Hy's law case;
- Follow up: very rapid recovery.
Role of drugs: probable DILI considering the very close temporal relationship with the study drug and chemotherapy administration at each cycle: among them possible role for chemotherapy and palonosetron.

Case 11) PT ID 4209- 02 - female, 70 yrs

Treatment: palonosetron 0.50 mg + dexamethasone
Cancer type: breast adenocarcinoma.
Medical history: no data
First cycle on (b) (6)
Course of chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil.
Liver tests at baseline: normal ALT, AST, AP, total bilirubin and albumin.
On Day 2 post dosing: normal ALT, AP and bilirubin, with normal albumin. No AST.
On Day 6 post dosing: normal ALT, AST, AP, bilirubin albumin.
Analysis: No abnormality of liver tests during this cycle.
Cycle 2 on (b) (6)
Liver tests at baseline: normal for ALT, AST, AP, total bilirubin and albumin; all parameters remained normal on Day 2 and on Day 6 post dosing.
Analysis: No event during this cycle.
Cycle 3 on (b) (6)
Liver tests at baseline: normal for ALT, AST, AP, total bilirubin, and albumin.
On Day 2 post dosing: normal ALT, AST, AP bilirubin and albumin.
On Day 6 post dosing: increase of AST 134 U/L (3.3 ULN), ALT 81 U/L (1.8 ULN), total bilirubin 27 micromol/L (1.2 ULN), AP 221 U/L (1.7 ULN) with normal albumin.

Analysis: mild liver reaction occurring on Day 6 post dosing.
Cycle 4 on (b) (6)
Liver tests at baseline, on Day 2 and on Day 6 post dosing: normal for ALT, AST, AP, total bilirubin, and albumin.
Analysis: no abnormality of liver tests during this cycle.
Cycle 5 on (b) (6)
Liver tests at baseline, on Day 2 and on Day 6 post dosing: normal for ALT, AST, AP, total bilirubin,and albumin.
Analysis: no abnormality of liver tests during this cycle.
Cycle 6 on (b) (6)
Liver tests at baseline, on Day 2 and on Day 6 post dosing: normal for ALT, AST, AP, total bilirubin and albumin.
Analysis: no abnormality of liver tests during this cycle.
There is no data on GGT, PTT, INR.
Other co-medications: none
Further follow-up: no liver event since cycle 3 up to the completed planned sixth chemotherapeutic courses.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
Very mild cholestatic biochemical event on Day 6 of cycle 3.
- Grade 1 severity: very mild severity, since transaminases always below 5 ULN;
- No Hy's law case;
- Recovery and no relapse during the 3 following cycles.

Role of drugs: unlikely DILI considering the absence of event(s) in 5 of the 6 cycles; thus unlikely role for chemotherapy and palonosetron.

Case 12) PT ID 5706- 09 - female, 69 yrs

Treatment: palonosetron 0.50 mg + dexamethasone
Cancer type: breast adenocarcinoma.
Medical history: ischemic cardiomyopathy, hypertension, hypercholesterolemia since 2009.
First cycle on (b) (6)
Course of chemotherapy with epirubicin and cyclophosphamide.
Liver tests at baseline: normal for ALT, AST, AP, total bilirubin and albumin. All parameters remained normal on Day 2 and on Day 6 post dosing.
Analysis: no abnormality of liver tests during this cycle.
Cycle 2 on (b) (6)
Liver tests at baseline: normal for ALT, AST, AP, total bilirubin and albumin.
On Day 2 post dosing: normal ALT, AST, AP, total bilirubin, albumin.
On Day 6 post dosing: ALT 139 U/L (3.1 ULN), AST 55 U/L (1.3 ULN), total bilirubin 24micromol/L (1.1 ULN), normal AP and albumin.
Analysis: mild abnormality of transaminases during this cycle.
Cycle 3 on (b) (6)

Liver tests at baseline: normal for ALT, AST, AP, total bilirubin and albumin.
On Day 2 post dosing: normal ALT, AST, AP, total bilirubin, albumin.
On Day 6 post dosing: normal ALT, AST, AP, total bilirubin, albumin.
Analysis: no abnormality of liver tests during this cycle.
Cycle 4 on (b) (6)
Liver tests at baseline: normal for ALT, AST, AP, total bilirubin and albumin.
On Day 2 post dosing: normal ALT, AST, AP, total bilirubin, albumin.
On Day 6 post dosing: isolated and mild increase of total bilirubin 28 micromol/L (1.3 ULN), normal ALT, AST, AP, albumin.
Analysis: mild isolated increase of bilirubin during this cycle, assessed as not clinically significant.
There is no data on GGT, PTT, INR.
Other co-medications: bisoprolol, simvastatin, indapamide, glyceryltrinitrate, acetylsalicylic acid.
Further follow-up: no follow-up after the Day 6 of cycle 6 as patient completed the planned chemotherapy courses.
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
Mild hepatocellular event during cycle 2 and isolated mild increase of bilirubin during cycle 6. No liver events during other cycles.
- Grade 1 severity: very mild severity, since transaminases only 3.1 ULN;
- No Hy's law case;
- Event recovered and no relapses in further cycles.
Role of drugs: unlikely DILI considering the absence of event in 3 of the 4 cycles; thus unlikely role for chemotherapy and palonosetron.

Study PALO 10-01 (N= 2 cases).
Case 13) PT ID 1105- 03 - male, 55 yrs
Treatment: palonosetron 0.25 mg + dexamethasone
Cancer type: lung cancer
Medical history: hypertension (since 2007), dyslipidemia (since 2008), seasonal allergies and chronic tendonitis (since 2009), chronic obstructive pulmonary disease (since 2011).
Liver tests at baseline: normal ranges for ALT, AST, AP, total bilirubin and albumin.
On (b) (6), first cycle of chemotherapy with cisplatin.
On Day 2 post dosing: normal AST, ALT, AP and total bilirubin.
On Day 6 post dosing: ALT 137 U/L (3.04 ULN), AST 78 U/L (1.9 ULN), mild increase of total bilirubin 31 micromol/L (1.47 ULN), with normal AP and albumin.
There is no data on GGT, PTT, INR.
Other co-medications: lisinopril, pravastatin, hydrocodone, salbutamol, multivitamins and expectorants.
Follow-up: no further follow-up after Day 6 (last study lab evaluation) as these changes considered by the investigator not clinically significant.

There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
Mild hepatocellular event with mild increase of bilirubin.
Grade 1 severity: very mild severity, since transaminases no more than 3,1 ULN;
- No Hy's law case; (total bilirubin below 2 ULN);
- Follow-up none.
Role of drugs: possible DILI considering the time relationship with the treatment; thus possible role for chemotherapy and palonosetron.

Case 14) PT ID 5201- 01 - female, 55 yrs
Treatment: palonosetron 0.25 mg + dexamethasone
Cancer type: gastric cancer with metastases to liver and lymph nodes.
Medical history: duodenal ulcer (since 1999), hypertension (since 2006), musculoskeletal pain since 2011, abnormal weight loss. Cholecystectomy, gastrectomy, splenectomy and radical lymphadenectomy in September 2011.
Liver tests at baseline: normal AP, total bilirubin and albumin. No AST and ALT values.
From (b) (6) first cycle of chemotherapy with cisplatin and fluorouracil.
On Day 2 post dosing: ALT 84 IU/L (1.8 ULN), AST 75 IU/L (1.8 ULN) with normal albumin, AP and total bilirubin.
On Day 6 post dosing: ALT 191 IU/L (4.2 ULN), AST 76 IU/L (1.8 ULN), increase of total bilirubin 39 micromol/L (1.9 ULN) with normal AP and albumin.
There is no data on GGT, PTT, INR.
Follow-up: no further follow-up after Day 6 (last study lab evaluation) as these changes considered by the investigator non- clinically significant.
Other co-medications: bisoprolol, lacidipin, megestrol, nutritional supplement
There is no data on the etiological work-up allowing to eliminate common causes of acute hepatitis (e.g. acute HAV, HBV, HCV, autoimmunity).

Comment:
Type and severity of liver injury:
Mild hepatocellular event with mild increase of bilirubin.
Grade 1 severity: mild severity;
- No Hy's law case;
- Follow-up none.
Role of drugs: possible DILI considering the time relationship with the treatment; thus possible role for chemotherapy (cisplatin and fluorouracil) and palonosetron.

GENERAL COMMENTS
Synthesis of the selected cases
The type of liver injury and the causality assessment were analyzed separately and then compared in each group.

Group of patients with netupitant/palonosetron (N=6)
Type and severity of liver injury
There is no case of liver failure. There were:

☐ 4 cases of acute cytolytic/hepatocellular liver injury: cases 1,3,4,5;

☐ 2 case of mixed pattern/cholestatic liver injury: case 2, 8;

☐ All patients recovered or improved and no patients discontinued the study because of hepatotoxicity.

Causality assessment
A DILI is probable in the 6 cases (cases 1, 2, 3, 4, 5, 8).
The role of netupitant is:
• Highly probable: 0 cases;
• Probable: 0 cases;
• Possible: 6 cases: the 4 cases of hepatocellular/cytolytic liver injury followed by recovery: cases 1, 3, 4, 5 and in the 2 cases of mixed/cholestatic liver injury followed by recovery: cases 2, 8. In case 2 the presence of liver metastases may have contributed to enzyme increase.

In all these cases, the other anti-emetic (palonosetron) and chemotherapy exhibited the same causality level.

Group of patients with anti-emetic comparators including the 2 cases of the study PALO-10-01 assessing palonosetron formulations (N=8).
Type and severity of liver injury
This regards mostly palonosetron given in 7 cases (cases 7, 9, 10, 11, 12, 13, 14) whereas ondansetron-aprepitant combination was given in a single case (case 6).
There is no case of liver failure.
There were:

☐ 7 cases of acute cytolytic/hepatocellular liver injury: cases 6, 7, 9, 10, 12, 13, 14, including one Hy's law case (case 10) of moderate severity;

☐ 1 case of very mild cholestatic biochemical event: case 11;

All patients very rapidly improved or recovered including the Hy's law case except cases 9, 13 and 14 for which there was no follow-up since liver changes were considered by the investigator not clinically significant.

Causality assessment
A DILI is probable in 4 cases (cases 6, 7, 8, 10), possible in 3 cases (cases 9, 13, 14 because of the absence of follow-up); unlikely in 2 cases (cases 11, 12).
The role of the anti-emetic compounds has been assessed as follows:
• Highly probable: 0 cases;
• Probable: 0 cases;
• Possible: 7 cases: all associated with hepatocellular/cytolytic liver injury followed by recovery in cases 6, 7, 8, 10 (Hy's law case) and without follow-up to evaluate the

recovery for cases 9, 13, 14. In all of them, there is a possible role of other co-administered drugs.
• Unlikely: 2 cases including a case with mild hepatocellular liver injury: case 12 and one case of mild biological liver abnormalities occurring during a single cycle (cycle 3) without abnormalities during Cycle 1, 2, 4 and 5: case 11.
• Unrelated: 0 cases;
• Not assessable: 0 cases.

Again, the case evaluations above are directly from (b) (4) report and I concur with his assessments and conclusions. Increases in AST > 3 times the upper limit of normal (ULN) and/or ALT >3 times ULN and/or bilirubin (1.5 times ULN) were identified in clinical trials in patients exposed to Akynzeo (0.4%, 6/1442) and in patients exposed to palonosetron alone (0.4%, 7/1600), including one patient in each arm with both elevations of ALT > 3 times ULN and Bilirubin > 2 times ULN. Additional patient was in aprepitant arm. These abnormal values resolved or improved and typically these elevations were observed day 2 through 6 post chemotherapy and had resolved in time for the next cycle of chemotherapy if a patient remained on study and/or who had follow up laboratory to document resolution. Three patients did not have follow up laboratory values available for evaluation. In previous palonosetron clinical trials (see Aloxi labeling), asymptomatic increases in AST and/or ALT and bilirubin were observed. These changes which occurred in less than 1% of patients were observed predominantly in patients receiving cisplatin chemotherapy regimens.

ECG Assessment
For cycle 1 in the Phase 2/3 cancer patients, an analysis of ECG data showed that at 5 hours after treatment (approximate T_{max} for netupitant/palonosetron FDC), a comparable increase from baseline in QTcF was seen in the netupitant-palonosetron group, the palonosetron group, and the comparator group. Similar changes from baseline in QTcF values were also observed at 24 hours postdose with mean QTcF values returning to baseline values or lower at 120 hours after treatment. At subsequent cycles, in the multicycle studies a similar pattern was observed, with comparable changes from the same-cycle predose reference values for each treatment group.

In cycle 1, the percentage of patients with new treatment-emergent ECG abnormalities after baseline was comparable between the treatment groups (37.5%, 37.4%, and 39.1% in the netupitant-palonosetron, palonosetron, and aprepitant+palonosetron groups, respectively). The most frequently reported new treatment-emergent ECG abnormalities were flat T-wave (11.3% overall) followed by sinus tachycardia (9.2% overall), both of which occurred in similar percentages of patients across the treatment groups.

Left Ventricular Ejection Fraction
Mean LVEF values and change from the screening values in all cycles are summarized by method of assessment—ECHO or MUGA; however, only 6 patients were assessed by MUGA, and this small number of patients precludes meaningful analysis.

For patients assessed by ECHO, mean LVEF values were comparable across all treatment groups at screening (63.9%, 64.1%, and 63.1% for netupitant-palonosetron, palonosetron, and aprepitant+palonosetron, respectively) and at the end-of-study assessment (62.8%, 63.3%, and 62.3%, respectively). Within-group mean changes from baseline to the end-of-study

assessment in LVEF were small (netupitant-palonosetron: -1.1%; palonosetron: -0.7%; aprepitant+palonosetron: -1.4%).

Postmarketing Experience
Netupitant-palonosetron FDC is not marketed in any country.

In summary, safety was evaluated in 28 clinical studies and more than 3000 cancer patients participated in the Phase 2 and 3 program. The size of the safety database exceeds the minimum requirement suggested by ICH E1. In addition, there were 550 patients treated for 6 cycles or more (317 with the FDC).

I concur with Dr. Snow's safety conclusion that the combination of 300 mg netupitant and 0.50 mg -palonosetron was shown to be safe and tolerated in single and multiple cycle studies. TEAEs, SAEs, deaths and discontinuation due to AEs were reported in similar frequencies across the netupitant-palonosetron, and palonosetron alone treatment groups in cancer patients.

The nature and frequency of AEs in general was consistent with the disease under study. Adverse events most commonly reported were those associated with cytotoxic effects of chemotherapy, or the underlying malignancy. Only headache and constipation (were considered drug-related and reported in ≥2% of patients in the netupitant-palonosetron and palonosetron groups, respectively.

Adverse events of interest included cardiac and CNS events. There was no consistent pattern of these events across treatment groups.

ECGs were performed throughout the program, and analyzed according to standard methods, including mean changes, outlier analyses and new morphology. Mean values at baseline were comparable across the treatment groups, and the mean changes from baseline in the ECG parameters assessed were small and generally similar across the treatment groups at each study time point.

There are no results in the clinical development program suggesting the need for absolute contraindication of netupitant-palonosetron.

9. Advisory Committee Meeting

No AC meeting was hold for this NDA.

10. Pediatrics

The sponsor is required to conduct postmarketing studies in pediatric patients based on the Pediatric Research and Equity Act (PREA). Two studies will be required. The first is a PK/PD pediatric trial and the second is a safety and efficacy trial. The sponsor will need to develop an oral or I.V. formulation of netupitant+palonosetron that is suitable for all ages. If an oral or IV formulation of netupitant+palonosetron cannot be developed, the sponsor may qualify for a waiver of pediatric studies for the populations for which an age-appropriate formulation of

netupitant+palonosetron cannot be developed. Based on these contingencies, and the outcome of the pediatric PK/PD clinical study, a final (oral or I.V.) pediatric age appropriate formulation will be developed and used in pediatric clinical safety and efficacy study. The proposed pediatric study plan was presented to the Pediatric Review Committee (PeRC) and the committee concurred. The sponsor submitted revised timelines for the PREA studies.

The planned schedule for PK/PD Study #1 is:
• Protocol Submission to FDA: November 1, 2015
• Study Completion: April 30, 2018
• Study Report Submission to FDA: October 31, 2018

The planned schedule for safety and efficacy Study #2 is:
• Protocol Submission to FDA: April 30th, 2019
• Study Completion: December 31st, 2021
• Study Report Submission to FDA: April 30th, 2022

These dates appear reasonable. PMHS (Dr. Erica Radden) reviewed the background materials and provided input on the proposed pediatric plan, in addition to assisting in preparation for the Pediatric Review Committee (PeRC) meeting on May 14, 2014.

Toxicology team has one PREA PMR recommendation: An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone.

11. Other Relevant Regulatory Issues

OSI
Dr. Susan Leibenhaut, a Medical Officer from Good Clinical Practice Assessment Branch in Division of Good Clinical Practice Compliance of Office of Scientific Investigations, stated in her review dated May 14, 2014 that six clinical investigator sites and the sponsor were inspected for this NDA. Coverage of two clinical sites per protocol was achieved with the exception of NETU 07-07. All clinical sites had the classification of NAI or VAI with minor regulatory violations cited. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

In her updated Memo dated June 25, 2014, Dr. Leibenhaut stated that there was no evidence through the monitoring reports and QA audits performed to indicate non-compliant PIs (other than Site 120 for Study NETU 07-07) or any under-reporting of AEs. It appears that the issues noted at Site 120 for Study NETU 07-07 were an isolated occurrence and that, other than this instance, the Helsinn oversight of the CROs involved with the 4 studies appeared adequate. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

Dr. Michael Skelly from Bioequivalence Branch, DBGLPC, OSI reviewed the results from the clinical and bioanalytical portions of study NETU-09-07 and concluded that following review

of the inspectional findings, the results from the clinical and bioanalytical portions of study NETU-09-07 are acceptable.

Controlled Substance Evaluation

Dr. Katherine Bonson, a Controlled Substance Staff, has reviewed the nonclinical and clinical abuse-related data submitted in this NDA and concludes that this drug combination does not have abuse potential. In her review dated May 30, 2014, Dr. Bonson stated that the conclusion of the netupitant + palonosetron does not have abuse potential is based on the results from the following:

- Receptor binding studies show that palonosetron is a high affinity 5HT3 ligand and that netupitant is a high affinity ligand at NK-1 receptors. Netupitant also induces 67% inhibition at the dopamine transporter and 75-100% inhibition at calcium channels, but these data were not converted to Ki values. The abuse related binding profile for netupitant is incomplete because it did not test the affinity of netupitant for dopamine, glutamate, cannabinoid and 5HT2 receptors. However, an evaluation of the behavioral signs in animal studies conducted with netupitant does not show any abuse-related signals, as described below.
- Four toxicology studies with netupitant (with or without palonosetron) were conducted in rats (for 13 and 26 weeks) and beagle dogs (for 13 weeks and 9 months), each with an 8-week recovery period. There were no abuse-related behaviors observed during the drug administration period and no withdrawal-like behaviors observed during the drug discontinuation period.
- In a pharmacokinetic/pharmacodynamic study in baboons with netupitant +palonosetron, there were no behavioral effects observed.
- In an Irwin study of general behavior with rats, there were no abuse-related behaviors observed following administration of netupitant alone.
- In a drug discrimination study with baboons, netupitant + palonosetron did not generalize to either a sedative benzodiazepine (lorazepam or diazepam) or to the stimulant/hallucinogen MDMA. These data suggest that netupitant +palonosetron does not produce activity similar to that of a GABA agonist or an inhibitor of the dopamine/serotonin transporter.
- In a self-administration study with baboons, netupitant + palonosetron did not produce levels of self-administration that were different from those produced by vehicle. These data suggest that netupitant + palonosetron does not produce rewarding effects.
- In physical dependence studies conducted in rats, beagle dogs and olive baboons, chronic administration of netupitant + palonosetron, or netupitant alone, did not produce withdrawal-like behaviors upon drug discontinuation. This suggests that netupitant (with or without palonosetron) does not produce physical dependence.
- In human pharmacokinetic studies, netupitant has a Tmax of 4-5 hours and an elimination half-life of 30-100 hours. Palonosetron has a Tmax of 3-6 hours andan elimination half-life of 40-50 hour
- In humans, 3 major metabolites of netupitant (M1, M2 and M3) are produced, representing 11%, 47% and 16% of the parent drug, respectively. Since there are no abuse-related behavioral signals associated with chronic administration of netupitant alone (or with palonosetron) in humans, the data do not suggest that any of the active

metabolites of netupitant have abuse potential. There are no major metabolites of palonosetron.

- Clinical studies conducted with netupitant + palonosetron in healthy individuals and in cancer patients do not show a pattern of adverse events (AEs) indicative of abuse potential. The most frequently reported central nervous system (CNS)-related AE was headache (2.4%).

The draft label submitted by the Sponsor does not include Section 9.0 (Drug Abuse and Dependence), based on their conclusion that netupitant + palonosetron does not have abuse potential. This is consistent with FDA's Guidance entitled, "*Guidance for Industry, Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements"* dated February 2013 that states on page 18, "*The DRUG ABUSE AND DEPENDENCE section should be omitted for a drug that is not a controlled substance and has no potential for abuse or dependence."* CSS accepts the sponsor's proposal to eliminate Section 9 from the drug label for Akynzeo based on Dr. Bonson's review dated August 4, 2014.

CSS recommended the netupitant + palonosetron drug combination should not be listed for control under the CSA, because the results from abuse potential studies show that the drug combination lacks abuse potential. I concur.

PMHS
Dr. Carrie Ceresa from Maternal Health Team in her review dated May 23, 2014 stated that based on a lack of human pregnancy data and adverse embryo-fetal findings in animals, PMHS recommends that Akynzeo be classified as a Pregnancy Category C drug.

The pregnancy subsection of the labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. PMHS-MHT deleted the sponsor's proposed (b) (4) (b) (4) The labeling regulations allow omission of inapplicable subsections (see 21 CFR 201.56(d)(4)). (b) (4) . The nursing mothers' subsection of labeling was revised to comply with current labeling recommendations. I concur with PMHS's evaluation and labeling recommendations.

Kellie Taylor, Deputy Director from Office of Medication Error Prevention and Risk Management indicated in the letter dated December 13, 2013 stated that we have completed our review of the proposed proprietary name, Akynzeo and have concluded that it is acceptable.

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Gastroenterology and Inborn Error Products (DGIEP) concurred with the findings of OPDP's promotional assessment of the proposed name. Please refer to the review dated December 12, 2013.

12. Labeling

I concur with PMHS's labeling recommendations listed in Dr. Carrie Ceresa's review dated May 23, 2014.

Nathan Caulk, Patient Labeling Reviewer from Division of Medical Policy Programs (DMPP) did PPI review and made many specific changes to PPI. DMPP has:
• simplified wording and clarified concepts where possible
• ensured that the PPI is consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
• ensured that the PPI is consistent with the approved comparator labeling where applicable

I concur with DMPP's recommendations listed in review dated May 13, 2014.

Meeta Patel, PharmD, Regulatory Review Officer from Office of Prescription Drug Promotion (OPDP) reviewed draft labeling and provided comments in the review dated May 12, 2014. I concur with the recommendation.

QT-IRT has following labeling recommendation:
12.2 Pharmacodynamics
Cardiac Electrophysiology
At the dose 600 mg/1.50 mg of netupitant/palonosetron, AKYNZEO did not prolong the QT interval (b) (4)

Dr. Terri Wood-Cummings from Division of Medication Error Prevention and Analysis provided a medication error risk assessment and stated in the review dated January 19, 2014 that the product is supplied in an (b) (4) foil blister pack containing one capsule and packaged in a secondary, (b) (4) This packaging configuration is supported by the dosage and administration for this product which is one capsule prior to chemotherapy. DMEPA notes that the dosage form is missing and the established name and strength are blended together making each more difficult to differentiate. DMEPA provided label and labeling recommendations in Section 5 to increase prominence of important information to ensure safe use of the product. I concur with the recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend that NDA 205718 Akynzeo be approved for the indication of 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.

- Risk Benefit Assessment

The clinical trials in this NDA have shown that the netupitant-palonosetron FDC given 1 hour prior to chemotherapy is safe, tolerated and efficacious as an antiemetic in the prevention of CINV in patients receiving chemotherapy. The contribution of both entities in the combination product has been established, and the safety profile between the combination and palonosetron alone, a known entity, is essentially similar. There are no major safety concerns with the use of the netupitant-palonosetron 300/0.50 mg in the target population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

In addition to pediatric related PMRs listed under section of Pedatrics, Clinical pharmacology team has 2 PMC recommendations as followings:

PMC #1:	*In-vivo drug interaction study to evaluate the duration of inhibitory effects of AKYNZEO on CYP3A4 enzyme activity beyond 4 days after AKYNZEO administration*	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	01/31/2015
	Study/Trial Completion:	01/31/2016
	Final Report Submission:	06/30/2016
PMC #2:	*In-vitro study to evaluate the potential of netupitant being a substrate for P-gp transporter in a bi-directional transport assay system.*	

The sponsor informs us that the study is finished and the final study report will be submitted in October 2014.

- Recommended Comments to Applicant

None

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/s/

RUYI HE
09/10/2014