CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205718Orig1s000

STATISTICAL REVIEW(S)

Statistical Team Leader Memorandum

Submission: NDA 205718/000
Product: AKYNZEO™ Netupitant 300 mg and Palonosetron 0.5 mg Fixed-Dose Combination (FDC) capsule for oral use
Sponsor: Helsinn Healthcare SA (Helsinn)
Indication: Prevention of chemotherapy induced nausea and vomiting (CINV)
Medical Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Reference: Statistical Review and Evaluation dated July 2, 2014

The purpose of this memorandum is to summarize the conclusions in the primary reviewer's evaluations of this original NDA submission, and to provide more details on the background of the clinical program.

Helsinn submitted this NDA to support the marketing approval of the netupitant and palonosetron fixed-dose combination (FDC) capsules for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of moderately and highly emetogenic cancer chemotherapy (CINV MEC and HEC). However, the recently modified ASCO 2011 Guideline, Anti-emetic: American Society of Clinical Oncology Clinical Practice Guideline Update, has reclassified some MEC regime to HEC. This change was noted at the pre-NDA meeting on April 16, 2013, and it will be properly reflected in the labeling. However, in both the primary review and this memorandum, MEC and HEC are referring to the classification prior to the 2011 modification.

The four important clinical trials conducted in the clinical program are listed below. The three efficacy studies were evaluated in the primary review. The roles and details of these three efficacy studies are further elaborated below and in the regulatory history section.

- Study NETU-07-07: Superiority; HEC; single cycle
- Study NETU-08-18: Superiority; MEC; single and multiple cycles
- Study NETU-10-29: Safety; MEC and HEC; multiple cycles
- Study PALO-10-01: Non-inferiority; HEC; single cycle

The primary endpoint in all three efficacy studies was complete response (CR) defined as no emetic episodes and no rescue medication. Study NETU-07-07 supports the efficacy of the netupitant 300 mg and palonosetron 0.5 mg 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 non-inferior 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 MEC compared to oral palonosetron 0.5 mg alone. As stated in the primary review, with the collective evidence from these three efficacy studies, the netupitant 300 mg 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.

Medical Background

Nausea and vomiting are one of the side effects associated with cancer treatment that can influence all aspects 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.

Hypothetically, nausea and vomiting results from stimulation of a multistep reflex pathway controlled by the brain. The vomiting reflex involves both central and peripheral components and the emetic response is integrated in the vomiting center. Chemotherapy induced nausea and vomiting (CINV) is usually classified as either acute, occurring within the first 24 hours after chemotherapy, or delayed, occurring after the first 24 hours extending until the fifth day (120 hours).

The development of acute emesis is known to largely depend on serotonin (5-HT). The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response, thus providing a physiologic explanation for the clinically beneficial antiemetic effects of 5-HT_3 receptor antagonists (RAs). Approved 5-HT_3 inhibitors include: ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®), and palonosetron (ALOXI®).

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 NK_1 receptor. The SP-NK_1 receptor system is one of the best-characterized neurotransmitter pathways in both the central and peripheral nervous systems. Aprepitant (Emend®) is the first and only selective NK_1 RA approved for CINV in the US, administered in combination with other antiemetic agents.

The 5-HT_3 and NK_1 RAs are among the drugs of choice for an optimal antiemetic prophylaxis in cancer patients receiving chemotherapy. Clinical practice guidelines in oncology, 2010, recommend that patients receiving HEC or MEC regimens should be treated with a combination of a 5-HT_3 RA, NK_1 RA and a systemic corticosteroid to prevent CINV.

The proposed netupitant-palonosetron FDC is composed of palonosetron (ALOXI®), a registered 5-HT_3 RA, and the new molecular entity (NME), NK_1 RA netupitant. The IV formulation of palonosetron 0.25 mg was approved in the US since 2003 for CINV MEC acute and delayed phases, and for HEC acute phase. An oral formulation of palonosetron 0.5 mg was approved in 2008 for CINV MEC acute phase only. Netupitant is a novel, potent and selective NK_1 RA that has been reportedly shown to be a highly effective antiemetic in a variety of preclinical models. The development of the netupitant-palonosetron FDC product is intended to improve patient compliance with simplification and convenience of the therapy, and to increase adherence to guidelines for administration of both a 5-HT_3 RA and NK_1 RA.

Regulatory History

The clinical development program for the netupitant-palonosetron FDC capsules was conducted as an international program to support Marketing Authorizations in the US, EU and other countries worldwide. Helsinn had worked with the FDA in the US, the European Medicines Agency (EMA), and with the Australian Therapeutic Goods Administration for the specific aspects of the development program. A summary of the interactions between Helsinn and the FDA is provided below.

The initial pre-IND discussions began in April 2006. At the pre-IND meeting on April 5, 2006, the FDA agreed on the study design for a phase 2 trial of placebo and three doses netupitant in combination with one dose oral palonosetron. Helsinn was reminded at the meeting that acute and delayed phases should be evaluated separately. The dose range of 100 mg to 450 mg of netupitant in combination with palonosetron was agreed upon at the meeting. Subsequently, the IND application was submitted to the FDA (IND# 73,493) in September, 2006.

An end of phase 2 (EOP2) meeting was held on July 20, 2009. Helsinn had completed a phase 2 dose-response study (NETU-07-07) at that time. The study was a superiority study to compare the efficacy and safety of three single oral doses of netupitant (100 mg, 200 mg, and 300 mg) combined with oral palonosetron (0.5 mg) and given with dexamethasone (corticosteroid), versus oral palonosetron (0.5 mg) alone given with dexamethasone for the prevention of CINV HEC. An additional study arm consisting aprepitant and ondansetron was included as an active comparator for exploratory purposes. The primary efficacy endpoint was CR in the overall phase (within the first five days) after the start of HEC. In the meeting package, Helsinn proposed two phase 3 studies for the netupitant 300 mg and oral palonosetron 0.5 mg FDC: a (b) (4), and a MEC superiority trial comparing to (b) (4) palonosetron (b) (4) The FDA informed Helsinn that the proposed phase 3 HEC trial was inadequate (b) (4) However, the FDA confirmed that phase 2 HEC trial (NETU-07-07) demonstrated that netupitant was effective for HEC and an individual netupitant monotherapy trial would not be needed. Helsinn argued that Study NETU-07-07 showed oral palonosetron was as effective as (b) (4) for HEC; however, the FDA explained that more evidence would be required to support that statement. Furthermore, the FDA stated that HEC studies had been accepted to support proposed MEC indication, but not vice versa. Hence, two trials would be needed to support MEC indication if a path forward for HEC could not be found. Helsinn revised the phase 3 program at the meeting to include two superiority trials, one for HEC and one for MEC, both comparing the netupitant-palonosetron FDC to (b) (4) palonosetron. The FDA noted that this new proposal might be possible if it was ethical to use (b) (4) palonosetron alone for CINV HEC. Also at the meeting, the FDA agreed on the choice of netupitant dose of 300 mg for the phase 3 program while suggesting a consideration of including 100 mg dose based on the phase 2 trial results. Moreover, the FDA recommended a margin of 6% instead of sponsor-proposed (b) (4)

proposed in the meeting package. The FDA also stated that more than four cycles' data should be included in the safety database for both HEC and MEC indications.

Two special protocol assessments (SPAs), one for HEC and the other for MEC, with the revised phase 3 proposals at the EOP2 meeting were received on October 13, 2009. No-agreement letters for both SPAs were issued on November 27, 2009. For HEC, the FDA pointed out that the dose of oral palonosetron in the FDC was higher than that of (b) (4) . Hence, using this trial design, the assessment of netupitant's contribution to the efficacy could be hampered and the treatment effect of oral palonosetron in HEC delayed and overall phases could not be established. The FDA recommended adding a treatment arm of 0.5 mg oral palonosetron while recognizing more details would need to be worked out to establish the treatment effect of both the FDC and its each component for HEC. For MEC, the FDA expressed concerns on the palonosetron dose issue as for the MEC trial and proposed to use oral palonosetron 0.5 mg as the control arm. However, the FDA noted that since oral palonosetron was only approved for MEC acute phase, the contribution of oral palonosetron in the FDC for the delayed or overall phase would not be established with this trial design or the previous clinical trials. Moreover, the FDA recommended a CMH test instead of the proposed logistic regression model as the primary analysis method for both phase 3 trials.

A Type A meeting following the no-agreement letters was held on January 22, 2010. In the meeting package, Helsinn proposed to keep the two superiority trial designs with (b) (4) and CR in the overall phase as the primary endpoint, and to add a third HEC trial (PALO-10-01) designed as a non-inferiority trial comparing oral palonosetron to IV palonosetron with CR in the acute phase as the primary endpoint. At the meeting, the FDA informed Helsinn that due to the complexity of this clinical program, the FDA Office of Medical Policy (OMP) would be consulted and further recommendations would be provided after the meeting. For the newly proposed non-inferiority trial, a 15% margin was proposed and the FDA noted that this margin was used before. The FDA confirmed that the phase 2 trial (NETU-07-07) design isolated the effect of netupitant; however, it would be a review issue whether the study results supported netupitant 300 mg in the prevention of CINV HEC for overall, acute, and delayed phases. During the endpoint discussion, the FDA stated that delayed phase CR should be the primary endpoint for the superiority trials given the expected treatment effect of NK_1 RA netupitant.

Following the meeting, an advice letter was issued on March 8, 2010 to convey the OMP recommendations to Helsinn. Particularly, the phase 2 trial (NETU-07-07) combined with the non-inferiority trial of palonosetron (PALO-10-01) would be acceptable to support CINV HEC for both acute and delayed phases provided their outcomes could be confirmed positive. The superiority MEC trial (NETU-08-18) should include oral palonosetron as the control arm or a third arm, and the delayed phase CR should be the primary endpoint. In the advice letter issued on March 17, 2010, the FDA notified Helsinn that inclusion of repeat cycles and number of patients in the MEC trial might be sufficient for inclusion of "repeat cycle" wording in HEC indication.

Helsinn submitted SPA for the MEC trial (NETU-08-18) on March 30, 2010 and a no-agreement letter was issued on May 14, 2010 due to the safety database concerns and the proposed (b) (4) significance level. The proposed trial included oral palonosetron 0.5 mg as the comparator arm and used CR in the delayed phase as the primary endpoint. A SPA for the HEC trial (PALO-10-01) was received on May 5, 2010 and a no-agreement letter was issued on June 18, 2010. The FDA recommended a type I error rate of two-sided 0.01 while accepting the non-inferiority margin of 15%, and agreed on the proposed CMH-adjusted confidence intervals for the non-inferiority testing.

Another Type A meeting following the no-agreement letters was held on July 15, 2010. All the questions in the two SPAs were discussed and reached agreement. Particularly, Helsinn clarified that a two-sided 0.05 significance level was proposed for the MEC trial (NETU-08-18) and accepted 0.01 as the significance level for the HEC trial (PALO-10-01). During the meeting, more discussion occurred regarding the phase 2 trial (NETU-07-07). The FDA stated that CR in the delayed phase was the primary analysis of interest although overall phase CR was the pre-specified primary endpoint; and a CMH test instead of the pre-specified logistic regression model should be the primary analysis. Moreover, the FDA noted that a multiplicity adjustment plan was only pre-specified for the primary endpoint of overall phase CR, but not for the secondary endpoints of delayed and acute phase CR. Helsinn stated that re-analyses of Study NETU-07-07 data according to the recommendations would be conducted. During the meeting, the FDA pointed out that the full analysis set (FAS), defined as all randomized subjects who received study treatment, was used as the primary analysis population, and stated that the intent-to-treat (ITT) population, defined as all randomized subjects, should be used instead. The preliminary results showed statistical insignificance in treatment comparisons using the ITT population. Helsinn clarified that the subjects excluded from the FAS did not receive chemotherapy and so did not receive the study treatment. The FDA requested more details on these subjects and agreed that the FAS analysis could be the primary analysis with the ITT analysis as a sensitivity analysis. Helsinn expressed concerns that Study NETU-07-07 might not be considered an adequate study to support the netupitant-palonosetron FDC for HEC. The FDA informed Helsinn that the acceptability of Study NETU-07-07 would be a review issue at the NDA stage.

Subsequently, SPAs for MEC Study NETU-08-18 and HEC Study PALO-10-01 were received on September 22, 2010. Agreement letters for both SPAs were issued on November 3, 2010. A pre-NDA was held on April 16, 2013 to discuss the format and contents of the NDA submission.

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/s/

FREDA COONER
07/04/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 205-718
Drug Name:	Akynzeo (netupitant and palonosetron) capsules for oral use
Indication(s):	Chemotherapy-induced nausea and vomiting (CINV)
Applicant:	Helsinn Healthcare SA
Date(s):	Receipt date: September 27, 2013 PDUFA goal date: September 26, 2014
Review Priority:	Standard
Biometrics Division:	DBIII
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewer:	Freda Cooner, Ph.D.
Medical Division:	Division of Gastrointestinal and Inborn Error Products
Clinical Team:	Nancy Snow, D.O. Ruyi He, M.D.
Project Manager:	Mary Chung

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1 EXECUTIVE SUMMARY

The sponsor submitted three efficacy studies to support the use of 300 mg netupitant (NETU) combined with 0.5 mg palonosetron (PALO) in the prevention of patients' acute and delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. To claim the chemotherapy-induced nausea and vomiting (CINV) indication, one efficacy study for the moderately emetogenic cancer chemotherapy (MEC) indication, and two efficacy studies for the highly emetogenic cancer chemotherapy (HEC) indication were conducted. All three submitted efficacy studies showed statistically significant treatment differences on the protocol specified primary endpoints.

Note that one efficacy study for the HEC indication (Study NETU-07-07) was originally planned as a phase 2 study including three study doses (i.e., PALO 0.5 mg and NETU 100 mg, PALO 0.5 mg and NETU 200 mg, and PALO 0.5 mg and NETU 300 mg) and active control (PALO 0.5 mg). During a meeting with the FDA on the clinical development of this product when planning the phase 3 program, the sponsor was notified that this phase 2, Study NETU-07-07 could have had the potential to provide confirmatory evidence, but the efficacy should be based on the complete response (CR) in the delayed phase instead of the CR in the overall phase, which was the pre-specified primary endpoint in the protocol.

After reviewing this NDA application, we concluded that two out of the three efficacy studies showed statistical significant results in favor of the study product; Study NETU-08-18 supports the use of PALO and NETU combination product (PALO+NETU) for the MEC indication and Study PALO-10-01 supports the use of PALO oral as the comparator instead of (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 and included the results in the original NDA submission. The sponsor concluded that all three doses were significant for the endpoint of CR in the delayed phase, but this conclusion would no longer hold when the protocol-specified multiple comparison procedure, i.e., Holm-Bonferroni method, was applied to control the type I error rate for the multiple study doses comparisons. It should be noted that all the analyses on this endpoint were post-hoc because it was not the original primary endpoint and the recommendation of using the CR in the delayed phase as the primary phase 3 endpoint was made after the study had been completed.

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 re-analyses 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. The statistical reviewer 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.

2 INTRODUCTION

2.1 Overview

The Applicant is seeking the following indications for netupitant-palonosetron combination capsules at a recommended dose of 300 mg netupitant/0.5 mg palonosetron approximately one hour prior to the start of chemotherapy:

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

The combination capsule contains two components:

- Palonosetron oral formulation, approved for "moderately emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses[1,2]", and
- Netupitant, a new molecular entity.

Note that the above two indications represent eight subtypes defined by the timing of nausea and vomiting (acute or delayed), the number of courses of chemotherapy (initial or repeat) and the type of chemotherapy (HEC or MEC):

- Acute nausea and vomiting, initial course of HEC
- Delayed nausea and vomiting, initial course of HEC
- Acute nausea and vomiting, multiple courses of HEC
- Delayed nausea and vomiting, multiple courses of HEC
- Acute nausea and vomiting, initial course of MEC
- Delayed nausea and vomiting, initial course of MEC
- Acute nausea and vomiting, multiple courses of MEC
- Delayed nausea and vomiting, multiple courses of MEC

Acute nausea and vomiting occurs within the first 24 hours after chemotherapy, and delayed nausea and vomiting occurs between 25 and 120 hours after chemotherapy. Optimal treatments contain a 5-HT_3 receptor analog, which is included to prevent acute chemotherapy-induced nausea and vomiting (CINV), in combination with a neurokinin-1 (NK_1) receptor analog, which is included to prevent delayed CINV. The proposed combination capsule contains palonosetron – a 5-HT_3 receptor analog, and netupitant – an investigational NK_1 receptor analog.

The Applicant submitted four studies to support the above indications; see Table 1. Some of the studies contain palonosetron (Aloxi) and ondanestron (Zofran), which was approved 5-HT_3 receptor analogs. Two studies contain aprepitant (Emend), a NK_1 receptor analog, in combination with either ondanestron or palonosetron. Aprepitant (Emend) is the only NK_1 receptor analog approved in combination with other antiemetic agents for the prevention of acute and delayed CINV in HEC,

[1] Source: approved labeling, 2008 (http://www.accessdata fda.gov/drugsatfda_docs/label/2008/022233LBL.pdf)
[2] An IV formulation of palonosetron was approved in 2003, and is indicated for both MEC and HEC for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses.

and for the prevention of CINV in MEC without specification of the acute and delayed phases. In this statistical review, only the three efficacy studies, i.e., NETU-07-07, NETU-08-18 and PALO-10-01 were thoroughly evaluated. The analysis results for Study NETU-10-29 were briefly described in the statistical reviewer's finding #6 in Section 3.2.4.

Table 1 Major Studies

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

Source: Sponsor's Table 1 of Clinical Overview of the NDA

2.2 Data Sources

The sponsor's original NDA submission including the data sets is stored in the following link: \\cdsesub1\evsprod\NDA205718\0000.

During the review, the FDA requested the sponsor to provide the tabular displays and narrative discussion of results by study site for the complete response endpoint at the overall, acute, and delayed phases (\\cdsesub1\evsprod\NDA205718\0002) and the subgroup analysis results for all four major studies (\\cdsesub1\evsprod\NDA205718\0008). In the clinical study report addendum #2 for Study NETU-07-07, the sponsor included the re-analysis results by excluding Site #120. However, only the descriptive complete response rates were provided. During the review cycle, the FDA requested the sponsor to repeat all the efficacy analysis results including confidence intervals and p-values (\\cdsesub1\evsprod\NDA205718\0021).

Prior to the late cycle meeting, FDA requested the sponsor to perform more sensitivity analyses to assess the impact of protocol violations recorded in Site #120. In addition to the different types of re-analysis results, the sponsor also included a table to list patients' violations in that site (\\cdsesub1\evsprod\NDA205718\0035).

During the review cycle, the statistical reviewer found that for Study PALO-10-01, the variable of treatment arm was erroneously coded in almost all of the data sets. The sponsor had confirmed the mistake and had submitted the correct data sets (\\cdsesub1\evsprod\NDA205718\0037).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical reviewer confirmed the sponsor's analysis results for the three major efficacy studies. Overall, the data and analysis quality of this NDA submission are acceptable. However, as noted in Section 2.2 above, for Study PALO-10-01, one of the treatment arm variables was erroneously coded in all data sets but one. The sponsor confirmed and corrected the errors. They also emphasized that this type of errors did not affect any efficacy findings because the efficacy analyses were conducted using the other treatment arm variable.

3.2 Evaluation of Efficacy

The following sections contain the study description, where mostly was extracted directly from the sponsor's Clinical Study Report (CSR). If there is any major discrepancy between the CSR and the study protocol or amendments, the detailed discussion will be included in the Section of Reviewer's Findings and Conclusions.

3.2.1 Study NETU-07-07

Study NETU-07-07 is titled "A Randomized, Double-Blind, Parallel Group, Dose-Ranging, Multicenter Study Assessing the Effect of Different Doses of Netupitant or Placebo Administered with Palonosetron and Dexamethasone on the Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting in Cancer Patients". It was conducted from February 2008 through November 2008 in Russia (29 sites) and Ukraine (15 sites).

3.2.1.1 Study Objective and Study Design

The objective of Study NETU-07-07 was to compare the efficacy and safety of three single oral doses of netupitant combined with palonosetron and dexamethasone to palonosetron and dexamethasone alone in the prevention of highly emetogenic chemotherapy-induced nausea and vomiting. An additional arm, aprepitant administered with ondanestron and dexamethasone, was included for exploratory purposes only.

Adult patients who had no history of cytotoxic chemotherapy, were confirmed to have solid tumor malignancy historically or cytologically with karnofsky index ≥ 70% and were scheduled to receive the first course of cisplatin-based chemotherapy regimen (dose of cisplatin ≥ 50 mg/m2 to be administered over 1 to 4 hours on Day 1 alone or in combination with other chemotherapy agents) were randomized to one of the five treatments groups shown below:

Group 1 – 0.5 mg oral palonosetron on Day 1 (with dexamethasone standard regimen: 20 mg on Day 1 and 8 mg BID from Day 2 to Day 4)
Group 2 – 100 mg oral netupitant and 0.5 mg oral palonosetron on Day 1 (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)
Group 3 – 200 mg oral netupitant and 0.5 mg oral palonosetron on Day 1 (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)
Group 4 – 300 mg oral netupitant and 0.5 mg oral palonosetron on Day 1 (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)
Group 5 – 125 mg on Day 1 and 80 mg daily on Day 2 and Day 3 oral aprepitant and 32 mg I.V. ondansetron (with dexamethasone adjusted regimen: 12 mg on Day 1 and 8 mg daily from Day 2 to Day 4)

Patients were assigned to treatment groups using a randomization list stratified by gender. Within strata (gender), patients meeting the inclusion and exclusion criteria were assigned to one of the above five treatment groups in a balanced design (i.e., in the ratio 1:1:1:1:1). Patients remained on study for up to 22 days, including up to 7 days screening period, 6 days on study including 4 days on active treatment, and a follow-up visit or a telephone call 9 days after the end of the treatment period.

A randomization list was prepared prior to the start of the study. According to this randomization list, sealed cartons containing the study drug and additional study drug were supplied to the investigational sites. Patients were randomized by the investigator using an interactive voice response system (IVRS) in accordance with study-specific procedures.

A dynamic adaptive stratification type of randomization method that balanced the five treatment groups according to the patient gender was used. Treatments were balanced across the entire study, not within each individual site.
The general strategy of this randomization was to give additional probability to receiving a specific treatment if it was underrepresented in the current randomization status. Patients who were randomized but never received study treatment were not considered during the following patient randomization/treatment assignment. This ensured that a balance among treatment groups in the treated population was being maintained. The investigator was trained to immediately notify the IVRS if a randomized patient did not receive study treatment. The relevant algorithm to this method tailored for this study was described in the appropriate IVRS document.

The IVRS also checked the availability of treatment kits at the trial site. The IVRS then provided the investigator with the randomization code number for the patient. The randomization code number, the patient number and the kit number were all the same. The medication contained in the kit assigned by the IVRS was administered to the patient.

Any unblinding of the study treatment could be performed by the IVRS (24-hour coverage) according to the detailed unblinding procedure described in the IVRS Instructional Manual provided to the investigator.

Regarding the sample size planning, with a total of 680 subjects – 136 subjects per treatment group, the power of the study was estimated to be 85% for the three pairwise comparisons of netupitant plus palonosetron versus palonosetron alone based on a one-sided test at α=0.05 adjusted for three multiple comparisons using the Holm-Bonferroni method. These calculations assumed a responder rate of 70% in the netupitant plus palonosetron groups and 50% in the palonosetron only group.

Reviewer's Note:

To support the validity of the implemented dynamic allocation procedure for the randomization, the sponsor performed re-randomization test and included the results in the NDA submission. Based on the protocol-specified primary analysis, i.e., logistic regression model adjusted for the covariate (i.e., gender), the sponsor concluded that "Low p-values were obtained for the randomization test p-values for CR in the delayed and overall phase. For all three endpoints, CR in delayed, acute and overall phases, p-values were very close to the p-values of the asymptotic tests reported in the main analysis of the trial, and would lead exactly to the same conclusions as reported in the original analysis." The sponsor also performed the re-randomization test using the FDA recommended Cochran-Mantel-Haenszel (CMH) test stratified by gender. The resulting p-values were also very close to those of the asymptotic CMH tests.

3.2.1.2 Efficacy Endpoints & Analyses

According to the protocol, the primary efficacy endpoint was the CR (defined as no emetic episodes and no rescue medication) in the overall phase, i.e., within 120 hours after the start of highly emetogenic chemotherapy based on the modified full analysis set population (MFAS) population. The MFAS population included all randomized patients (excluding the aprepitant

group) who received highly emetogenic chemotherapy and at least one study treatment dose. The CR in the overall phase will be summarized by treatment arm. The number and proportion of patients with CR in the overall phase will be presented by frequency table. For the response rate and for the difference in response rate between each Palonosetron combined with Netupitant dose group and Palonosetron alone group 95% confidence interval (CI) will be provided.

The study hypothesis was as follows: at least one dose of oral Netupitant and Palonosetron is superior to oral Palonosetron alone (0.5 mg), considering the CR rate in the overall phase (0-120 hours). The primary test was performed using a logistic regression adjusted for the covariate, where each dose of Netupitant combined with a fixed dose of Palonosetron and Dexamethasone was compared with placebo combined with Palonosetron and Dexamethasone. Gender was included in the model as the covariate. For each hypothesis test, the three comparisons were made using one-sided p-values according to the Holm-Bonferroni method. That is, in order to claim a significant difference, the smallest of the three p-values must not exceed 0.05/3. If this is achieved, the second smallest p-value must not exceed 0.05/2 in order to be significant, and if this is also achieved, the significance threshold for the third p-value is 0.05. This sequential procedure stops, if the respective threshold is exceeded. The procedure guarantees the study-wise type I error level of 0.05.

Patients with missing data were classified as not having a complete response for the primary analysis. Moreover, the same logistic regression model was used to compare each dose of Palonosetron plus Netupitant to each other. This was done on a descriptive level, i.e., without adjustment for multiplicity.

Reviewer's Note:

(1) Study NETU-07-07 was originally designed as a phase 2 study to compare the efficacy and safety of three single oral doses of netupitant (100, 200, or 300 mg) combined with palonosetron (0.5 mg) to palonosetron alone (0.5 mg) in the prevention of highly emetogenic chemotherapy-induced nausea and vomiting (CINV-HEC). During the interactions with FDA for the sponsor's planning on the phase 3 development, this trial was determined to have the potential being considered as the sole pivotal trial for the CINV-HEC indication given the following analysis to be performed:
- analysis using CR in the delayed phase as the primary efficacy variable (instead of CR in the overall phase)
- analysis using the CMH test stratified for gender (instead of a logistic regression model with gender as covariate)
- hierarchical procedure to control type I error for CR in the delayed, acute and overall phase
- sensitivity analysis on the Intent to Treat (ITT) population defined as all randomized patients

(2) Either based on the sponsor's study protocol or the clinical study report, it was stated that a one-sided test at α=0.05 was used to determine the drugs' efficacy. The statistical reviewer noted that the sponsor's reported p-values for all three doses were actually two-sided, which conforms to the FDA's standard. Therefore, those p-values can be used in the hypothesis testing.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

This study has a total of 694 patients randomized and 679 receiving study medication. Table 2 displays the number of patients randomized into each treatment group, patient disposition and the reasons for early discontinuation.

Of the 15 patients who were randomized but not treated, 5 patients withdrew consent, 5 patients were ineligible for the study, 2 patients discontinued due to pre-treatment adverse events, 2 patients were erroneously randomized at screening, and 1 patient did not have screening results available in time to be randomized.

Four patients discontinued after being treated with study medication. One patient (netupitant 100 mg) died due to multiple organ failure not related to study medication, and one patient (netupitant 200 mg) discontinued due to an SAE (loss of consciousness, possibly related). The other two patients were lost to follow-up (aprepitant) or withdrew consent (palonosetron alone).

Patient retention was excellent; 97% of the randomized patients and 99% of the treated patients completed the study.

Table 2 Patient Disposition for Study NETU-07-07

	PALO alone n (%)	PALO+NETU 100 mg n (%)	PALO+NETU 200 mg n (%)	PALO+NETU 300 mg n (%)	Aprepitant n (%)
Randomized	136 (100)	135 (100)	142 (100)	143 (100)	138 (100)
Never Treated	0 (0.0)	0 (0.0)	4 (2.8)	7 (4.9)	4 (2.9)
Treated	136 (100)	135 (100)	138 (97.2)	136 (95.1)	134 (97.1)
Completed Study	135 (99.3)	134 (99.3)	137 (96.5)	136 (95.1)	133 (96.4)
Discontinued	1 (0.7)	1 (0.7)	5 (3.5)	7 (4.9)	5 (3.6)
Reason for discontinuation					
Adverse event	0 (0)	0 (0)	1 (0.7)	1 (0.7)	1 (0.7)
Death	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0.0)
Lost to follow up	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Other reason	0 (0)	0 (0)	3 (2.1)	4 (2.8)	1 (0.7)
Withdrew consent	1 (0.7)	0 (0)	1 (0.7)	2 (1.4)	2 (1.4)

Source: Sponsor's Table 8 of CSR

Table 3 summarizes patients' baseline demographics for the safety population, which was comprised of 387 (57%) males and 292 (43%) females who ranged in age from 19 to 82 years, with mean and median ages of approximately 54 years and 55 years, respectively. One patient (0.1%) was Asian, and 678 (99.9%) patients were white. More patients were enrolled at research sites in Russia (64%) than at research sites in Ukraine (36%).

Table 3 Patients' Baseline Demographics based on MFAS Population for Study NETU-07-07

Parameter	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=137)	PALO+NETU 300 mg (N=135)	Aprepitant (N=134)
Gender					
Male	78 (57.4%)	77 (57.0%)	79 (57.7%)	77 (57.0%)	75 (56%)
Female	58 (42.6 %)	58 (43.0%)	58 (42.3%)	58 (43%)	59 (44%)
Age (years), mean (SD)	54.2 (9.7)	55.0 (9.5)	54.2 (9.8)	54.2 (9.8)	54.4 (10.3)
Race					
White	136 (100%)	135 (100%)	136 (99.3%)	135 (100%)	134 (100%)
Asian			1 (0.7%)		
Weight (kg), mean (SD)	72 (15.1)	73.4 (15.4)	70.8 (14.3)	72 (15.7)	71.7 (14)

Source: Sponsor's Table 4.1 of CSR

3.2.1.4 Sponsor's Efficacy Results & Conclusions

As mentioned earlier in Section 3.1.1.2. Although the protocol specified primary efficacy endpoint was the CR in the overall phase, if FDA would like to consider this trial being a pivotal trial, the primary endpoint should be CR in the delayed phase and the specified sequential testing procedure should be CR in the delayed phase, CR in the acute phase and CR in the overall phase. In addition, the protocol specified primary analysis as the logistic regression adjusted by the gender covariate, but the FDA suggested the sponsor re-analyze the data by the CMH test. The sponsor's results for all three endpoints based on the MFAS population and for two aforementioned statistical methods are shown in Table 4.

Table 4 Sponsor's Results for Complete Response Rate in the Delayed Phase, Acute Phase and Overall Phase based on MFAS Population for Study NETU-07-07

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

Source: Sponsor's Table in 2 Summary of Clinical Study Report Addendum #1 (Page 3 of 17)
*including gender as covariate **stratified by gender

Based on the results for the protocol specified primary endpoint, i.e., CR in the overall phase, the sponsor concluded that "oral netupitant combined with oral palonosetron and given with oral dexamethasone was significantly superior to oral palonosetron alone and given with oral dexamethasone in the prevention of highly emetogenic chemotherapy-induced nausea and vomiting." In particular, they stated that "Statistically significant superiority to palonosetron and dexamethasone alone was observed for each dose of netupitant: differences in complete response 0-120 hours between netupitant treatment groups and palonosetron alone ranged between 10.9% and 13.2%."

When the CMH test was applied on the post-hoc primary endpoint, CR in the delayed phase and two key secondary endpoints, i.e., CR in the acute phase and CR in the overall phase, the sponsor confirmed that the conclusions were the same as those based on the original analyses.

The sponsor's summary is that "The additional analyses performed on NETU-07-07 data confirm the original results and support the robustness of study conclusion. It is noteworthy that for delayed CR, which is the endpoint of major interest for establishing the efficacy of netupitant according to the FDA, as for CR in the overall phase, all three netupitant with palonosetron groups were statistically superior to the palonosetron alone group."

3.2.2 Study NETU-08-18

Study NETU-08-18 is titled as "a Phase 3 multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group study of the efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone for the prevention of nausea and vomiting in cancer patients receiving moderately emetogenic chemotherapy". It was conducted from April 2011 through November 2012 at 177 sites in 15 countries distributed among the US, Latin America including Mexico, Europe, Commonwealth of Independent States, and Asia.

3.2.2.1 Study Objective and Study Design

This was a phase 3 , multicenter, multinational, randomized, double-blind, double-dummy, parallel group, stratified study in patients receiving MEC. The stratification criteria were region (US, Latin America including Mexico, Europe, Commonwealth of Independent States [i.e., former Soviet Republics], Asia) and age class (<55 years and ≥55 years).

The primary objective of the study was to compare the efficacy of a single oral dose of a fixed combination of netupitant/palonosetron (300 mg/0.50 mg) with oral dexamethasone versus oral palonosetron 0.50 mg with oral dexamethasone in terms of CR in the delayed phase (25-120 hours) at cycle 1.

The secondary objectives of the study were as follows:

- To compare the efficacy, safety and tolerability of a single oral dose of a fixed combination of netupitant/palonosetron (300 mg/0.50 mg) with oral dexamethasone to oral palonosetron

0.50 mg with oral dexamethasone for the prevention of MEC induced nausea and vomiting in initial and repeat cycles.

- To assess the population pharmacokinetics (PK) and pharmacodynamics (PD) of netupitant (and its metabolites M1, M2 and M3) and palonosetron in patients that have received the combination product.

Patients were randomized to receive either the oral netupitant/palonosetron (300 mg/0.50 mg) fixed dose combination (FDC) with oral dexamethasone 12 mg or oral palonosetron 0.50 mg with oral dexamethasone 20 mg preceding the administration of MEC on the first day of chemotherapy cycle 1. After cycle 1, patients could continue in a multiple-cycle extension phase, i.e., they could participate in the consecutive repeat cycles (at least 21 days apart) for as long as they continued to fulfill the inclusion/exclusion criteria. On Day 1 of each repeat cycle, the patients received the same study treatment as in cycle 1.

During cycle 1, patients were to participate in the study for a maximum of 37 days (including up to 14 days screening period, one day of treatment, and a follow-up visit or a telephone call 21±2 days after Day 1). In the multiple-cycle extension, patients were to participate for a maximum of 30 days in every repeat cycle (including up to 7 days screening period, one day of treatment, and a follow-up visit or a telephone call 21±2 days after Day 1).

This study involved chemotherapy-naïve patients, defined as patients having no prior history of cytotoxic chemotherapy. Adult male and female patients scheduled to receive the first course of an anthracycline and cyclophosphamide-containing MEC regimen for the treatment of a malignant solid tumor were randomly allocated to receive one of the two treatment regimens.

Regarding the method of assigning patients to treatment groups, patients meeting the inclusion and exclusion criteria were assigned to one of the two treatment groups in a balanced design (1:1), according to specific procedures using the Randomization and Trial Supply Management (RTSM) system, accessed by Electronic Data Capture (EDC) or Interactive Voice Response System (IVRS). Two randomization lists were prepared, one for each age class. For each region a different block of the relevant list was allocated, i.e., each time a new region started to randomize patients or each time a block for the relevant region was completed, the next unused block was attributed to that region.

Separate lists were prepared for patients' randomization and study medication packaging. According to this packaging list, sealed cartons containing the study drugs and additional study drug were supplied to the investigational sites. An appropriate number of kits were supplied to the designated investigational sites at the beginning of the study, with further re-supplies scheduled once the number of treatment kits remaining reached a pre-set threshold at each site.

The sample size was estimated to be 1460 patients, equally distributed in 2 treatment groups (730 patients per group). The assumption was a CR rate in the time interval 25-120 hours of cycle 1 of 60% in the netupitant/palonosetron fixed combination group and 51% in the palonosetron group. For a 2-sided test of difference using α=0.050, a sample size of 661 evaluable patients per group was needed to ensure 90% power to detect the above mentioned 9% difference. This

number was increased to 730 patients per treatment group for a total of 1460 patients, to ensure an adequate number of evaluable patients.

Regarding the key secondary efficacy endpoints, this same sample size gave the study a power of about 60% (61%) to detect a difference of 6% in the CR rate in the acute phase (assuming rates of 70% and 64% in the fixed combination and palonosetron groups, respectively). The power to detect a difference of 9% in terms of CR in the overall phase was close to 90%.

3.2.2.2 Efficacy Endpoints and Analyses

The primary endpoint was complete response, defined as no emetic episode and no rescue medication in the delayed phase (time interval of 25-120 hours after the start of MEC administration) at Cycle 1. The two key secondary endpoints were patients CR in the acute and overall phases.

The primary analysis was to be performed on the FAS using a 2-sided stratum-adjusted CMH test including treatment, age class and region as strata. All missing data were to be imputed as treatment failures. The null hypothesis was rejected (and superiority of the FDC versus oral palonosetron alone demonstrated), if the 2-sided p-value from the CMH test was less than or equal to 0.050 and in the right direction i.e., the Odds Ratio (OR) was in favor of the fixed combination. The ORs and the 2-sided 95% CI for the ORs from the CMH test were to be presented.

In addition, a supportive PP analysis imputing all missing data as treatment failures was to be performed. Furthermore, to further assess the missing data impact on the study results, the following sensitivity analyses of the primary endpoint were to be performed:

- ITT population imputing all missing data as treatment failures. Patients who did not receive the chemotherapy (and therefore the emetogenic stimulus) were to be considered as treatment failures.
- Complete case, i.e., excluding patients with missing or non-completed diaries who were to be considered as treatment failures in the primary analysis based on the FAS.

Treatment-by-factor (age class and region) interactions were to be explored using a logistic regression model, but were to be not included in the primary analysis model. In the event that significant interactions (i.e., p-value ≤ 0.100) were found, additional analyses could have been run in order to understand the reason for the heterogeneity.

For exploratory purposes only, the primary efficacy endpoint analysis was also to be presented on the FAS by age class and region.

The number and percentage of patients with CR in the acute and overall phases by treatment group and the difference in response rate between the 2 treatment groups was to be summarized. The 95% CIs for the response rate (using the Wilson score method) and for the difference in the response rate (using Newcombe-Wilson method) were also provided. If the null hypothesis of no difference between treatments for the primary endpoint was rejected, analysis of the first key secondary

endpoint, CR in the acute phase (0-24 hours) at cycle 1 was to be performed. CR in the acute phase was to be tested using the same 2-sided CMH test as for the primary endpoint. The fixed combination was to be considered superior to palonosetron in the acute phase if the 2-sided p-value from the CMH was less than or equal to 0.050 and in the right direction. The OR and 2-sided 95% CI for the OR from the CMH test were to be presented.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 5 displays patient disposition and the reasons for early discontinuation, and Table 6 displays patients' baseline demographic information. Of the 1455 randomized patients, 1438 patients (98.8%) completed cycle 1 and 1286 patients (88.4%) were scheduled for treatment and treated in the multiple-cycle extension. A total of 907 patients (62.3%) completed the multiple-cycle extension; the maximum number of treatment cycles was 8, which were completed by 5 patients (0.3%).

Table 5 Patient Disposition Based on Intent-to-Treat Population for Study NETU-08-18

	NETU/PALO FDC, n (%)	PALO alone n (%)	Overall n (%)
Randomized	726 (100)	729 (100)	1455 (100)
Treated	724 (99.7)	726 (99.6)	1450 (99.7)
Completed Planned/Unplanned Chemotherapy Cycles	453 (62.4)	463 (63.5)	916 (63.0)
Completed Planned Chemotherapy Cycles but Discontinued During Additional Unplanned Cycle	2 (0.3)	0	2 (0.1)
Completed a Cycle But Not Continuing in the Next Planned Cycle	253 (34.8)	245 (33.6)	498 (34.2)
Discontinued After Randomization and During any Planned Chemotherapy Cycle	18 (2.5)	21 (2.9)	39 (2.7)
Reason for Discontinuation			
Inclusion/Exclusion Criteria not Met (Multiple-Cycle Extension)	55 (7.6)	66 (9.1)	121 (8.3)
Adverse event	10 (1.4)	19 (2.6)	29 (2.0)
Death	0	2 (0.3)	2 (0.1)
Protocol Violation	5 (0.7)	6 (0.8)	11 (0.8)
Lost to Follow-up	0	5 (0.7)	5 (0.3)
Withdrawal of Consent	65 (9.0)	42 (5.8)	107 (7.4)
Lack of Efficacy	1 (0.1)	3 (0.4)	4 (0.3)
Sponsor's Decision	0	0	0
Other	136 (18.7)	123 (16.9)	259 (17.8)

Source: Sponsor's Table 4 of CSR

Table 6 Patients' Baseline Demographics based on FAS in Cycle 1 for Study NETU-08-18

	NETU/PALO FDC n=724	PALO alone n=725	Overall n=1449
Gender, n (%)			
Male	13 (1.8)	15 (2.1)	28 (1.9)
Female	711 (98.2)	710 (97.9)	1421 (98.1)
Childbearing Potential	222 (31.2)	223 (31.4)	445 (31.3)
Race, n (%)			
White	573 (79.1)	580 (80.0)	1153 (79.6)
Black	1 (0.1)	2 (0.3)	3 (0.2)

Asian	101 (14.0)	103 (14.2)	204 (14.1)
Hispanic	46 (6.4)	36 (5.0)	82 (5.7)
Other	3 (0.4)	4 (0.6)	7 (0.5)
Age at Randomization (years)			
Mean (SD)	53.7 (10.67)	54.1 (10.65)	53.9 (10.66)
Weight (kg)			
Mean (SD)	71.3 (15.65)	71.85 (15.88)	71.58 (15.76)
Height (cm)			
Mean (SD)	160.4 (7.74)	160.7 (7.22)	160.6 (7.48)
BMI (kg/m^2)			
Mean (SD)	27.69 (5.81)	27.77 (5.69)	27.73 (5.75)

Source: Sponsor's Table 14.1.2.1.1.1 of CSR

3.2.2.4 Sponsor's Efficacy Results & Conclusions

The sponsor's analysis results for the primary endpoint CR rate in the delayed phase, the acute phase and the overall phase based on the FAS as well as the Per-Protocol (PP) subsets are summarized in Table 7. For the FAS subset, the sponsor noted that the percentage of patients with CR over 25-120 hours after the start of MEC administration in cycle 1 was 7.4% higher in the netupitant/palonosetron group than the palonosetron group. Superiority of the netupitant/ palonosetron FDC compared to palonosetron alone was demonstrated using a two-sided CMH test with age class and region as strata (OR: 1.48 with 95% CI from 1.16 to 1.87; p=0.001). Based on the sponsor's results for the per-protocol subset, the findings are similar. The sponsor also conducted sensitivity analyses on complete cases as well as the ITT population (results are not shown in this review), and concluded that the primary analysis results are robust.

Table 7 Sponsor's Results for Complete Response for FAS and PP Populations for Study NETU-08-18

Complete Response Cycle 1 Delayed Phase (25-120 hours)	**NETU/PALO FDC (N=724)**	**PALO alone (N=725)**
Full Analysis Set		
Responder, n (%)	557 (76.9)	504 (69.5)
95% C.I.	(73.7; 79.9)	(66.1; 72.8)
Difference from palonosetron alone, % (95% C.I.)	7.4 (2.9; 11.9)	
Odds ratio (95% C.I.)	1.48 (1.16; 1.87)	
p-value	0.001	
Per-Protocol Set		
Responder, n (%)	520 (76.9)	480 (70.2)
95% C.I.	(73.6; 79.9)	(66.6; 73.5)
Difference from palonosetron alone, % (95% C.I.)	6.7 (2.1; 11.4)	
Odds ratio (95% C.I.)	1.42 (1.11; 1.82)	
p-value	0.005	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Full Analysis Set		
Responder, n (%)	640 (88.4)	616 (85.0)
95% C.I.	(85.9; 90.5)	(82.2; 87.4)
Difference from palonosetron alone, % (95% C.I.)	3.4 (-0.1; 6.9)	
Odds ratio (95% C.I.)	1.37 (1; 1.87)	
p-value	0.047	

Per-Protocol Set		
Responder, n (%)	597 (88.3)	585 (85.5)
95% C.I.	(85.7; 90.5)	(82.7; 88.0)
Difference from palonosetron alone, % (95% C.I.)	2.8 (-0.8; 6.4)	
Odds ratio (95% C.I.)	1.29 (0.93; 1.78)	
p-value	0.122	
Complete Response Cycle 1 Overall Phase (0-120 hours)		
Full Analysis Set		
Responder, n (%)	538 (74.3)	483 (66.6)
95% C.I.	(71.0; 77.4)	(63.1; 70.1)
Difference from palonosetron alone, % (95% C.I.)	7.7 (3.0; 12.3)	
Odds ratio (95% C.I.)	1.47 (1.17; 1.85)	
p-value	0.001	
Per-Protocol Set		
Responder, n (%)	501 (74.1)	459 (67.1)
95% C.I.	(70.7; 77.3)	(63.5; 70.5)
Difference from palonosetron alone, % (95% C.I.)	7.0 (2.2; 11.8)	
Odds ratio (95% C.I.)	1.41 (1.11; 1.79)	
p-value	0.004	

Source: Sponsor's Tables 16, 17, 18 and 19 of CSR

According to the sponsor's efficacy analysis results, they concluded that "This study demonstrated the superiority of the netupitant/palonosetron (300 mg/0.5 mg) FDC over palonosetron alone with respect to the primary endpoint CR in the delayed phase and both key secondary endpoints, CR in the acute and overall phases after the administration of moderately emetogenic chemotherapy during the first chemotherapy cycle." They also noted that "In general, the results of the secondary endpoints consistently supported those of the primary and key secondary endpoints for the delayed and overall phases."

3.2.3 Study PALO-10-01

Study PALO-10-01 is titled as "single-dose, multicenter, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of oral palonosetron 0.5 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 study was conducted from June of 2011 to November of 2012 with 80 study sites in 12 countries including India, Russian Federation, Ukraine, Bulgaria, Croatia, Germany, Hungary, Italy, Poland, Romania, Argentina and the United States.

3.2.3.1 Study Objective and Study Design

The primary objective of the study was to demonstrate the non-inferiority of single dose oral palonosetron 0.50 mg versus single dose I.V. palonosetron 0.25 mg in terms of percentage of patients with Complete Response (CR) during the acute phase (0-24 hours).

The secondary objectives of the study were as follows:

- To assess the efficacy of single dose oral palonosetron 0.50 mg versus single dose I.V. palonosetron 0.25 mg by the evaluation of further secondary efficacy variables during the acute phase (0-24 hours) and to describe the efficacy during the delayed (25-120 hours) and overall (0-120 hours) phases.
- To evaluate the safety and tolerability of oral palonosetron 0.50 mg versus I.V. palonosetron 0.25 mg for the prevention of HEC induced nausea and vomiting.

Patients were randomized on Day 1 of the chemotherapy cycle before administration of cisplatin to receive either oral palonosetron 0.50 mg (Aloxi®) with oral dexamethasone 20 mg or I.V. palonosetron 0.25 mg (Aloxi®) with oral dexamethasone 20 mg. Patients also received oral dexamethasone (8 mg in the morning and evening) on Days 2-4.

Patients were to participate in the study for a maximum of 37 days (including a screening period of up to 14 days, 6+2 days on study of which 4 days on active treatment, and a follow-up visit or a telephone call 21±2 days after Day 1).

According to the study protocol, a total of 740 patients (i.e., 370 patients/group) were planned to be randomized at approximately 90 study sites distributed among the US, Latin America, Europe, Commonwealth of Independent States (i.e., former Soviet Republics) and Asia.

This study involved chemotherapy naïve patients, defined as patients having no prior history of cytotoxic chemotherapy. Adult male and female patients scheduled to receive the first course of a highly emetogenic cisplatin-based chemotherapy regimen (administered as a single I.V. dose of ≥70 mg/m2 over 1-4 hours on study Day 1, either alone or in combination with other chemotherapeutic agents) for the treatment of a malignant solid tumor were randomly allocated to receive one of the two treatment regimens.

The sample size was estimated to be 740 patients, equally distributed in 2 treatment groups (370 patients per group).

The assumption was a CR rate in the acute phase (0-24 hours) of 69% in the oral palonosetron group and 70% in the I.V. palonosetron group. For a 2-sided test of difference using $\alpha = 0.010$, a sample size of 322 evaluable patients per group was needed to ensure 90% power with a non-inferiority margin set at -15%. This number was increased to 370 patients per treatment group for a total of 740 patients, to ensure an adequate number of evaluable patients.

3.2.3.2 Efficacy Endpoints and Analyses

The primary efficacy endpoint was the proportion of patients with CR (defined as no emesis and no rescue medications) within 24 hours after the start of the HEC administration on Day 1.

The secondary efficacy endpoints included patients' CR during the delayed and overall phase, the proportion of no emesis, no rescue medication, no significant nausea, no nausea, and with total

control (no emetic, no rescue medications and on nausea) during the acute, delayed and overall phase, separately. The other type of secondary endpoints were severity of nausea, time to first emetic episode, time to first rescue medications intake, time to treatment failure and impact on patients' daily life activities in the acute and delayed phase following the administration of cisplatin as assessed by the Functional Living Index-Emesis (FLIE) questionnaire.

The primary efficacy analysis was based on the 2-sided stratum adjusted Cochran-Mantel-Haenszel (CMH) method on the proportion of patients with CR in the acute phase. The model included gender and region as strata. The non-inferiority margin was set at -15%. The null hypothesis of no difference between treatments was to be rejected, and the non-inferiority of oral palonosetron 0.50 mg versus I.V. palonosetron 0.25 mg demonstrated if the lower limit of the two-sided 99% Confidence Interval (CI) for the difference in the proportions of patients with CR was greater (i.e., closer to zero) than -15%. The primary efficacy analysis was performed on the Full Analysis Set (FAS) and Per-Protocol (PP) populations; all missing data were imputed as treatment failures. To further assess the missing data impact on the study results in the non-inferiority conclusion, a number of sensitivity analyses were also performed.

The number and percentage of patients with CR in the acute phase and 95% CI for the response rate (using the Wilson score method) was presented by treatment group. The difference in response rate between the two groups and the 95% CI (using Newcombe-Wilson's method) was also provided. The risk difference and the 99% CI for the risk difference were calculated. In addition, the odds ratio (ORs), the 2-sided 95% CI for the OR and p-value from the CMH test were presented.

Reviewer's Note:
The sponsor proposed non-inferiority margin -15% was agreed upon by the FDA prior to the trial initiation. Not that this margin was derived based on the available history information and has also been used in the pivotal CINV studies for other 5-HT_3 antagonists. In particular, Sancuso granisetron transdermal patch sole pivotal efficacy study used a non-inferiority margin of -15% to support approval.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

The number of patients randomized into each treatment group, patient disposition, and the reasons for early discontinuation are summarized in Table 8. Out of the 743 randomized patients, there were 33 (4.4%) patients prematurely discontinued the study after randomization. Main reasons for discontinuation were death reported in 6 (1.6%) patients in the oral palonosetron group and 11 (3.0%) patients in the I.V. palonosetron group, withdrawal of consent in 2 (0.5%) and 3 (0.8%) patients, respectively, and lost to follow-up in 1 (0.3%) and 3 (0.8%), respectively.

Table 8 Patient Disposition Based on Intent-to-Treat Population for Study PALO-10-01

	Oral PALO n (%)	L.V. PALO n (%)	Overall n (%)
Randomized	371 (100.0)	372 (100.0)	743 (100.0)
Treated	370 (99.7)	369 (99.2)	739 (99.5)
Discontinued after randomization	12 (3.2)	21 (5.6)	33 (4.4)
Reason for discontinuation			
Adverse event	1 (0.3)	1 (0.3)	2 (0.3)
Death	6 (1.6)	11 (3.0)	17 (2.3)
Protocol violation	0	3 (0.8)	3 (0.4)
Lost to follow-up	1 (0.3)	3 (0.8)	4 (0.5)
Withdrawal of consent	2 (0.5)	3 (0.8)	5 (0.7)
Lack of efficacy	0	0	0
Sponsor's decision	1 (0.3)	0	1 (0.1)
Other	1 (0.3)	0	1 (0.1)

Source: Sponsor's Table 5 of CSR

Note that of the 743 randomized patients, four did not receive treatment. Therefore, the safety population included 739 (99.5%) treated patients. Overall, 5 patients were excluded from the FAS for not receiving highly emetogenic chemotherapy and/or study medications such that the FAS included 738 (99.3%) patients. A total of 76 (10.2%) patients randomized were excluded from the PP population which comprised 667 patients (89.8%). The detailed numbers for each treatment group for each analysis set are shown in Table 9.

Table 9 Analysis Population and Reasons for Exclusion from All Randomized Patients for Study PALO-10-01

	Oral PALO n (%)	L.V. PALO n (%)	Overall n (%)
Intent-To-Treat (ITT) Population			
Patients included	371 (100)	372 (100)	743 (100)
Full Analysis Set (FAS)			
Patients included	369 (99.5)	369 (99.2)	738 (99.3)
Patients included	2 (0.5)	3 (0.8)	5 (0.7)
Reasons for exclusion from FAS			
No HEC regimen received	2 (0.5)	3 (0.8)	5 (0.7)
No study treatment medications	1 (0.3)	3 (0.8)	4 (0.5)
Per-Protocol (PP) Population			
Patients included	329 (88.7)	338 (90.9)	667 (89.8)
Patients excluded	42 (11.3)	34 (9.1)	76 (10.2)
Reasons for exclusion from PP Population			
Not included in FAS	2 (0.5)	3 (0.8)	5 (0.7)
Major protocol violation in 0-24 hour period	42 (11.3)	34 (9.1)	76 (10.2)
Safety Population			
Patients included	370 (99.7)	369 (99.2)	739 (99.5)
Patients excluded			4 (0.5)
Reasons for exclusion from Safety Population			
No study treatment received			4 (0.5)

Source: Sponsor's Table 7 of CSR

As the sponsor's primary efficacy analyses were based on FAS and PP population, patients' baseline demographics data are summarized for these two populations in Tables 10 and 11. As seen from the tables, demographic characteristics were comparable between the two treatment groups.

Table 10 Baseline Demographics for FAS for Study PALO-10-01

	Oral PALO N=369	L.V. PALO N=369	Overall N=738
Gender – n (%)			
Male	219 (59.3)	217 (58.8)	436 (59.1)
Female	150 (40.7)	152 (41.2)	302 (40.9)
Childbearing potential	25 (16.7)	30 (19.7)	55 (18.2)
Race – n (%)			
White	320 (86.7)	320 (86.7)	640 (86.7)
Black	0	0	0
Asian	49 (13.3)	47 (12.7)	96 (13.0)
Hispanic	0	1 (0.3)	1 (0.1)
Other	0	1 (0.3)	1 (0.1)
Age at randomization (years)			
Mean (SD)	58 (9.42)	57.7 (9.92)	57.9 (9.67)
Weight (kg)			
Mean (SD)	68.56 (16.4)	68.78 (16.52)	68.67 (16.45)
Height (cm)			
Mean (SD)	166.2 (9.41)	166.5 (8.29)	166.3 (8.86)
BMI (kg/m^2)			
Mean (SD)	24.72 (5.17)	24.76 (5.65)	24.74 (5.42)

Source: Sponsor's Table 14.1.2.1.1.1 of CSR

Table 11 Baseline Demographics for PP Population for Study PALO-10-01

	Oral PALO N=329	L.V. PALO N=338	Overall N=667
Gender – n (%)			
Male	194 (59.0)	197 (58.3)	391 (58.6)
Female	135 (41.0)	141 (41.7)	276 (41.4)
Childbearing potential	23 (17.0)	29 (20.6)	52 (18.8)
Race – n (%)			
White	281 (85.4)	291 (86.1)	572 (85.8)
Black	0	0	0
Asian	48 (14.6)	45 (13.3)	93 (13.9)
Hispanic	0	1 (0.3)	1 (0.1)
Other	0	1 (0.3)	1 (0.1)
Age at randomization (years)			
Mean (SD)	57.8 (9.48)	57.6 (9.98)	57.7 (9.73)
Weight (kg)			
Mean (SD)	68.27 (16.4)	68.84 (16.58)	68.55 (16.49)
Height (cm)			
Mean (SD)	166.1 (9.39)	166.4 (8.28)	166.2 (8.84)
BMI (kg/m^2)			
Mean (SD)	24.64 (5.18)	24.81 (5.68)	24.73 (5.44)

Source: Sponsor's Table 14.1.2.1.1.4 of CSR

3.2.3.4 Sponsor's Efficacy Results & Conclusions

The sponsor's analysis results for the primary endpoint, i.e., the non-inferiority testing for the oral palonosetron versus I.V. palonosetron in terms of proportion of patients with CR in the acute phase after the start of the HEC administration based on the FAS population are presented in Table 12. As seen in the table, the difference in proportion between the oral and I.V. palonosetron groups was 3.21% with 99% C.I. as (-2.74%, 9.17%). Since the lower bound of -2.74 is greater than the pre-defined margin set at -15%, the sponsor concluded that the non-inferiority of oral palonosetron versus I.V. palonosetron was demonstrated.

The sponsor performed many sensitivity analyses which included the non-inferiority test using Newcombe-Wilson method, using the exact method and also using the CMH test for CR in the acute phase based on the FAS, separately. For the CMH test, the sponsor also tried to impute missing data in the experimental group as failures and missing data in the control group as successes based on either the ITT population or FAS. The results of all the planned sensitivity analyses supported the conclusion of non-inferiority of oral versus I. V. palonosetron. These results are not shown in this review.

Table 12 Sponsor's Results for Non-Inferiority Test Based on CR in the Acute Phase for FAS & PP for Study PALO-10-01

For FAS	**Oral PALO (N=369)**	**I.V. PALO (N=369)**
Acute phase (0-24 hours)		
Responder, n (%)	330 (89.4)	318 (86.2)
95% C.I.	(85.9, 92.2)	(82.3, 89.3)
Risk difference, % (99% C.I.)	3.21 (-2.74, 9.17)	
For PP	Oral PALO (N=329)	I.V. PALO (N=338)
Acute phase (0-24 hours)		
Responder, n (%)	297 (90.3)	294 (87.0)
95% C.I.	(86.6, 93.0)	(83.0, 90.2)
Risk difference, % (99% C.I.)	3.77 (-3.22, 10.76)	

Source: Sponsor's Tables 13 and 14 of CSR

The sponsor's analysis results for the CR rate during the delayed and overall phases are summarized in Table 13 for the FAS. In the delayed phase, the percentage of patients with CR was 76.2% in the oral palonosetron group and 74.8% in the I.V. palonosetron group. There was no statistically significant difference between the treatment groups with the difference from I.V. palonosetron, 1.4 and the 95% C.I., (-4.8, 7.5). In the overall phase, the percentage of patients with CR was 73.7% in the oral palonosetron group and 70.2% in the I.V. palonosetron group. The difference between the treatment groups was not significant, either, where the difference from I.V. palonosetron is 3.5 and the 95% C.I. is (-3.0, 10.0).

The sponsor's analysis results for the other secondary endpoints also showed similar efficacy between two treatments. Therefore, the sponsor concluded that this study demonstrated the non-inferiority of oral palonosetron versus I.V. palonosetron.

Table 13 Sponsor's Complete Response in the Delayed and Overall Phases Based on FAS for Study PALO-10-01

	Oral PALO (N=369)	I.V. PALO (N=369)
Delayed phase (25-120 hours)		
Responder, n (%)	281 (76.2)	276 (74.8)
95% C.I.	(71.5, 80.2)	(70.1, 79.0)
Risk difference, % (99% C.I.)	1.4 (-4.8, 7.5)	
Overall phase (0-120 hours)		
Responder, n (%)	272 (73.7)	259 (70.2)
95% C.I.	(69.0, 77.9)	(65.3, 74.6)
Risk difference, % (99% C.I.)	3.5 (-3.0, 10.0)	

Source: Sponsor's Table 15 of CSR

3.2.4 Statistical Reviewer's Findings and Comments

1. **(Re-Analysis Results for Study NETU-07-07)** The statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints using both the logistic regression model and the CMH method based on the MFAS in the clinical study report.

   Although Study NETU-07-07 was originally planned to be a phase 2 trial, the sponsor noted in the Clinical Study Report Addendum #2 the following:

> On March 8th of 2010, the FDA Division of Gastroenterology Products, after discussion with the Office of Medical Policy, commented in their advice/information letter that this study would be acceptable to support the NDA for the proposed fixed dose combination capsule for the prevention of acute and delayed CINV in the HEC setting provided that "FDA would be able, after review of the trial data, to confirm the positive study outcome." For this reason, besides the routine quality assurance (QA) auditing process conducted during the study at 8 sites, an additional in-depth QA audit plan was implemented after the study had been completed. Following a risk-based analysis, 12 of the top recruiting sites were selected to undergo an additional auditing process.
>
> As a result of the overall QA process, 55% of the records of all patients enrolled in the study were audited. One site in Russia (site #120) presented multiple major audit findings, ranging from failure to meet eligibility criteria and administration of prohibited medications to inconsistencies between source data and Case Report Forms (CRFs). Regardless of these findings, according to intent to treat principles, the site must be and remains part of all planned analyses. However, to explore whether this site has had any impact on the treatment effect, as a conservative approach the sponsor is providing here the CR rates (defined as no emetic episodes and no rescue medication) with and without all 39 patients enrolled at this site.

   The following Table 14 presents both the sponsor's and the statistical reviewer's re-analysis results after excluding site #120. Of note, although the sponsor had been notified that the primary endpoint should be CR in the delayed phase and the data should be analyzed by the CMH test stratified by "gender" if Study NETU-07-07 would be treated as a pivotal trial, in the sponsor's

1.11.3 Efficacy Information Amendment, the sponsor used the original primary endpoint, the CR in the overall phase, and the re-analyses were performed based on the original primary analysis method, i.e., logistic regression model with "gender" as covariate, not the recommended CMH method stratified by "gender" factor. The statistical reviewer had confirmed the sponsor's results and also performed the analyses by CMH. All of the p-values were very close using the two analysis methods.

Table 14 Re-Analysis Results for CR in Overall, Acute and Delayed Phases after Excluding Site 120 for MFAS for Study NETU-07-07

	PALO alone (N=129)	PALO+NETU 100 mg (N=128)	PALO+NETU 200 mg (N=129)	PALO+NETU 300 mg (N=126)
Overall Phase (0-120 hours)				
Number (%) of Subjects	99 (76.7)	111 (86.7)	114 (88.4)	112 (88.9)
Difference from PALO alone (%) with 95% C.I.		10.0 (0.6, 19.3)	11.6 (2.5, 20.8)	12.1 (3.0, 21.3)
p-value by logistic model*		0.036	0.015	0.011
p-value by CMH**		0.036	0.014	0.010
Acute Phase (0-24 hours)				
Number (%) of Subjects	115 (89.1)	119 (93.0)	119 (92.2)	124 (98.4)
Difference from PALO alone (%) with 95% C.I.		3.8 (-3.1, 10.8)	3.1 (-4.0, 10.2)	9.3 (3.5, 15.1)
p-value by logistic model*		0.274	0.398	0.008
p-value by CMH**		0.275	0.398	0.002
Delayed Phase (25-120 hours)				
Number (%) of Subjects	104 (80.6)	115 (89.8)	119 (92.2)	113 (89.7)
Difference from PALO alone (%) with 95% C.I.		9.2 (0.6, 17.8)	11.6 (3.4, 19.9)	9.1 (0.4, 17.7)
p-value by logistic model*		0.037	0.008	0.044
p-value by CMH**		0.036	0.006	0.042

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".
Source: Sponsor's Table in 1.11.3 Efficacy Information Amendment and the statistical reviewer's results

The statistical reviewer noted that the sponsor concluded that "Results are consistent with those reported in the CSR." They particularly emphasized that "In the acute phase, the highest percentage of subjects with complete response is in the netupitant 300 mg group (98.4%) with a difference from the palonosetron alone group of 9.3% (p=0.008)." and also "In the delayed phase, the differences between the three netupitant dose groups and palonosetron alone range from 9.1% to 11.6%. The differences versus palonosetron alone are statistically significant for all three netupitant doses**,** which is also consistent with the results obtained in the original analyses as presented in the CSR." The statistical reviewer would like to point out that if this phase 2 trial is used to serve as a confirmatory trial, then the primary endpoint of clinical interest should be the CR in the delayed phase. This was clearly stated in the sponsor's Clinical Study Report Addendum #1.

As there were three doses of the study drug in the trial, to control the type I error rate, it was reasonable to analyze data using the originally proposed Holm-Bonferroni multiplicity adjustment method in the study protocol. As a result, only PALO+NETU 200 mg is statistically significantly superior to PALO alone with the smallest p-value of 0.006. Since the p-value of

0.036 for the comparison between PALO+NETU 100 mg and PALO alone is greater than 0.025, the Holm-Bonferroni method precludes the test for the comparison between PALO+NETU 300 mg and PALO alone to proceed.

2. (ITT Results for Study NETU-07-07) As noted on Page 8 of Section 3.2.1.2 earlier, for the purpose of considering Study NETU-07-07 as the sole pivotal trial for CINV-HEC indication, the FDA requested the sponsor to perform some additional analyses, including the sensitivity analysis on the Intent to Treat (ITT) population, which was defined as all randomized patients.

The sponsor's ITT analysis results are presented in Table 15. There was only 17 patients excluded from the FAS population; however, it would alter the final conclusions. The ITT results were all insignificant for all doses and all phases when the Holm-Bonferroni multiplicity method was implemented.

Table 15 Sponsor's Sensitivity Analysis Results Based on ITT Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=142)	PALO+NETU 300 mg (N=143)
Delayed Phase (25-120 hours)				
Number (%) of Subjects	109 (80.1)	122 (90.4)	125 (88.0)	122 (85.3)
Difference from Palo alone (%) with 95% C.I.		102 (1.9, 18.6)	7.9 (-0.7, 16.5)	5.2 (-3.7, 14.0)
p-value by CMH**		0.017	0.072	0.241
Acute Phase (0-24 hours)				
Number (%) of Subjects	122 (89.7)	126 (93.3)	127 (89.4)	133 (93.0)
Difference from Palo alone (%) with 95% C.I.		3.6 (-3.0, 10.2)	-0.3 (-7.5, 6.9)	3.3 (-3.3, 9.9)
p-value by CMH**		0.278	0.934	0.317
Overall Phase (0-120 hours)				
Number (%) of Subjects	104 (76.5)	118 (87.4)	120 (84.5)	121 (84.6)
Difference from Palo alone (%) with 95% C.I.		10.9 (1.9, 20.0)	8.0 (-1.3, 17.3)	8.1 (-1.1, 17.4)
p-value by CMH**		0.018	0.089	0.078

** stratified for gender. Source: Sponsor's Table 5 of CSR Addendum #1

3. (Sensitivity Analysis Results for Study NETU-07-07 Regarding Site 120) To further investigate the protocol violations found in Russian Site #120 on the efficacy assessment for Study NETU-07-07, FDA requested the sponsor to perform the following sensitivity analyses for the CR in all three phases (i.e., delayed, acute and overall):

a. Excluding the patients with major protocol violations (including taking disallowed concomitant medications) in Site #120
b. Excluding the patients with any protocol violations in Site #120
c. Including all patients in Site #120 but treating the patients with major protocol violations (including taking disallowed concomitant medications) as "treatment failures"

d. Including all patients in Site #120 but treating the patients with any protocol violations as "treatment failures"
e. Per-protocol analyses for the CR-delayed phase and -acute phase (including and excluding Site #120)

Of note, the sponsor had identified 13 out of the 39 randomized patients in Site #120 with major violations impacting efficacy and one of them had both a major and a minor violation. In addition, one more patient with minor violations that would impact efficacy.

The statistical reviewer confirmed the sponsor's sensitivity analysis results. Results by the logistic model from the sponsor and by the CMH test from the statistical reviewer for all three phases are included in the tables of the Appendix. Regarding findings for the CR in the delayed phase, i.e., the endpoint that the FDA would focus on if NETU-07-07 has been treated as a pivotal trial, when Holm-Bonferroni method is applied, PALO+NETU 300 mg could not show significant difference against Palonosetron alone on the items " d" neither "e" (the one by excluding Site 120). PALO+NETU 100 mg and 200 mg fail to show significant difference against palonosetron alone on the item "e" and "d", respectively.

It is should be noted that there was only one additional patient being treated as "failure" in "d" than in "c"; however, it would alter the conclusion for PALO+NETU 300 mg. Note that the sponsor seems to have drawn an incorrect conclusion for 1(d). In particular, the sponsor stated in the response that the statistical p-values were significant for all three doses even applying the Holm-Bonferroni method to adjust for multiplicity. However, this error does not affect the overall conclusion for the P+N 300 mg efficacy.

In summary, based on the sensitivity analyses results, the impact of Site #120 on the efficacy of PALO+NETU in the three doses do not seem to be markedly severe and should not be a concern although not all the efficacy results shown for the PALO+NETU 300 mg are statistically significant.

4. **(US Results for Study NETU-08-18)** The statistical reviewer confirmed the sponsor's analysis results for the primary and two key secondary endpoints. Although based on the results this study demonstrated significant treatment effect of P+N 300mg overall, this reviewer would like to note that Study NETU-08-18 was conducted worldwide with only about four percent of patients from the U.S. and the observed treatment difference between the study drug and palonosetron in the U.S. subgroup was not consistent with the rest of the world. Although due to the small samples this finding is likely due to play of chance, we can conclude that the U.S. data did not contribute to the evidence for the study drug's efficacy .

5. **(Efficacy Findings for Study PALO-10-01)** The statistical reviewer confirmed the sponsor's analysis results for the primary endpoint and important secondary endpoints. This study data support the non-inferiority of oral palonosetron versus I.V. palonosetron.

6. **(Efficacy Results for Study NETU-10-29)** Study NETU-10-29 was titled as "a phase 3, multicenter, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles." Patients were enrolled from 59 sites in 10 countries including Bulgaria, Czech Republic, Germany, Hungary, India, Poland, Russia, Serbia, Ukraine and the United States. The sponsor's results, directly extracted from the clinical study report are shown in the following. The statistical reviewer has confirmed the sponsor's analysis results for the CR and no significant nausea in the delayed, acute and overall phases.

In cycle 1, the proportion of patients with CR was numerically higher for the netupitant/ palonosetron FDC group than in the aprepitant+palonosetron group in the delayed (83.2% vs. 77.7%) and overall phases (80.6% vs. 75.7%), with differences of 5.5% and 4.9%, respectively, while the CR rates were similar between these treatment groups in the acute phase (92.9% vs. 94.2%, difference of -1.3%). The proportion of patients with no significant nausea in the netupitant/palonosetron FDC and in the aprepitant+palonosetron group was generally similar in the delayed (85.1% vs. 81.6%), overall (84.1% vs. 80.6%) and acute (90.6% vs. 93.2%) phases, with a difference between treatment groups of 3.6% both in the delayed and overall phases and -2.6% in the acute phase. Efficacy based on CR and no significant nausea was maintained throughout all study cycles at levels similar to that observed in cycle 1. In cycles 2 to 6, the proportion of patients with CR was consistently numerically higher for the netupitant/palonosetron FDC group than the aprepitant+palonosetron group in the delayed and overall phases. Results in the acute phase were more similar between groups. The same trend was also observed for no significant nausea in cycles 3 to 6, while in cycle 2 the values were more similar in all phases between treatment groups. In summary, the netupitant/palonosetron FDC combined with dexamethasone shows high response rates in the prevention of nausea and vomiting, in the delayed, acute and overall phases of initial and repeated cycles of chemotherapy.

7. **(Low Discontinuation Rates)** The discontinuation rates were low for all four studies. Particularly, they were 2.7%, 1.2%, 4.4%, and 1.9% for Study NETU-07-07, the cycle 1 of Study NETU-08-18, Study PALO-10-01 and the cycle 1 of Study NETU-10-29, respectively. Therefore, no sensitivity analysis results for assessing the impact of dropouts were reported in this review.

3.3 Evaluation of Safety

The safety evaluation is not conducted in this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 For Study NETU-07-07

The following Tables 16 to 18 present the reviewers' subgroup analysis results for all the three phases. Of note, almost all of the patients were Caucasians except one patient, so roughly 100%; thus the subgroup analysis for race was not performed and reported in this review.

Table 16 Statistical Reviewer's Gender Subgroup Analysis Results Based on MFAS Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=142)	PALO+NETU 300 mg (N=143)
Female (N)	N=58	N=58	N=58	N=58
Delayed Phase (25-120 hours)				
Number (%) of Subjects	42 (72.4%)	52 (89.7%)	50 (86.2%)	49 (84.5%)
Difference from PALO alone		17.3%	13.8%	12.1%
Acute Phase (0-24 hours)				
Number (%) of Subjects	49 (84.5%)	52 (89.7%)	51 (87.9%)	56 (96.6%)
Difference from PALO alone		5.2%	3.4%	12.1%
Overall Phase (0-120 hours)				
Number (%) of Subjects	39 (67.2%)	48 (82.8%)	47 (81.0%)	48 (82.8%)
Difference from PALO alone		15.5%	13.8%	15.5%
Male (N)	N=78	N=77	N=79	N=77
Delayed Phase (25-120 hours)				
Number (%) of Subjects	67 (85.9%)	70 (90.9%)	75 (94.9%)	73 (94.8%)
Difference from PALO alone		5%	9%	8.9%
Acute Phase (0-24 hours)				
Number (%) of Subjects	73 (93.6%)	74 (96.1%)	76 (96.2%)	77 (100%)
Difference from PALO alone		2.5%	2.6%	6.4%
Overall Phase (0-120 hours)				
Number (%) of Subjects	65 (83.3%)	70 (90.9%)	73 (92.4%)	73 (94.8%)
Difference from PALO alone		7.6%	9.1%	11.5%

Table 17 Statistical Reviewer's Age Subgroup Analysis Results Based on MFAS Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=142)	PALO+NETU 300 mg(N=143)
Age < 55 Years	N=67	N=63	N=67	N=73
Delayed Phase (25-120 hours)				
Number (%) of Subjects	50 (74.6%)	55 (87.3%)	59 (88.1%)	66 (90.4%)
Difference from PALO alone		12.7%	13.5%	15.8%
Acute Phase (0-24 hours)				
Number (%) of Subjects	58 (86.6%)	59 (93.7%)	58 (86.6%)	71 (97.3%)
Difference from PALO alone		7.1%	0%	10.7%
Overall Phase (0-120 hours)				
Number (%) of Subjects	47 (70.1%)	54 (85.7%)	54 (80.6%)	65 (89.0%)
Difference from PALO alone		15.6%	10.5%	18.9%

Age >=55 Years	N=69	N=72	N=70	N=62
Delayed Phase (25-120 hours)				
Number (%) of Subjects	59 (85.5%)	67 (93.1%)	66 (94.3%)	56 (90.3%)
Difference from PALO alone		7.6%	8.8%	4.8%
Acute Phase (0-24 hours)				
Number (%) of Subjects	64 (92.8%)	67 (93.1%)	69 (98.6%)	62 (100%)
Difference from PALO alone		0.3%	5.8%	7.2%
Overall Phase (0-120 hours)				
Number (%) of Subjects	57 (82.6%)	64 (88.9%)	66 (94.3%)	56 (90.3%)
Difference from PALO alone		6.3%	11.7%	7.7%

Note: The sponsor only conducted the subgroup analyses by using 65 years as a cut-off.

Table 18 Statistical Reviewer's Region Subgroup Analysis Results Based on MFAS Population for Study NETU-07-07

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=142)	PALO+NETU 300 mg(N=143)
Russia (N)	N=86	N=86	N=88	N=87
Delayed Phase (25-120 hours)				
Number (%) of Subjects	68 (79%)	80 (93%)	81 (92%)	80 (92%)
Difference from PALO alone		14%	13%	13%
Acute Phase (0-24 hours)				
Number (%) of Subjects	75 (87.2%)	81 (94.2%)	82 (93.2%)	86 (98.9%)
Difference from PALO alone		7%	6%	11.7%
Overall Phase (0-120 hours)				
Number (%) of Subjects	65 (75.6%)	77 (89.5%)	77 (87.5%)	79 (90.8%)
Difference from PALO alone		14.0%	11.9%	15.2%
Ukraine (N)	N=50	N=49	N=49	N=48
Delayed Phase (25-120 hours)				
Number (%) of Subjects	41 (82%)	42 (85.7%)	44 (89.8%)	42 (87.5%)
Difference from PALO alone		3.7%	7.8%	5.5%
Acute Phase (0-24 hours)				
Number (%) of Subjects	47 (94%)	45 (91.8%)	45 (91.8%)	47 (97.9%)
Difference from PALO alone		-2.2%	-2.2%	3.9%
Overall Phase (0-120 hours)				
Number (%) of Subjects	39 (78.0%)	41 (83.7%)	43 (87.8%)	42 (87.5%)
Difference from PALO alone		5.7%	9.8%	9.5%

Note: The sponsor indeed conducted the analysis for the overall phase and the results were the same as shown.

4.1.2 For Study NETU-08-18

For Study NETU-08-18, the majority of patients were white (79.6%) and females (98.1%). Therefore, only the subgroup analysis results for age and region were reported in this review; Table 19 presents the statistical reviewer's subgroup analysis results of CR for age in all three phases and Table 20 presents the sponsor's results for regions in the delayed phases. Note that for patients who were at least 55 years old, their observed treatment difference for the CR in the overall phase as well as those in US, their observed treatment difference for the CR in the delayed phase were trended in the opposite direction although these findings are likely due to play of chance.

Table 19 Statistical Reviewer's Age Subgroup Analysis Results Based on FAS Population for Study NETU-08-18

	NETU/PALO FDC(N=724)	PALO alone(N=725)
Age <55 Years	N=371	N=372
Complete Response Cycle 1 Delayed Phase (25-120 hours)		
Responder, n (%)	279 (75.2%)	232 (62.4%)
Difference from PALO alone, %	12.8%	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	313 (84.4%)	295 (79.3%)
Difference from PALO alone, %	5.1%	
Complete Response Cycle 1 Overall Phase (0-120 hours)		
Responder, n (%)	266 (71.7%)	217 (29.9%)
Difference from PALO alone, %	41.8%	
Age >=55 Years		
Complete Response Cycle 1 Delayed Phase (25-120 hours)	N=353	N=353
Responder, n (%)	278 (78.8%)	272 (77.1%)
Difference from PALO alone, %	1.7%	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	327 (92.6%)	321 (90.9%)
Difference from PALO alone, %	1.7%	
Complete Response Cycle 1 Overall Phase (0-120 hours)		
Responder, n (%)	272 (77.1%)	266 (75.4%)
Difference from PALO alone, %	-3.7%	

Note: The sponsor indeed conducted the analysis for the delayed phase and the results were the same as shown.

Table 20 Sponsor's Region Subgroup Analysis Results for CR in the Cycle 1 Delayed Phase on FAS Population for Study NETU-08-18

	NETU/PALO FDC (N=724)	PALO alone(N=725)
US (N)	N=32	N=32
Responder, n (%)	15 (46.9 %)	16 (50.0%)
Difference from PALO alone, %	-3.1%	
Latin America (including Mexico) (N)	N=59	N=58
Responder, n (%)	43 (72.9%)	29 (50.0%)
Difference from PALO alone, %	22.9%	
Europe (N)	N=300	N=301
Responder, n (%)	230 (76.7%)	226 (75.1%)
Difference from PALO alone, %	1.6%	
Commonwealth of Independent States (N)	N=233	N=234
Responder, n (%)	191 (82.0%)	165 (70.5%)
Difference from PALO alone, %	11.5%	
Asia (N)	N=100	N=100
Responder, n (%)	78 (78%)	68 (68%)
Difference from PALO alone, %	10.0%	

Source: Sponsor's Table 31 of CSR

4.1.3 For Study PALO-10-01

Most patients in the FAS population were white (86.7%). Thus only the subgroup analysis results for age, gender and region for the primary endpoint, i.e., CR in the acute phase after the start of the HEC administration, are presented in this section. Tables 21 and 22 present the sponsor's results for gender and region subgroups. As the sponsor only performed the subgroup analysis using 65 years

old as cut-off, but the mean of age is about 55. Table 23 presents the statistical reviewer's age subgroup analysis results.

Table 21 Sponsor's Gender Subgroup Analysis Results for CR in Acute Phase on FAS Population for Study PALO-10-01

	Oral PALO (N=369)	L.V. PALO (N=369)
Male (N)	N=219	N=217
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	206 (94.1%)	206 (94.9%)
Difference from PALO alone, %	**-0.9%**	
Female (N)	N=150	N=152
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	124 (82.7%)	112 (73.7%)
Difference from PALO alone, %	9.0%	

Source: Sponsor's Table 23 of CSR

Table 22 Sponsor's Region Subgroup Analysis Results for CR in Acute Phase on FAS Population for Study PALO-10-01

	Oral PALO (N=369)	L.V. PALO (N=369)
Europe (N)	N=203	N=204
Responder, n (%)	187 (92.1%)	178 (87.3%)
Difference from PALO alone, %	4.9%	
Commonwealth of Independent States (N)		
Responder, n (%)	95 (86.4%)	92 (84.4%)
Difference from PALO alone, %	2.0%	
Asia (N)		
Responder, n (%)	43 (87.8%)	41 (87.2%)
Difference from PALO alone, %	0.5%	

Source: Sponsor's Table 24 of CSR

Table 23 Statistical Reviewer's Subgroup Analysis Results for CR in the Acute Phase on FAS Population for Study PALO-10-01

	Oral PALO (N=369)	L.V. PALO (N=369)
Age <55 Years	N=124	N=127
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	107 (86.3%)	98 (77.2%)
Difference from PALO alone, %	9.1%	
Age >=55 Years	N=245	N=242
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	223 (91%)	220 (90.9%)
Difference from PALO alone, %	0.11%	

4.2 Other Special/Subgroup Populations

Besides those demographic and region subgroups reported in Section 4.1, there are no other pre-planned subgroup analyses of interests or to be reported in this review. However, during the auditing of Study NETU-07-07, the sponsor found Site #120 had significant numbers of violations,

thus performed the re-analyses by excluding Site #120. The issue regarding the sponsor's reanalysis results has been discussed in Section of 3.2.4.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor submitted three efficacy studies to support the use of 300 mg NETU combined with 0.5 mg PALO in the prevention of patients' acute and delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. To claim the CINV indication, one efficacy study for MEC indication, and two efficacy studies for the HEC indication were conducted. All three submitted efficacy studies showed statistically significant treatment differences on the protocol specified primary endpoints.

Note that one efficacy study for the HEC indication (Study NETU-07-07) was originally planned as a phase 2 study including three study doses (i.e., PALO 0.5 mg + NETU 100 mg, PALO 0.5 mg + NETU 200 mg and PALO 0.5 mg + NETU 300 mg) and active control (PALO 0.5 mg). During a meeting with the FDA on the clinical development of this product when planning the Phase 3 program, the sponsor was notified that this Phase 2, NETU-07-07 study could have had the potential to provide confirmatory evidence, but the efficacy should be based on the CR in the delayed phase instead of CR in the overall phase, which was the pre-specified primary endpoint in the protocol.

The FDA also informed the sponsor that the primary analysis should have been the CMH test, not the logistic regression model. Moreover, the primary analysis population for the Study NETU-07-07 remained to be the full analysis data set, but during that meeting, the FDA requested the sponsor to perform the sensitivity analysis on the traditional intent to treat (i.e., ITT) population.

To treat Study NETU-07-07 as a pivotal trial, the sponsor performed in depth auditing and found one Russia Site (#120) had a relatively large number of protocol violations; hence, the sponsor performed re-analysis for the CR in all three phases based on the MFAS population after excluding Site #120 data. Based on the analyses results for the CR in the delayed phase, the sponsor concluded that all three doses demonstrated statistically significant findings in comparing with the control group. This reviewer noted that the sponsor's conclusion was not based on the protocol specified Holm-Bonferroni multiplicity adjustment method. When this method was applied, only the PALO+NETU 200 mg could be claimed to be statistically significant. However, it should be noted that all these analyses are post-hoc.

Regarding the efficacy study for MEC, i.e., NETU-08-18, data supported the NETU/PALO's efficacy. However, the results from the U.S. were inconsistent with those from the rest of the world and the U.S. only accounted for 4.4% of the overall population. Finally, Study PALO-10-01 has successfully demonstrated the non-inferiority of oral palonosetron versus I.V. palonosetron in terms of the CR in the acute phase endpoint.

5.2 Conclusions and Recommendations

Of three submitted efficacy studies in this NDA, two studies are positive; Study NETU-08-18 supports the use of PALO+NETU for the MEC indication and Study PALO-10-01 supports the use of PALO oral as the comparator instead of the (b) (4) Study NETU-07-07, however, during the data monitoring after the trial has been completed, had been identified to have a Russian site (#120) encountering a large number of protocol violations; hence the sponsor performed some re-analyses by completely excluding that site from the final analysis and included their reanalysis results in the NDA submission.

Although based on the sponsor's results, they concluded that all three doses are significant for the CR in the delayed phase endpoint, this conclusion would be changed simply when we applied the protocol-specified multiple comparison procedure, i.e., Holm-Bonferroni method to control the type I error rate due to the three study doses in the study.

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 re-analyses 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. The statistical reviewer 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 re-analysis results showed significant findings based on the Holm-Bonferroni multiplicity adjustment method.

_____
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6 Appendix: Sponsor's Sensitivity Analysis Results Regarding Site 120

To further investigate the protocol violations found in Russian Site 120 on the efficacy assessments for Study NETU-07-07, we asked the sponsor to perform the following sensitivity analyses for the complete response (CR) in all three phases (i.e., the delayed, acute and overall):

a. Excluding the patients with major protocol violations (including taking disallowed concomitant medications) in Site 120
b. Excluding the patients with any protocol violations in Site 120
c. Including all patients in Site 120 but treating the patients with major protocol violations (including taking disallowed concomitant medications) as "treatment failures"
d. Including all patients in Site 120 but treating the patients with any protocol violations as "treatment failures"
e. Per-protocol analyses for the CR-delayed phase and -acute phase (including and excluding Site 120)

The sponsor's re-analysis results with the statistical reviewer's p-values using CMH adjusted by gender are displayed in Tables 24 to 29. The following are the sponsor's conclusions about their findings:

The conclusions of the requested sensitivity analyses on the CR-delayed phase and CR-overall phase are summarized here below. For the sensitivity analyses of CR-acute phase please refer to the tables.

1(a). Exclusion of the 13 patients with major violations impacting efficacy from the FAS analysis resulted in statistically significant p-values for the three doses in the overall phase (pre-specified primary endpoint) and in the delayed phase, even after applying the Bonferroni-Holm method to adjust for multiplicity.
1(b). Exclusion of the 14 patients with any violations impacting efficacy from the FAS analysis resulted in statistically significant p-values for the three doses in the overall phase (pre-specified primary endpoint) and in the delayed phase, even after applying the Bonferroni-Holm method to adjust for multiplicity.
1(c). Inclusion of all patients but treating the 13 patients with major violations impacting efficacy as "treatment failures" resulted in statistically significant p-values for the three doses in the overall phase (pre-specified primary endpoint) and in the delayed phase, even after applying the Bonferroni-Holm method to adjust for multiplicity.
1(d). Inclusion of all patients but treating the 14 patients with any violations impacting efficacy as "treatment failures" resulted in statistically significant p-values for the three doses in the overall phase (pre-specified primary endpoint) and in the delayed phase, even after applying the Bonferroni-Holm method to adjust for multiplicity.

1(e). The per-protocol analyses <u>including all</u> 39 patients of Site#120, resulted in statistically significant p-values for the three doses in the overall phase (pre-specified primary endpoint, see CSR) and in the delayed phase, even after applying the Bonferroni-Holm method to adjust for multiplicity.

When performing the per-protocol analyses excluding all 39 patients of Site#120, the overall phase (pre-specified primary endpoint) resulted in statistically significant p- values for the three doses. However not all the differences between the combination product versus palonosetron alone were statistically significant in the delayed phase. In our opinion, this depends primarily on the substantially lower number of patients included in this analysis.

Table 24 Sponsor's CR Results for MFAS after Excluding All Violators at Site #120

	PALO alone (N=133)	PALO+NETU 100 mg (N=133)	PALO+NETU 200 mg (N=132)	PALO+NETU 300 mg (N=131)
Overall Phase (0-120 hours)				
Number (%) of Subjects	101 (75.9)	116 (87.2)	115 (87.1)	117 (89.3)
Difference from PALO alone (%) with 95% C.I.		11.3 (2.1, 20.5)	11.2 (1.9, 20.4)	13.4 (4.4, 22.4)
p-value by logistic model*		0.016	0.020	0.004
p-value by CMH**		0.016	0.019	0.004
Acute Phase (0-24 hours)				
Number (%) of Subjects	119 (89.5)	124 (93.2)	122 (92.4)	129 (98.5)
Difference from PALO alone (%) with 95% C.I.		3.8 (-3.0, 10.5)	3.0 (-4.0, 9.9)	9.0 (3.4, 14.6)
p-value by logistic model*		0.263	0.417	0.008
p-value by CMH**		0.264	0.417	0.002
Delayed Phase (25-120 hours)				
Number (%) of Subjects	106 (79.7)	120 (90.2)	120 (90.9)	118 (90.1)
Difference from PALO alone (%) with 95% C.I.		10.5 (2.0, 19.0)	11.2 (2.8, 19.6)	10.4 (1.8, 18.9)
p-value by logistic model*		0.016	0.012	0.019
p-value by CMH**		0.015	0.010	0.017

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".

Table 25 Sponsor's CR Results for MFAS with Major Violators at Site #120 as Failures

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=137)	PALO+NETU 300 mg (N=135)
Overall Phase (0-120 hours)				
Number (%) of Subjects	101 (74.3)	116 (85.9)	115 (83.9)	118 (87.4)
Difference from PALO alone (%) with 95% C.I.		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 22.0)
p-value by logistic model*		0.014	0.045	0.005
p-value by CMH**		0.014	0.044	0.005
Acute Phase (0-24 hours)				
Number (%) of Subjects	119 (87.5)	124 (91.9)	122 (89.1)	130 (96.3)
Difference from PALO alone (%) with 95% C.I.		3.6 (-3.0, 10.2)	3.0 (-3.7, 9.7)	8.8 (3.3, 14.3)
p-value by logistic model*		0.225	0.691	0.010
p-value by CMH**		0.228	0.692	0.067
Delayed Phase (25-120 hours)				
Number (%) of Subjects	106 (77.9)	120 (88.9)	120 (87.6)	119 (88.2)
Difference from PALO alone (%) with 95% C.I.		10.2 (1.9, 18.6)	11.1 (2.9, 19.3)	10.2 (1.9, 18.6)
p-value by logistic model*		0.014	0.033	0.023
p-value by CMH**		0.014	0.031	0.022

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".

Table 26 Sponsor's CR Results for MFAS with All Violators at Site #120 as Failures

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=137)	PALO+NETU 300 mg (N=135)
Overall Phase (0-120 hours)				
Number (%) of Subjects	101 (74.3)	116 (85.9)	115 (83.9)	117 (86.7)
Difference from PALO alone (%) with 95% C.I.		10.9 (1.9, 20.0)	11.1 (2.1, 20.1)	13.2 (4.4, 22.0)
p-value by logistic model*		0.014	0.045	0.009
p-value by CMH**		0.014	0.044	0.008
Acute Phase (0-24 hours)				
Number (%) of Subjects	119 (87.5)	124 (91.9)	122 (89.1)	129 (95.6)
Difference from PALO alone (%) with 95% C.I.		3.6 (-3.0, 10.2)	3.0 (-4.0, 9.9)	8.8 (3.3, 14.3)
p-value by logistic model*		0.225	0.691	0.019
p-value by CMH**		0.228	0.692	0.015
Delayed Phase (25-120 hours)				
Number (%) of Subjects	106 (77.9)	120 (88.9)	120 (87.6)	118 (87.4)
Difference from PALO alone (%) with 95% C.I.		10.2 (1.9, 18.6)	11.1 (2.9, 19.3)	~~10.2~~ 9.5(1.9, 18.6)
p-value by logistic model*		0.014	0.033	0.035
p-value by CMH**		0.014	0.031***	0.034***

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".
Note that the red highlight shows the corrected value. The blue highlighted values are not statistically significant in terms of Homes Bonferroni method.

Table 27 Sponsor's CR Results for PP Including Site #120

	PALO alone (N=128)	PALO+NETU 100 mg (N=133)	PALO+NETU 200 mg (N=135)	PALO+NETU 300 mg (N=131)
Acute Phase (0-24 hours)				
Number (%) of Subjects	115 (89.9)	125 (94.0)	126 (93.3)	129 (98.5)
Difference from PALO alone (%) with 95% C.I.		4.1 (-2.5, 10.8)	3.5 (-3.2, 10.2)	8.6 (3.0, 14.3)
p-value by logistic model*		0.218	0.303	0.009
p-value by CMH**		0.217	0.303	0.003
Delayed Phase (25-120 hours)				
Number (%) of Subjects	103 (80.5)	121 (91.0)	123 (91.1)	118 (90.1)
Difference from PALO alone (%) with 95% C.I.		10.5 (2.1, 18.9)	10.6 (2.3, 19.0)	9.6 (1.0, 18.2)
p-value by logistic model*		0.016	0.014	0.029
p-value by CMH**		0.015	0.012	0.028

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".

Table 28 Sponsor's CR Results for PP Excluding Site #120

	PALO alone (N=122)	PALO+NETU 100 mg (N=127)	PALO+NETU 200 mg (N=127)	PALO+NETU 300 mg (N=122)
Overall Phase (0-120 hours)				
Number (%) of Subjects	94 (77.1)	111 (87.4)	113 (89.0)	108 (88.5)
Difference from PALO alone (%) with 95% C.I.		10.4 (0.9, 19.8)	11.9 (2.7, 21.2)	11.5 (2.1, 20.8)
p-value by logistic model*		0.030	0.012	0.019
p-value by CMH**		0.030	0.012	0.018
Acute Phase (0-24 hours)				
Number (%) of Subjects	109 (89.3)	119 (93.7)	118 (92.9)	120 (98.4)
Difference from PALO alone (%) with 95% C.I.		4.4 (-2.6, 11.3)	3.6 (-3.5, 10.6)	9.0 (3.1, 14.9)
p-value by logistic model*		0.213	0.327	0.010
p-value by CMH**		0.212	0.327	0.004
Delayed Phase (25-120 hours)				
Number (%) of Subjects	99 (81.2)	115 (90.6)	117 (92.1)	109 (89.3)
Difference from PALO alone (%) with 95% C.I.		9.4 (0.8, 18.0)	11.0 (2.6, 19.4)	8.2 (-0.6, 17.0)
p-value by logistic model*		0.033***	0.012	0.077***
p-value by CMH**		0.032***	0.011	0.075***

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".
Note that the blue highlights denote not significant in terms of Holm-Bonferroni method.

Table 29 Sponsor's CR Results for MFAS after Excluding Major Violators at Site #120

	PALO alone (N=133)	PALO+NETU 100 mg (N=133)	PALO+NETU 200 mg (N=132)	PALO+NETU 300 mg (N=132)
Overall Phase (0-120 hours)				
Number (%) of Subjects	101 (75.9)	116 (87.2)	115 (87.1)	118 (89.4)
Difference from PALO alone (%) with 95% C.I.		11.3 (2.1, 20.5)	11.2 (1.9, 20.4)	13.5 (4.5, 22.4)
p-value by logistic model*		0.016	0.020	0.004
p-value by CMH**		0.016	0.019	0.004
Acute Phase (0-24 hours)				
Number (%) of Subjects	119 (89.5)	124 (93.2)	122 (92.4)	130 (98.5)
Difference from PALO alone (%) with 95% C.I.		3.8 (-3.0, 10.5)	3.0 (-4.0, 9.9)	9.0 (3.4, 14.6)
p-value by logistic model*		0.263	0.417	0.007
p-value by CMH**		0.264	0.417	0.002
Delayed Phase (25-120 hours)				
Number (%) of Subjects	106 (79.7)	120 (90.2)	120 (90.9)	119 (90.2)
Difference from PALO alone (%) with 95% C.I.		10.5 (2.0, 19.0)	11.2 (2.8, 19.6)	10.5 (1.9, 19.0)
p-value by logistic model*		0.016	0.012	0.017
p-value by CMH**		0.015	0.010	0.016

* from logistic regression including "gender" as covariate ** CMH stratified by "gender".
Note that the blue highlight shows a p-value by CMH which is very different the one by logistic regression.

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/s/

YEH FONG CHEN
07/02/2014

FREDA COONER
07/02/2014
Concur with the conclusions. Please see the Statistical Team Leader Memorandum.